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Carbohydrate Research 329 (2000) 667-679

CARBOHYDRATE RESEARCH

Note

Syntheses of β -D-GalpNAc4SO₃-(1 \rightarrow 4)-L-IdopA2SO₃, a disaccharide fragment of dermatan sulfate, and of its methyl α -L-glycoside derivative

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Received 22 June 2000; accepted 31 July 2000

Abstract

The syntheses of sodium (sodium 2-acetamido-2-deoxy-4-*O*-sulfonato- β -D-galactopyranosyl)-(1 \rightarrow 4)-(sodium 2-*O*-sulfonato-L-idopyran)uronate, a disaccharide fragment of dermatan sulfate, and of its methyl α -L-glycoside derivative are reported for the first time. The use of 4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-trichloroacetamido-1-*O*-trichloroace-timidoyl- α -D-galactopyranose, readily prepared from a D-gluco precursor, allowed the stereocontrolled and high yielding coupling with the low reactive 4-hydroxyl group of L-iduronic acid ester derivatives. Classical transformation of the disaccharide products into the target molecules was achieved in high yield. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Glycosylation reactions; 2-Deoxy-2-trichloroacetamido-D-galacto derivatives; Dermatan sulfate disaccharides

1. Introduction

Dermatan sulfate (DeS) is a proteoglycan ubiquitous in most mammalian tissues. It was first isolated from pig skin [1], and is mainly composed of disaccharide repeating units of L-iduronic acid and 2-acetamido-2-deoxy-Dgalactose, namely [4)- α -L-IdopA-(1 \rightarrow 4)- β -D-GalpNAc-(1 \rightarrow]_n. Structural studies on DeS showed different patterns of sulfation substitutions depending on its origin [2]. The Dgalactosamine residues are mainly sulfated at C-4, but 6-sulfated [3] as well as 4,6-disulfated species [4,5] were also isolated, and the adjacent L-iduronic acid residues are sulfated or not at C-2. DeS binds to the serine protease inhibitor heparin cofactor II (HC II), and enhances its thrombin inhibitory potency [6]. This interaction is associated with disulfated sequences, namely [4)- α -L-IdopA2SO₃-(1 \rightarrow 3)- β -D-Galp NAc4SO₃- $(1 \rightarrow]_n$, and the minimal requirement for the HC II binding site was first postulated to be a trimeric sequence [7], and more recently a tetrameric species [8]. In oncology surgery, DeS prevents venous thromboembolism more effectively than heparin without increasing bleeding complications [9]. It was also recently reported [10] that DeS released during wound repair should be a potent promoter of fibroblast growth factor-2 (FGF-2) function.

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Several syntheses of DeS fragments have been reported, such as those of a monosulfated disaccharide [11,12], a disulfated disaccharide [13], as well as those of a hexasaccharide [14,15] containing three disulfated sequences. For the syntheses of these hexasaccharide species, the strategy was edicted by the encountered difficulties [15] to obtain an efficient β-interglycosidic linkage between a D-galactosamine donor and the 4hydroxyl group of L-iduronic acid esters. Thus, L-idose derivatives were used as intermediates, and these residues were oxidized into the corresponding L-iduronic acid after construction of the oligosaccharide backbone.

We now report for the first time on an efficient and stereocontrolled elaboration of this β -interglycosidic linkage through syntheses of disaccharide **1** and its methyl α -L-glycoside derivative **2**, in which the methyl group is suitable as a marker for NMR studies, using an activated 2-deoxy-2-trichloroacetamido-D-*galacto* glycosyl donor readily prepared from a D-*gluco* precursor. An improved expeditious preparation of 3-O-benzyl-L-*ido* derivatives is also reported.



2. Results and discussion

The availability of L-*ido* synthons is a key point for the synthesis of L-iduronic acid containing oligosaccharides, and constant efforts were achieved for their efficient preparation. Recent syntheses mainly involved modifications at C-5 of D-gluco precursors through, for example, diastereoselective hydroboration of *exo*-glucal derivatives [16–18], functionalization of Δ^4 -uronic acid species [19] or D-xylodialdose derivatives [20], epimerization of D-glucurono-6,3-lactone [21], or intramolecular Tischenko reaction of aldonic acid esters [22]. However, for large scale preparations, older procedures [23] starting from known 3-O-benzyl-1,2-O-isopropylidene- α -D-gluco-furanose (3) [24] were still used [25]. We now report on a slightly modified and expeditious preparation of the tetrabenzoate **6**, for which efficiency and reproducibility was the main feature.

Treatment of **3** with pivaloyl chloride (1.5)equiv) in pyridine at 0 °C afforded the crystalline 6-O-pivaloyl derivative 4 in 85% yield, isolated by simple crystallization. Some dipivaloylated species were present in the mother liquors, but were easily recycled through transesterification. Trifluoromethanesulfonylation of 4 with triflic anhydride (1.1 equiv) and pyridine in 1,2-dichloroethane at -15 °C, followed by treatment in situ with water [26] and heating at 85 °C afforded a mixture of 5- and 6-O-pivaloyl-L-ido intermediates, which were directly transesterified with methanolic sodium methoxide to provide the known crystalline diol 5 in 72% overall yield (61% yield from 3). The physical data for 5 are in agreement with those reported [27]. The route described here, the overall yield for the D-gluco \rightarrow L-ido transformation, as well as the ease of isolation of the intermediates, compare well with those previously reported. Acid hydrolysis of 5, as reported [23], afforded the intermediate 3-Obenzyl-L-idose, which was directly treated with benzoyl chloride in pyridine to afford nearly exclusively the β -benzoate **6** in 62% overall yield, the anomeric configuration of which was deduced from its ¹H NMR spectrum (Table 1). Treatment of 6 with methyl and benzyl alcohols, respectively, in dichloromethane, and in the presence of trimethylsilyl triflate gave the methyl (7) and benzyl (8) α -L-glycosides in 90 and 70% yields, respectively. The physical data for 7 (not described in Section 3) are in agreement with those reported [28].

Transformation of 7 and 8 into the Liduronyl acceptors 15 and 16 was then achieved as follows (Scheme 1). Transesterification of 7 and 8 gave the corresponding triol derivatives, which were treated with 2methoxypropene and 10-D,L-camphorsulfonic acid in N,N-dimethylformamide to give the corresponding 4,6-*O*-isopropylidene derivatives, which were, in turn, benzoylated to give **9** and **10** in 75 and 63% yields, respectively. Mild acid hydrolysis of **9** and **10** with aqueous acetic acid, followed by *tert*-butyldimethylsilylation of the intermediate diols gave **11** and **12**, both in 90% overall yield. Jones oxidation of **11** and **12** in acetone, followed by esterification of the intermediate acids with methyl chloroformate and 4-dimethylaminopyridine gave the uronic acid esters **13** and **14** in 65 and 62% yields, respectively. Desilylation of **13** and **14** with tetrabutylammonium fluoride in dry tetrahydrofuran at 0 °C afforded the target glycosyl acceptors **15** and **16** in 60 and 74% yields, respectively. In these reactions, no β-elimination reaction caused by the basicity of fluoride ion was observed, as was the case in the D-glucuronic acid ester series [29]. The ¹H NMR spectra of the L-*ido* derivatives **8–16** (Table 1) showed, with the exception of **11** and **12**, long-range coupling constants (J_{1,3})

Table 1

¹H NMR data: carbohydrate ring protons for monosaccharide derivatives 4–6 and 8–16 a

Proton	4	5	6	8	9	10	11	12	13	14	15	16
H-1	5.93	6.00	6.54	5.13	4.92	5.14	4.96	5.13	5.09	5.32	5.09	5.24
$J_{1.2}$	3.8	3.8	1.8	1.0	2.2	2.0	3.1	3.1	2.2	2.6	1.2	1.2
$J_{13}^{1,2}$				0.5	0.5	0.7			1.0	1.0	0.8	0.8
H-2	4.61	4.66	5.53	5.26	5.24	5.33	5.12	5.22	5.11	5.18	5.28	5.31
J_{23}	~ 0	~ 0	3.0	3.0	4.2	4.0	3.3	5.2	2.5	2.7	2.4	2.5
$J_{24}^{2,2}$			1.0	0.5	0.5	0.7	1.0		0.8	0.9	1.2	1.2
H-3	4.15	4.03	4.33	4.07	3.68	3.72	3.78	4.12	3.80	4.10	3.93	3.90
J_{34}	4.0	3.5	3.0	2.0	3.6	3.6	3.0	2.8	3.4	3.2	3.2	1.4
H-4	4.15	4.21	5.34	5.30	3.92	4.03	3.78	3.88	4.13	3.75	4.15	4.12
J_{45}		5.2	2.0	2.0	2.6	2.4	2.3	2.5	2.7	2.7	1.7	1.8
H-5	4.15	4.08	4.81	4.88	3.98	3.94	4.04	3.88	4.85	4.81	4.98	4.95
$J_{5.6a}$	6.2	4.3	1.5	5.0	3.2	4.6	5.2	6.0				
$J_{5.6b}$		5.4	3.0	8.0	2.6	2.6	5.7	4.4				
H-6a	4.37	3.64	4.65	4.63	4.11	4.05	3.89	3.92				
$J_{6a,6b}$	-12.3		-12.0	-12.0	-13.2	-12.4	-10.6	-10.7				
H-6b	4.25	3.64	4.64	4.43	3.93	3.86	3.80	3.80				

^a Chemical shifts (δ , ppm) and coupling constants (J, in Hz) for solutions in CDCl₃.





Scheme 2.

Table 2 ¹H NMR data: carbohydrate ring protons for aminosugar derivatives **18–24** ^a

Proton	18	19	20	21	22	23	24
H-1	5.49	5.51	5.40	5.32	5.36	6.50	5.01
$J_{1,2}$	8.4	8.4	8.4	8.4	8.5	3.5	9.7
H-2	3.75	3.81	3.75	3.93	3.85	4.48	4.25
$J_{2,3}$	10.0	10.2	10.3	10.7	11.0	11.3	10.7
H-3	4.46	4.44	4.18	4.24	4.29	3.86	3.61
$J_{3.4}$	9.0	8.8	8.4	3.3	3.5	3.0	3.1
H-4	3.90	3.90	3.88	4.16	5.71	5.78	5.71
J_{45}	9.5	9.6		0.8	0.6	1.0	0.9
H-5	3.75	3.70	3.75	3.83	3.90	4.25	3.90
$J_{5.6a}$	9.0	9.3			6.1	5.7	5.3
$J_{5.6b}$	4.6	5.0			6.7	7.7	7.8
H-6a	3.90	3.94	3.88	3.83	3.52	3.58	3.60
$J_{6a,6b}$	-10.7	-10.4			-9.6	-9.4	-9.3
H-6b	4.48	3.82	3.88	3.83	3.59	3.50	3.49
NH	7.00	7.00	7.00	6.95	6.88	6.37	6.53
$J_{2,\rm NH}$	7.0	7.0	7.0	7.0	7.2	7.8	8.2

^a Chemical shifts (δ , ppm) and coupling constants (J, in Hz) for solutions in CDCl₃.

and $J_{2,4}$) indicating a large predominance, if not the only one, of ${}^{1}C_{4}$ conformation for these intermediates.

Preparation of the D-galactosaminyl donor 23 from a D-glucosamine precursor was studied next (Scheme 2). Transesterification of the easily available 4-methoxyphenyl 3,4,6-tri-Oacetyl-2-deoxy-2-trichloroacetamido-B-D-glucopyranoside (17) [30] with methanolic sodium methoxide, followed by acetalation with benzaldehyde and trifluoroacetic acid gave crystalline 18 in 65% yield. Protection at O-3 was then achieved by treatment of 18 with benzyl bromide and sodium hydride in N,Ndimethylformamide to give crystalline 19 in 82% yield. No N-benzylation reaction was observed under these conditions. Regioselective reductive cleavage of the benzylidene acetal in 19 with triethylsilane and trifluoroacetic acid [31] gave the crystalline 3,6-di-O-benzyl derivative 20 in 69% yield. The use of boron trifluoride-ethyl etherate [32] instead of trifluoroacetic acid did not improve the yield of this reaction. Inversion of configuration at C-4 was then achieved by treatment of 20 with triflic anhydride and pyridine in dichloromethane at -15 °C, followed by nucleophilic displacement of the intermediate triflate with sodium nitrite in N,N-dimethylformamide [33,29] to give the crystalline D-galacto derivative 21 in 89% yield, the structure of which was evident from its ¹H NMR spectrum (Table 2). Acetylation of 21 gave 22, which was submitted to oxidative removal of the anomeric 4-methoxyphenyl glycoside with followed nitrate, ceric ammonium by trichloroacetimidoylation with trichloroacetonitrile and 1,8-diazabicyclo[5,4,0]undec-7ene (DBU) to afford the target α -imidate 23 in 88% overall yield, the anomeric configuration of which was deduced from its ¹H NMR spectrum (Table 2).

Condensation of 15 and 16 (1 equiv) with a moderate excess of 23 (1.1–1.3 equiv), in

dichloromethane at -15 °C, in the presence of trimethylsilyl triflate, afforded readily the β -linked disaccharide derivatives 25 and 26, both in 60% yield. The ¹H NMR spectra for 25 and 26 (Table 3) are in agreement with the expected structures. A major by-product was identified as the N-trichloroacetyl glycoside 24. rather unexpected species, since а trichloroacetamide released by the glycosylation reaction is known [34] to be a rather poor nucleophile. However, an intramolecular rearrangement of the trichloroacetimidovl group should be excluded since the corresponding 2-trichloromethyl oxazoline (not described in Section 3) reacted slowly with trichloroacetamide under the glycosylation reaction conditions. The N-trichloroacetyl groups in 25 and 26 were readily transformed [35] into N-acetyl groups by radical reduction with tributyltin hydride and azobisisobutyronitrile

(AIBN) to give the crystalline acetamides 27 and 28 in 76 and 83% yields, respectively. Saponification of the ester groups in 27 and 28 with lithium hydroperoxide [36] in tetrahydrofuran, followed by methanolic sodium hydroxide afforded the corresponding hydroxy acids, which were directly O-sulfonated by treatment with the sulfur trioxidetrimethylamine complex in N,N-dimethylformamide at 50 °C, followed by ion-exchange chromatography (Na⁺ resin) to provide the sodium salts 29 and 30 in 65 and 68% overall yields, respectively. As previously reported [37], 4-O-sulfonation of the D-galactosamine moiety was troublesome, and required a large excess of reagent and prolonged reaction time to go to completion. Comparison of the ¹H recorded in NMR spectra, deuterated methanol, of 29 and 30 (Table 3) and of their non-sulfated hydroxy acid precursors (details

Table 3

 $^1\mathrm{H}$ NMR data: carbohydrate ring protons for disaccharide derivatives 25–30, 1 and 2 $^{\mathrm{a}}$

Proton	25	26	27	28	29 b	30 b	1 ^c	2 °	
H-1 ^I	4.97	5.18	5.00	5.20	5.03	5.30 5.25, 5.12		4.84	
$J_{1,2}$	1.2	1.2	1.1	1.2	1.2	1.2	1.0, 1.5	1.0	
$J_{1,3}^{-}$	0.8	0.9	0.8	0.9	0.8	0.8		1.0	
H-2 ^I	5.08	5.18	5.07	5.14	4.94	4.94	4.25, 4.05	4.07	
$J_{2,3}$	2.0	1.8	2.0	1.8	1.6	1.6	3.5	3.6	
$J_{2,4}^{-,-}$	0.9	0.8	0.9	0.8	0.6	0.6		0.6	
H-3 ¹	4.06	4.09	3.98	4.02	4.06	4.10	4.27, 4.17	4.19	
$J_{3.4}$	3.1	3.0	3.1	3.0	2.6	2.5	3.0	3.2	
H-4 ^I	4.25	4.30	4.17	4.24	4.15	4.21	3.96, 3.95	3.93	
$J_{4.5}$	1.7	1.9	1.5	1.9	2.0	2.0	2.2	2.3	
H-5 ¹	4.83	4.88	4.83	4.86	4.53	4.56	4.52, 4.51	4.32	
H-1 ¹¹	4.85	4.89	4.89	4.94	4.46	4.49	4.50, 4.47	4.55	
$J_{1.2}$	8.4	8.2	8.4	8.2	8.2	8.2	8.0	8.0	
H-2 ¹¹	3.48	3.49	3.78	3.20	4.01	4.04	3.83	3.79	
$J_{2,3}$	10.8	10.5	10.7	10.2	10.5	10.3	10.5	10.5	
H-3 ¹¹	4.02	4.02	4.32	4.34	3.51	3.60	3.72	3.70	
$J_{3,4}$	3.3	3.1	3.1	2.8	3.0	3.2	3.0	3.0	
$H-4^{II}$	5.50	5.50	5.45	5.44	4.83	4.86	4.60, 4.58	4.58	
$J_{4,5}$	0.8	0.9	0.7	0.9	0.8	0.8	0.6	0.6	
H-5 ¹¹	3.60	3.64	3.60	3.65	3.68	3.70	3.73	3.73	
$J_{5,6a}$	5.9	6.0	5.7	6.0	5.0	4.7			
$J_{5,6b}$	6.9	6.9	7.2	7.0	6.5	6.5			
H-6a ^{II}	3.13	3.19	3.07	3.10	3.88	3.93	3.78	3.78	
$J_{6a,6b}$	-9.1	-9.2	-9.1	-9.2	-9.8	-10.0			
H-6b ^{II}	3.08	3.13	3.04	3.02	3.75	3.82	3.74	3.73	
NH	6.72	6.82	5.52	5.54					
$J_{2,\rm NH}$	7.6	7.5	7.2	6.6					

^a Chemical shifts (δ , ppm) and coupling constants (J, in Hz) for solutions in CDCl₃, unless otherwise stated.

^b CD₃OD.

^c D₂O.

in Section 3) showed the expected [38] downfield shifts (~ 0.8 ppm) of the signals for H-4^{II} in sulfates 29 and 30, and downfield shifts (~ 0.8 ppm) of the signals for H-2^I in **29** and 30, in good agreement with those reported [13,28] for 2-O-sulfonated L-iduronic acid residues in DeS oligosaccharides. These chemical shift differences indicate clearly that sulfonation occurred at O-2^I and O-4^{II}. Final hydrogenation of 29 and 30 with Pd-C in aqueous methanol afforded the target molecules 2 and 1 in 78 and 90% yields, respectively. The ¹H (Table 3) and ¹³C NMR data for 1 and 2 are in agreement with the expected structures. The coupling constants observed for the reducing methyl α -Liduronate residue in 2 indicate a predominance of ${}^{1}C_{4}$ conformation, as reported [28] for a similar reducing moiety in a synthetic heparan sulfate fragment.

In conclusion, expeditious preparations of L-idose and D-galactosamine derivatives from D-gluco precursors are reported. A stereocontrolled and good-yielding coupling reaction with the low reactive 4-hydroxyl group of L-iduronic acid esters was achieved using the glycosyl donor 23, exemplifying the efficiency of activated 2-deoxy-2-trichloroacetamido-Dgalacto derivatives in syntheses of 1,2-trans-2amino-2-deoxy-D-glycosides. The way is now open for the construction of fragments of higher molecular size, which is currently being investigated in our group.

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. ¹H and ¹³C NMR spectra were recorded at 27 °C with a Bruker DPX-250 spectrometer operating at 250 and 63 MHz, respectively, with Me_4Si as internal standard, unless otherwise stated. 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. Flashcolumn chromatography was performed on Silica gel (E. Merck, $40-63 \mu m$). Elemental analyses were performed by the Service Central de Microanalyse du CNRS (Vernaison, France).

3-O-Benzyl-1,2-O-isopropylidene-6-O-pivaloyl- α -D-glucofuranose (4).—Pivaloyl chloride (10.1 mL, 82 mmol) was added at 0 °C to a solution of 3-O-benzyl-1,2-O-isopropylidene- α -D-glucofuranose (3) [24] (17.0 g, 55 mmol) in anhyd pyridine (90 mL) and anhyd CH₂Cl₂



(45 mL), and the mixture was allowed to attain rt within 3.5 h, then was cooled to 0 °C. Methanol (20 mL) was added, and the mixture was diluted with CH₂Cl₂ (50 mL), washed with water, satd aq NaHCO₃, and water, dried (MgSO₄) and concentrated. The residue was crystallized from EtOAc-petroleum ether to give 4 (18.47 g, 85%); mp 100-101 °C; $[\alpha]_{\rm D} - 32^{\circ}$ (c 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 1); 7.30 (m, 5 H, Ph), 4.65 (ABq, 2 H, CH₂Ph), 1.47, 1.32 (2 s, 6 H, $(CH_3)_2C$), 1.21 (s, 9 H, $(CH_3)_3C$; ISMS: m/z 417, $[M + Na]^+$, 412, $[M + NH_4]^+$, 395, $[M + H]^+$. Anal. Calcd for C₂₁H₃₀O₇: C, 63.94; H, 7.66. Found: C, 63.81; H, 7.53.

3-O-Benzyl-1,2-O-isopropylidene-β-L-idofuranose (5).—Triflic anhydride (5 mL, 30.5 mmol) was added dropwise at -15 °C to a solution of 4 (11.13 g, 28.2 mmol) in anhyd 1,2-dichloroethane (140 mL) and anhyd pyridine (11.4 mL), and the mixture was stirred for 2 h at this temperature. Water (14 mL) was added, and the mixture was stirred for 30 min at 85 °C, then cooled, diluted with CH_2Cl_2 (75 mL), washed with water, cold 5% aq HCl, satd aq NaHCO₃, and water, dried (MgSO₄) and concentrated. The residue was eluted from a column (100 g) of silica gel with $6:1 \rightarrow 4:1$ petroleum ether-EtOAc to give a mixture of 5- and 6-O-pivaloyl-L-ido derivatives (10.04 g, 90%).

A solution of the above intermediates in MeOH (100 mL) was treated overnight at rt with methanolic MeONa (1 M, 3 mL), then it was deionized with Amberlite IR-120 [H⁺] resin, filtered, and concentrated. The residue was eluted from a column (100 g) of silica gel with 5:2 AcOEt-CH2Cl2, and crystallized from EtOAc-petroleum ether to afford 5 (6.31 g, 72% from 4); mp 84 °C, lit. 86–87 °C [27]; $[\alpha]_{\rm D} - 58^{\circ}$ (c 1, CHCl₃), lit. -61° [27]; ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 1); 7.40 (m, 5 H, Ph), 4.60 (ABq, 2 H, CH₂Ph), 3.05 (d, 1 H, J 2.5 Hz, HO-5), 2.12 (dd, 1 H, J 5.6 and 6.7 Hz, HO-6), 1.49, 1.34 (2 s, 6 H, $(CH_3)_2C$); ISMS: m/z 333, $[M + Na]^+$, 328, $[M + NH_4]^+$.

1,2,4,6-Tetra-O-benzoyl-3-O-benzyl- β -Lidopyranose (6).—Sulfuric acid (0.1 M, 220 mL) was added to a solution of 5 (6.5 g, 22 mmol) in dioxane (130 mL), and the mixture was stirred for 5 h at 80 °C, then cooled, deionized with Dowex 1X2-400 $[OH^-]$ resin, filtered, and concentrated.

Benzoyl chloride (14 mL, 121 mmol) was added at 0 °C to a solution of the residue in anhyd CH₂Cl₂ (40 mL) and anhyd pyridine (32 mL), and the mixture was stirred for 5 h at rt, then cooled to 0 °C. Methanol (20 mL) was added, and the mixture was diluted with CH_2Cl_2 (50 mL), washed with water, satd aq NaHCO₃ and water, dried (MgSO₄) and concentrated. The residue was eluted from a column (200 g) of silica gel with 4:1 petroleum ether-EtOAc to give 6 as a white foam (8.36 g, 62% from 5); $[\alpha]_{\rm D} - 27^{\circ}$ (c 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 1); 8.10-7.10 (m, 25 H, Ph), 4.90 (s, 2 H, CH₂Ph); ISMS: m/z 709, $[M + Na]^+$, 704, $[M + NH_4]^+$, 687, $[M + H]^+$. Anal. Calcd for C₄₁H₃₄O₁₀: C, 71.71; H, 4.99. Found: C, 71.79; H, 4.98.

Benzyl 2,4,6-tri-O-benzoyl-3-O-benzyl-α-Lidopyranoside (8).—A mixture of 6 (8.39 g, 12.2 mmol), benzyl alcohol (1.9 mL, 18.4 mmol), and 4 Å powdered molecular sieves (5 g) in anhyd CH₂Cl₂ (40 mL) was stirred for 1 h at rt under dry Ar, then cooled to 0 °C. Trimethylsilyl triflate (2.3 mL, 12.2 mmol) was added, and the mixture was stirred for 3 h at 0 °C. Triethylamine (5.5 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 Et₃N, and crystallized from the same mixture of solvents to give 8 (5.7 g, 70%); mp 113–114 °C; $[\alpha]_{\rm D} - 5^{\circ}$ (c 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 1); 8.20-7.10 (m, 25 H, Ph), 4.83, 4.70 (2 ABq, 4 H, CH₂Ph); ISMS: m/z 695, $[M + Na]^+$, 690, $[M + NH_4]^+$, 565, $[M - OCH_2Ph]^+$. Anal. Calcd for $C_{41}H_{36}O_9$: C, 73.20; H, 5.39. Found: C, 73.18; H, 5.24.

Methyl 2-O-benzoyl-3-O-benzyl-4,6-O-isopropylidene- α -L-idopyranoside (9).—A solution of 7 (4.13 g, 7 mmol) in MeOH (20 mL) was treated for 4 h at rt with methanolic MeONa (1 M, 0.5 mL), then it was deionized with Amberlite IR-120 [H⁺] resin, filtered and concentrated to give the corresponding triol as an oil (2.47 g, quantitative). A mixture of the above isolated triol, 2methoxypropene (1.4 mL, 14 mmol), and 10-D,L-camphorsulfonic acid (0.28 g) in dry DMF (28 mL) was stirred for 3 h at 0 °C. Triethylamine (0.5 mL) was added, and the mixture was diluted with EtOAc (200 mL), washed with water, satd aq NaHCO₃ and water, dried (MgSO₄) and concentrated. The residue was eluted from a column (100 g) of silica gel with 3:1 petroleum ether–EtOAc to give the corresponding 4,6-*O*-isopropylidene derivative (1.98 g, 87%).

Benzoyl chloride (0.84 mL, 7.2 mmol) was added at 0 °C to a solution of the above isolated alcohol in anhyd pyridine (20 mL), and the mixture was stirred for 30 min at rt, then cooled to 0 °C. Methanol (5 mL) was added, and the mixture was diluted with CH₂Cl₂ (100 mL), washed with water, satd aq NaHCO₃, and water, dried, and concentrated. The residue was eluted from a column (50 g) of silica gel with 3:1 petroleum ether-EtOAc containing 0.2% of Et₃N, and crystallized from the same mixture of solvents to give 9 (2.25 g, 75% from 7); mp 110–111 °C; $[\alpha]_{\rm D}$ – 29° (c 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 1); 8.10-7.30 (m, 10 H, Ph), 4.74 (ABq, 2 H, CH₂Ph), 3.44 (s, 3 H, OC H_3), 1.47, 1.42 (2 s, 6 H, (C H_3)₂C); ISMS: m/z 451, $[M + Na]^+$, 429, $[M + H]^+$, 397, $[M - OCH_3]^+$. Anal. Calcd for $C_{24}H_{28}O_7$: C, 67.28; H, 6.59. Found: C, 67.12; H, 6.39.

Benzyl 2-O-benzoyl-3-O-benzyl-4,6-O-iso*propylidene* $-\alpha$ -L-*idopyranoside* (10).—Compound 8 (5.63 g, 8.4 mmol) was transesterified, acetalated, and benzoylated as described for the preparation of 9. The residue was eluted from a column (150 g) of silica gel with 5:1 petroleum ether-EtOAc containing 0.2% of Et₃N to afford amorphous 10 (2.53 g, 63%); $[\alpha]_{\rm D} - 51^{\circ}$ (c 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 1); 8.10-7.20 (m, 15 H, Ph), 4.75, 4.70 (2 ABq, 4 H, CH₂Ph), 1.45, 1.42 (2 s, 6 H, (CH₃)₂C); ISMS: m/z 527, $[M + Na]^+$, 522, $[M + NH_4]^+$, 397, $[M - OCH_2Ph]^+$. Anal. Calcd for $C_{30}H_{32}O_7$: C, 71.41; H, 6.39. Found: C, 71.31; H, 6.51. Methyl 2-O-benzoyl-3-O-benzyl-4,6-di-Otert-butyldimethylsilyl- α -L-idopyranoside (11). —A solution of 9 (1.97 g, 4.6 mmol) in AcOH (20 mL) and water (10 mL) was stirred for 15

min at 80 °C, then cooled, concentrated, evaporated with water $(2 \times 10 \text{ mL})$ and toluene $(2 \times 10 \text{ mL})$.

A mixture of the residue, imidazole (5.1 g, 75 mmol), and tert-butyldimethylsilyl chloride (5.7 g, 37 mmol) in dry DMF (20 mL) was stirred for 18 h at 50 °C, then cooled, diluted with EtOAc (100 mL), washed with water, 5% aq HCl and water, dried (MgSO₄) and concentrated. The residue was eluted from a column (50 g) of silica gel with 14:1 petroleum ether-EtOAc to give 11 as an oil (2.55 g, 90%); $[\alpha]_{\rm D} - 22^{\circ}$ (c 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 1); 8.10-7.10 (m, 10 H, Ph), 4.75 (ABq, 2 H, CH₂Ph), 3.45 (s, 3 H, OCH₃), 0.93, 0.76 (2 s, 18 H, $(CH_3)_3$ C), 0.11, 0.09, -0.08, -0.25 (4 s, 12 H, CH₃Si); ISMS: m/z 639, $[M + Na]^+$, 634, $[M + NH_4]^+$, 585, $[M - OCH_3]^+$. Anal. Calcd for $C_{33}H_{52}O_7Si_2$: C, 64.24; H, 8.65. Found: C, 64.08; H, 8.81.

Benzyl 2-O-benzoyl-3-O-benzyl-4,6-di-Otert-butyldimethylsilyl-α-L-idopyranoside (12). —Compound 10 (3.04 g, 6 mmol) was treated as described for the preparation of 11 to give oily 12 (3.74, 90%); $[\alpha]_D - 40^\circ$ (c 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 1); 8.10–7.20 (m, 15 H, Ph), 4.76, 4.70 (2 ABq, 4 H, CH₂Ph), 0.90, 0.78 (2 s, 18 H, (CH₃)₃C), 0.09, 0.05, -0.03, -0.16 (4 s, 12 H, CH₃Si); ISMS: m/z 716, $[M + Na]^+$, 711, $[M + NH_4]^+$, 586, $[M - OCH_2Ph]^+$. Anal. Calcd for C₃₉H₅₆O₇Si₂: C, 67.59; H, 8.14. Found: C, 67.60; H, 7.98.

Methyl (methyl 2-O-benzoyl-3-O-benzyl-4-O - tert - butyldimethylsilyl - α - L - idopyranosid)uronate (13).—A solution of chromium trioxide (1.34 g) in H₂SO₄ (18 M, 1.15 mL) and water (2.85 mL) was added dropwise at 0 °C to a solution of 11 (2.79 g, 4.5 mmol) in acetone (100 mL) until thin-layer chromatography (TLC) (15:1 CH₂Cl₂-MeOH) indicated complete disappearance of the starting material. The mixture was then poured into icecold water, and extracted with EtOAc $(2 \times 100 \text{ mL})$. The organic extracts were washed with water, dried (MgSO₄), and concentrated. The residue was eluted from a column (80 g) of silica gel with 15:1 CH₂Cl₂-MeOH to give the corresponding acid as an oil (1.91 g).

Methyl chloroformate (0.32 mL, 4.1 mmol) was added at 0 °C to a solution of the above isolated acid, Et₃N (0.62 mL, 4.5 mmol), and 4-dimethylaminopyridine (46 mg, 0.4 mmol) in anhyd CH₂Cl₂ (50 mL), and the mixture was stirred for 90 min at 0 °C, then for 2 h at rt. The mixture was poured into ice-cold water, extracted with EtOAc $(2 \times 100 \text{ mL})$, washed with water, satd aq NH₄Cl and water, dried (MgSO₄) and concentrated. The residue was eluted from a column (80 g) of silica gel with 5:1 petroleum ether-EtOAc to give 13 as a white foam (1.55 g, 65% from 11); $[\alpha]_{\rm D} - 41^{\circ}$ (c 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 1); 8.15-7.30 (m, 10 H, Ph), 4.88 (ABq, 2 H, CH₂Ph), 3.79 (s, 3 H, COOCH₃), 3.50 (s, 3 H, OCH₃), 0.69 (s, 9 H, $(CH_3)_3C$, -0.13, -0.37 (2 s, 6 H, CH_3Si); ISMS: m/z 553, $[M + Na]^+$, 531, $[M + H]^+$, 499, $[M - OCH_3]^+$. Anal. Calcd for C₂₈H₃₈O₈Si: C, 63.37; H, 7.22. Found: C, 63.13; H, 7.34.

Methyl (benzyl 2-O-benzoyl-3-O-benzyl-4-O-tert-butyldimethylsilyl- α -L-idopyranosid)uronate (14).—Compound 12 (3.2 g, 4.6 mmol) was oxidized and esterified as described for the preparation of 13 to give 14 (1.73 g, 62% from 12); $[\alpha]_D - 73^\circ$ (c 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 1); 8.0–7.20 (m, 15 H, Ph), 4.82, 4.77 (2 ABq, 4 H, CH₂Ph), 3.77 (s, 3 H, COOCH₃), 0.60 (s, 9 H, (CH₃)₃C), -0.10, -0.30 (2 s, 6 H, CH₃Si); ISMS: m/z 629, [M + Na]⁺, 607, [M + H]⁺, 499, [M – OCH₂Ph]⁺. Anal. Calcd for C₃₄H₄₂O₈Si: C, 67.08; H, 6.95. Found: C, 67.10; H, 6.78.

Methyl (methyl 2-O-benzoyl-3-O-benzyl- α -L-idopyranosid)uronate (15).—A mixture of 13 (2.62 g, 4.9 mmol) and Bu₄NF (2.58 g, 9.9 mmol) in anhyd THF (30 mL) was stirred for 20 min at 0 °C, then it was diluted with cooled (0 °C) EtOAc (100 mL), washed with satd aq NH₄Cl, and water, dried (MgSO₄) and concentrated. The residue was eluted from a column (50 g) of silica gel with 5:2 petroleum ether–EtOAc to give syrupy **15** (1.24 g, 60%); [α]_D – 19° (*c* 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 1); 8.0– 7.20 (m, 10 H, Ph), 4.84 (ABq, 2 H, CH₂Ph), 3.91 (s, 3 H, COOCH₃), 3.52 (s, 3 H, OCH₃), 2.85 (d, 1 H, *J* 11.5 Hz, HO-4); ¹³C (CDCl₃): δ 170.04, 165.01 (C=O), 137.47–127.89 (aromatic C), 100.07 (C-1), 74.27 (C-5), 72.07 (CH₂Ph), 68.05, 67.57, 67.50 (C-2,3,4), 56.48 (OCH₃), 52.53 (COOCH₃); ISMS: *m*/*z* 439, [M + Na]⁺, 417, [M + H]⁺, 385, [M – OCH₃]⁺. Anal. Calcd for C₂₂H₂₄O₈: C, 63.45; H, 5.81. Found: C, 63.35; H, 5.89.

Methyl (benzyl 2-O-benzoyl-3-O-benzyl-a-L-idopyranosid)uronate (16).—Compound 14 (1.29 g, 2.1 mmol) was treated as described for the preparation of 15. The residue was eluted from a column (80 g) of silica gel with 5:1 petroleum ether-EtOAc to afford syrupy 16 (0.77 g; 74%); $[\alpha]_{\rm D} - 36^{\circ}$ (c 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 1); 8.0-7.20 (m, 15 H, Ph), 4.77, 4.75 (2 ABq, 4 H, CH₂Ph), 3.82 (s, 3 H, COOCH₃), 2.80 (d, 1 H, J 11.7 Hz, HO-4); ¹³C (CDCl₃): δ 169.99, 165.05 (C=O), 137.55-127.77 (aromatic C), 98.27 (C-1), 74.46 (C-5), 72.07, 70.28 (CH₂Ph), 68.29, 67.94, 67.39 (C-2,3,4), 52.52 (COOCH₃); ISMS: m/z 515, $[M + Na]^+$, 385, $[M - OCH_2Ph]^+$. Anal. Calcd for $C_{28}H_{28}O_8$: C, 68.28; H, 5.12. Found: C, 68.12; H, 5.25.

4-Methoxyphenyl 4,6-O-benzylidene-2-deoxy-2-trichloroacetamido- β -D-glucopyranoside (18).—A suspension of 4-methoxyphenyl 3,4,6-tri-O-acetyl-2-deoxy-2-trichloroacetamido- β -D-glucopyranoside (17) [30] (32.0 g, 57.4 mmol) in MeOH (150 mL) was treated for 2 h at rt with methanolic MeONa (1 M, 3 mL). The solution was then deionized with Amberlite IR-120 [H⁺] resin, filtered and concentrated to give the corresponding triol as a white powder (24.65 g).

Trifluoroacetic acid (9 mL) was added to a suspension of the above isolated triol in benzaldehyde (200 mL), and the mixture was stirred for 3 h at rt. Triethylamine (15 mL), then Et₂O (500 mL) were added, and the mixture was stirred for 15 min at 0 °C. The solids were filtered off, and washed with Et₂O to give **18** as a white powder (19.2 g, 65%); mp 222–223 °C (from MeOH); $[\alpha]_D + 1^\circ$ (*c* 1, MeOH); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 2); 7.50–6.80 (m, 9 H, Ph), 5.66 (s, 1 H, PhCH), 3.85 (s, 3 H, OCH₃), 2.85 (d, 1 H, *J* 2.9 Hz, *H*O-3); ISMS: *m*/*z* 541, [M + Na]⁺, 519, [M + H]⁺, 395, [M – OC₆H₄OCH₃]⁺ for ³⁵Cl. Anal. Calcd for $C_{22}H_{22}Cl_3NO_7$: C, 50.93; H, 4.27; N, 2.70. Found: C, 50.88; H, 4.41; N, 2.68.

4-Methoxyphenyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-trichloroacetamido- β -D-glucopyranoside (19).—Sodium hydride (60% in mineral oil, 3.0 g, 74 mmol) was added portionwise at 0 °C to a solution of 18 (19.17 g, 37 mmol) in dry DMF (150 mL), and the mixture was stirred for 30 min at this temperature. Benzyl bromide (5.8 mL, 49 mmol) was then added, and the mixture was stirred for 30 min at 0 °C and for 90 min at rt. Methanol (10 mL) was cautiously added, and the mixture was diluted with EtOAc (1 L), washed twice with water, dried (MgSO₄) and concentrated. The solid residue was recrystallized from MeOH to give 19 (18.37 g, 82%); mp $261-262 \text{ °C}; [\alpha]_{D} + 4^{\circ} (c 1, \text{ CHCl}_{3}); ^{1}\text{H NMR}$ (CDCl₃): carbohydrate ring protons (see Table 2); 7.50-6.80 (m, 14 H, Ph), 5.70 (s, 1 H, PhCH), 4.91 (ABq, 2 H, CH₂Ph), 3.84 (s, 1 H, OCH₃); ISMS: m/z 631, $[M + Na]^+$, 609, $[M + H]^+$, 485, $[M-OC_6H_4OCH_3]^+$ for ³⁵Cl. Anal. Calcd for C₂₉H₂₈Cl₃NO₇: C, 57.11; H, 4.63; N, 2.30. Found: C, 57.14; H, 4.64; N, 2.37.

4-Methoxyphenyl 3,6-di-O-benzyl-2-deoxy-2 - trichloroacetamido - β - D - glucopyranoside (20).—A mixture of 19 (6.42 g, 10.5 mmol), 4 Å powdered molecular sieves (5 g), and triethylsilane (8.5 mL, 53 mmol) in anhyd CH₂Cl₂ (80 mL) was stirred for 1 h at rt under dry Ar, then cooled to 0 °C. Trifluoroacetic acid (4.1 mL, 53 mmol) was added, and the mixture was stirred for 1 h at 0 °C and 1 h at rt. Triethylamine (15 mL) was added, and the mixture was filtered and concentrated. A solution of the residue in EtOAc (250 mL) was washed with water, satd aq NaHCO₃ and water, dried (MgSO₄) and concentrated. The residue was eluted from a column (100 g) of silica gel with 20:1 CH₂Cl₂-EtOAc and crystallized from EtOAc-petroleum ether to afford **20** (4.43 g, 69%); mp 141–142 °C; $[\alpha]_{\rm D} - 15^{\circ}$ (c 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 2); 7.50-6.80 (m, 14 H, Ph), 4.88, 4.67 (2 ABq, 4 H, CH_2Ph), 3.83 (s, 3 H, OC H_3), 2.82 (d, 1 H, J 2.6 Hz, HO-4); ISMS: m/z 632, $[M + Na]^+$, 4.88, $[M - OC_6H_4OCH_3]^+$ for ³⁵Cl. Anal.

Calcd for C₂₉H₃₀Cl₃NO₇: C, 57.11; H, 4.79; N, 2.30. Found: C, 56.86; H, 4.83; N, 2.11.

4-Methoxyphenyl 3,6-di-O-benzyl-2-deoxy-2-trichloroacetamido - β - D - galactopyranoside (21).—Triflic anhydride (1.9 mL, 11.6 mmol) was added dropwise at -15 °C under dry Ar to a solution of 20 (4.55 g, 7.5 mmol) in anhyd CH₂Cl₂ (70 mL) and anhyd pyridine (4.2 mL), and the mixture was stirred for 2 h at this temperature. Crushed ice (5 g) was then added, and the mixture was diluted with CH₂Cl₂ (100 mL), washed with water, brine and water, dried (MgSO₄), concentrated and evaporated twice with toluene.

Sodium nitrite (5.17 g, 75 mmol) was added at rt to a solution of the residue in dry DMF (90 mL), and the mixture was stirred for 1 h at rt, then was poured into ice-cold water and extracted with EtOAc ($2 \times 100 \text{ mL}$). The combined extracts were washed with water, 5% aq HCl and water, dried (MgSO₄) and concentrated. The residue was crystallized from EtOAc-petroleum ether to afford 21 (4.06 g, 89%); mp 142–143 °C; $[\alpha]_{\rm D} + 6.5^{\circ}$ (c 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 2); 7.50-6.70 (m, 14 H, Ph), 4.64, 4.57 (2 ABq, 4 H, CH₂Ph), 3.75 (s, 3 H, OCH₃); ISMS: m/z 634, $[M + Na]^+$, 488, $[M - OC_6H_4OCH_3]^+$ for ³⁵Cl. Anal. Calcd for $C_{29}H_{30}Cl_3NO_7$: C, 57.11; H, 4.79; N, 2.30. Found: C, 56.91; H, 4.81; N, 2.36.

4-Methoxyphenyl 4-O-acetyl-3,6-di-O-benzyl-2-deoxy-2-trichloroacetamido- β -D-galactopyranoside (22).—Conventional acetylation (Ac₂O in pyridine) of **21** (6.69 g, 10.9 mmol) followed by concentration of the mixture and crystallization of the residue from EtOAcpetroleum ether gave 22 (6.09 g, 85%); mp 144–145 °C; $[\alpha]_{\rm D}$ + 13° (c 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 2); 7.40-6.70 (m, 14 H, Ph), 4.58, 4.53 (2 ABq, 4 H, CH₂Ph), 3.75 (s, 3 H, OCH₃), 2.10 (s, 3 H, Ac); ISMS: m/z 671, $[M + NH_4]^+$, 530, $[M - OC_6H_4OCH_3]^+$ for ³⁵Cl. Anal. Calcd for $C_{31}H_{32}Cl_3NO_8$: C, 57.02; H, 4.94; N, 2.15. Found: C, 57.03; H, 4.98; N, 2.26.

4-O-Acetyl-3,6-di-O-benzyl-2-deoxy-2trichloroacetamido-1-O-trichloroacetimidoyl- α -D-galactopyranose (23).—A mixture of 22 (2.20 g, 3.4 mmol) and ceric ammonium nitrate (9.2 g, 16.8 mmol) in 1:1.5:1 toluene– MeCN–water (56 mL) was vigorously stirred for 15 min at rt, then was diluted with EtOAc (100 mL), washed with water, dried (MgSO₄) and concentrated. The residue was eluted from a column (80 g) of silica gel with 4:1 petroleum ether–EtOAc to give the corresponding free hemiacetal (1.67 g).

A mixture of the above isolated hemiacetal, CCl₃CN (3 mL, 30 mmol) and DBU (0.11 mL, 0.74 mmol) in anhyd CH₂Cl₂ (40 mL) was stirred for 1 h at 0 °C, then concentrated. The residue was eluted from a column (80 g)of silica gel with 4:1 petroleum ether-EtOAc containing 0.2% of Et₃N to give 23 as a white foam (1.94 g, 88% from 22); $[\alpha]_{\rm D} + 78^{\circ}$ (c 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 2); 8.65 (s, 1 H, C=NH), 7.30 (m, 10 H, Ph), 4.59, 4.50 (2 ABq, 4 H, CH₂Ph), 2.10 (s, 3 H, Ac); ¹³C (CDCl₃): δ 170.16, 162.01 (C=O), 160.04 (C=N), 137.37-128.07 (aromatic C), 94.64 (C-1), 92.11, 90.79 (CCl₃), 73.80, 70.71 (CH₂Ph), 71.62, 70.77 (C-4,5), 67.35, 65.15 (C-6,3), 50.75 (C-2), 20.84 (COCH₃); ISMS: m/z 714, $[M + Na]^+$, 530, $[M - CCl_3CONH]^+$ for ³⁵Cl. Anal. Calcd for C₂₆H₂₆Cl₆N₂O₇: C, 45.17; H, 3.79; N, 4.05. Found: C, 44.94, H, 3.74; N, 4.24.

Methyl (4-O-acetyl-3,6-di-O-benzyl-2-deoxy - 2-trichloroacetamido - β - D - galactopyranosyl)- $(1 \rightarrow 4)$ -(methyl 2-O-benzoyl-3-O-benzyl- α -L-*idopyranosid*)uronate (25).—A mixture of alcohol 15 (427 mg, 1 mmol), imidate 23 (900 mg, 1.3 mmol) and 4 Å powdered molecular sieves (0.5 g) in anhyd CH₂Cl₂ (7 mL) was stirred for 1 h at rt under dry Ar, then cooled to -15 °C. A solution of Me₃SiOTf in toluene (1 M, 0.76 mL) was added and the mixture was stirred for 10 min at -15 °C. Triethylamine (0.11 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 Et₃N to give first amorphous **24** (276 mg, 31% from **23**); $[\alpha]_{\rm D}$ + 11.5° (c 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 2); 7.88 (d, 1 H, $J_{\rm NH,1}$ 8.8 Hz, NHCOCCl₃), 7.30 (m, 10 H, Ph), 4.59, 4.51 (2 ABq, 4 H, CH₂Ph), 2.10 (s, 3 H, Ac); ¹³C (CDCl₃): δ 170.18 (C=O), 164.14, 162.73 (COCCl₃), 137.38–128.22 (aromatic C), 92.49,

91.85 (CCl₃), 81.79 (C-1), 75.33, 74.38 (C-4,5), 73.93, 71.09 (CH₂Ph), 67.22, 64.75 (C-3,6), 52.30 (C-2), 20.96 (COCH₃). Anal. Calcd for $C_{26}H_{26}Cl_6N_2O_7$: C, 45.17; H, 3.79; N, 4.15. Found: C, 45.01; H, 3.92; N, 4.21.

Next eluted was **25**, isolated as a white foam (580 mg, 60%); $[\alpha]_D - 11.5^\circ$ (*c* 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 3); 8.10–7.20 (m, 20 H, Ph), 4.74, 4.73, 4.40 (3 ABq, 6 H, CH₂Ph), 3.82 (s, 3 H, COOCH₃), 3.48 (s, 3 H, OCH₃), 1.62 (s, 3 H, Ac); ISMS: *m*/*z* 963, [M + NH₄]⁺ , 946, [M + H]⁺ for ³⁵Cl. Anal. Calcd for C₄₆H₄₈Cl₃NO₁₄: C, 58.45; H, 5.12; N, 1.48. Found: C, 58.33; H, 5.23; N, 1.45.

(4-O-acetyl-3,6-di-O-benzyl-2-de-Methvl oxy - 2-trichloroacetamido - β - D - galactopyranosyl)- $(1 \rightarrow 4)$ -(benzyl 2-O-benzoyl-3-O-benzyl- α -L-*idopyranosid*)uronate (26).—A mixture of alcohol 16 (774 mg, 1.6 mmol) and imidate 23 (1.17 g, 1.7 mmol) was treated as described for the preparation of 25 to give 26 as a white foam (960 mg, 60%); $[\alpha]_{\rm D} - 27^{\circ}$ (c 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 3); 8.10-7.20 (m, 25 H, Ph), 4.73, 4.72, 4.44, 4.42 (4 ABq, 8 H, CH₂Ph), 3.80 (s, 3 H, COOCH₃), 1.60 (s, 3 H, Ac); ISMS: m/z1039, $[M + NH_4]^+$ for ³⁵Cl. Anal. Calcd for C₅₂H₅₂Cl₃NO₁₄: C, 61.15; H, 5.13; N, 1.38. Found: C, 61.05; H, 5.21; N, 1.41.

Methyl (2-acetamido-4-O-acetyl-3,6-di-O $benzyl-2-deoxy-\beta$ -D-galactopyranosyl)- $(1 \rightarrow 4)$ -(methyl 2-O-benzoyl-3-O-benzyl- α -L-idopyranosid)uronate (27).—A mixture of 25 (2.07 g, 2.2 mmol), Bu₃SnH (3.2 mL, 12 mmol) and AIBN (100 mg) in dry benzene (30 mL) was stirred for 30 min at rt under a stream of dry Ar, then heated for 1 h at 80 °C, cooled and concentrated. The residue was stirred with petroleum ether (40 mL), the crystalline material was filtered off and washed with petroleum ether to give 27 (1.41 g, 76%); mp $88-89 \,^{\circ}\text{C}; \ [\alpha]_{D} - 9^{\circ} \ (c \ 1, \ \text{CHCl}_{3}); \ ^{1}\text{H} \ \text{NMR}$ (CDCl₃): carbohydrate ring protons (see Table 3); 8.10-7.20 (m, 20 H, Ph), 4.73, 4.51, 4.30 (3 ABq, 6 H, CH₂Ph), 3.81 (s, 3 H, COOCH₃), 3.47 (s, 3 H, OCH₃), 1.96, 1.62 (2 s, 6 H, Ac); ISMS: m/z 864, $[M + Na]^+$, 842, $[M + H]^+$. Anal. Calcd for $C_{46}H_{51}NO_{14}$: C, 65.62; H, 6.10; N, 1.66. Found: C, 65.42; H, 6.20; N, 1.74.

Methyl (2-acetamido-4-O-acetyl-3,6-di-Obenzyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-(benzyl 2-O-benzoyl-3-O-benzyl-α-L-idopyranosid)uronate (**28**).—Compound **26** (825 mg, 0.81 mmol) was treated as described for the preparation of **27** to afford **28** (617 mg, 83%); mp 83–84 °C; $[\alpha]_D - 25^\circ$ (*c* 1, CHCl₃); ¹H NMR (CDCl₃): carbohydrate ring protons (see Table 3); 8.10–7.20 (m, 25 H, Ph), 4.88– 4.28 (m, 8 H, CH₂Ph), 3.77 (s, 3 H, COOCH₃), 2.0, 1.59 (2 s, 6 H, Ac); ISMS: *m*/*z* 941, [M + Na]⁺, 811, [M – OCH₂Ph]⁺. Anal. Calcd for C₅₂H₅₅NO₁₄: C, 68.03; H, 6.04; N, 1.53. Found: C, 67.93; H, 6.04; N, 1.63.

Sodium (sodium 2-acetamido-3,6-di-O-benzyl-2-deoxy-4-O-sulfonato- β -D-galactopyranosyl)- $(1 \rightarrow 4)$ -(sodium methyl 3-O-benzyl-2-Osulfonato- α -L-idopyranosid)uronate (29).—A solution of 27 (1.32 g, 1.6 mmol) in THF (30 mL) was treated at 0 °C with 30% H₂O₂ (3.9 mL) and LiOH (1 M, 7.8 mL) and the mixture was stirred for 1 h at 0 °C and for 15 h at rt, then cooled to 0 °C. Methanol (14 mL) and NaOH (4 M, 2.4 mL) were added and the mixture was stirred for 5 h at rt, then was diluted with water (50 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 (80 g) of silica gel with $15:1 \rightarrow 9:1$ CH₂Cl₂-MeOH to give the corresponding hydroxy acid (1.06 g, 90%); ¹H NMR (CD₃OD): δ 7.30 (m, 15 H, Ph), 4.82 (br s, 1 H, H-1^I), 4.73–4.43 (m, 6 H, CH₂Ph), 4.48 (d, 1 H, J_{4.5} 1.7 Hz, H-5^I), 4.41 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1^{II}), 4.10 (m, 2 H, H-2^I,4^I), 4.06 (dd, 1 H, $J_{2,3}$ 10.5 Hz, H-2^{II}), 4.02 (m, 2 H, H-3^I,4^{II}), 3.61 (m, 3 H, H- $5^{II},6a^{II},6b^{II}$), 3.46 (dd, 1 H, $J_{3,4}$ 3.0 Hz, H- 3^{II}), 3.37 (s, 3 H, OCH₃), 2.06 (s, 3 H, NAc); ISMS: m/z 704, $[M + Na]^+$, 699, $[M + NH_4]^+$, 682, $[M + H]^+$.

A mixture of the above isolated hydroxy acid and sulfur trioxide-trimethylamine complex (1.74 g, 12.5 mmol) was stirred for 2 days at 50 °C. More reagent (1.74 g, 12.5 mmol) was then added and the mixture was stirred for further 2 days at 50 °C, then cooled. Methanol (4 mL) was then added and the mixture was concentrated. The residue was eluted twice from columns (40 g) of silica gel with $6:1 \rightarrow 4:1$ CH₂Cl₂-MeOH, then from a column (1.5 × 20 cm) of Sephadex SP C25 [Na⁺] with 9:5:1 CH₂Cl₂–MeOH–water to give amorphous **29** (590 mg, 65%); $[\alpha]_D - 6^\circ$ (*c* 1, MeOH); ¹H NMR (CD₃OD): carbohydrate ring protons (see Table 3); 7.30 (m, 15 H, Ph), 4.65–4.35 (m, 6 H, CH₂Ph), 3.37 (s, 3 H, OCH₃), 1.99 (s, 3 H, NAc). Anal. Calcd for C₃₆H₄₀NNa₂O₁₈S₂: C, 47.63; H, 4.44; N, 1.54. Found: C, 47.35; H, 4.71; N, 1.44.

Sodium (sodium 2-acetamido-3,6-di-O-benzyl-2-deoxy-4-O-sulfonato- β -D-galactopyranosyl)- $(1 \rightarrow 4)$ -(sodium benzyl 3-O-benzyl-2-O*sulfonato-α*-*L*-*idopyranosid*)*uronate* (30).-Compound 28 (571 mg, 0.62 mmol) was treated as described for the preparation of **29** to afford the corresponding hydroxy acid (387 mg, 82%); ¹H NMR (CD₃OD): δ 7.30 (m, 20 H, Ph), 5.18 (br s, 1 H, H-1^I), 4.80-4.40 (m, 8 H, CH₂Ph), 4.50 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1^{II}), 4.47 (d, 1 H, $J_{4,5}$ 2.2 Hz, H-5^{$\tilde{1}$}), 4.14 (m, 2 H, H-2^I,4^I), 4.12 (dd, 1 H, $J_{2,3}$ 10.6 Hz, H-2^{II}), 3.99 (dd, 1 H, $J_{3,4}$ 3.0, $J_{4,5}$ 0.5 Hz, H-4^{II}), 3.78 (m, 1 H, H- 3^{I}), 3.63 (m, 3 H, H- 5^{I} , $6a^{I}$, $6b^{I}$), 3.50 (dd, 1 H, H-3^{II}), 2.10 (s, 3 H, NAc); ISMS: m/z 781, $[M + Na]^+$, 759, $[M + H]^+$.

The above isolated hydroxy acid (197 mg, 0.26 mmol) was O-sulfonated as described for the preparation of **29** to give amorphous **30** (174 mg, 68%); $[\alpha]_D - 10^\circ$ (*c* 1, MeOH); ¹H NMR (CD₃OD): carbohydrate ring protons (see Table 3); 7.30 (m, 20 H, Ph), 4.95–4.40 (m, 8 H, CH₂Ph), 2.0 (s, 3 H, NAc). Anal. Calcd for C₄₂H₄₄NNa₃O₁₈S₂: C, 51.27; H,4.51; N, 1.42. Found: C, 51.02; H, 4.72; N, 1.31.

Sodium (sodium 2-acetamido-2-deoxy-4-Osulfonato - β - D - galactopyranosyl) - $(1 \rightarrow 4)$ -(sodium 2-O-sulfonato-L-idopyran)uronate (1). —A solution of **30** (245 mg, 0.25 mmol) in 1:1 MeOH-water (8 mL) was hydrogenated in the presence of 10% Pd–C (100 mg) for 48 h at rt. The mixture was filtered through a pad of Celite and freeze-dried to give 1 (140 mg, 90%); $[\alpha]_{\rm D} = 2.5^{\circ}$ (c 1, equilibrium, water); ¹H NMR (D₂O, internal H₂O, $\delta_{\rm H}$ 4.754): carbohydrate ring protons (see Table 3); 2.0, 1.99 (2 s, 3 H, NAc);¹³C (D₂O, internal acetone, δ_C 30.45): δ 175.39, 175.29 (C=O), 103.13, 101.77 $(C-1^{II}), 92.78, 91.90 (C-1^{I}), 78.39, 77.60 (C-4^{I}),$ 75.81 (C-2^I, C-4^{II}), 74.48 (C-5^I), 70.10, 68.70, 67.70 (C-3^I, C-3^{II}, C-5^{II}), 60.97 (C-6^{II}), 52.78 $(C-2^{II})$, 22.71 (COCH₃). Anal. Calcd for C₁₄H₂₀NNa₃O₁₈S₂: C, 26.98; H, 3.23; N, 2.25. Found: C, 26.69; H, 3.51; N, 2.10.

Sodium (sodium 2-acetamido-2-deoxy-4-Osulfonato - β - D - galactopyranosyl) - $(1 \rightarrow 4)$ -(sodium methyl 2-O-sulfonato- α -L-idopyranosid)uronate (2).—Compound 29 (306 mg, 0.34 mmol) was treated as described for the preparation of 1 to give 2 (168 mg, 78%); $[\alpha]_{D}$ -14° (c 1, water); ¹H NMR (D₂O, internal H₂O, $\delta_{\rm H}$ 4.754): carbohydrate ring protons (see Table 3); 3.20 (s, 3 H, OCH₃), 2.04 (s, 3 H. NAc); ¹³C (D₂O, internal acetone, $\delta_{\rm C}$ 30.45): δ 177.00, 175.20 (C=O), 103.13 (C-1^I), 99.99 (C-1^{II}), 78.56 (C-4^I), 75.99 (C-4^{II}), 74.77 (C-2^I), 74.14 (C-5^I), 70.42, 68.47, 67.27 (C-3^I, $C-3^{II}$, $C-5^{II}$), 61.37 ($C-6^{II}$), 55.48 (OCH_3), 53.01 (C-2^{II}), 22.86 (COCH₃). Anal. Calcd for $C_{15}H_{22}NNa_{3}O_{18}S_{2}$: C, 28.26; H, 3.48; N, 2.20. Found: C, 27.92; H, 3.71; N, 2.08.

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