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Note

Syntheses of β-D-Gal*p*NAc4SO$_3$-(1 → 4)-L-Ido*p*A2SO$_3$, a disaccharide fragment of dermatan sulfate, and of its methyl α-L-glycoside derivative

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Abstract

The syntheses of sodium (sodium 2-acetamido-2-deoxy-4-*O*-sulfonato-β-D-galactopyranosyl)-(1 → 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*-trichloroacetimidoyl-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

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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-D-galactose, namely [4)-α-L-Ido*p*A-(1 → 4)-β-D-Gal*p*NAc-(1 →]$_n$. Structural studies on DeS showed different patterns of sulfation substitutions depending on its origin [2]. The D-galactosamine 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-Ido*p*A2SO$_3$-(1 → 3)-β-D-Gal*p*NAc4SO$_3$-(1 →]$_n$, 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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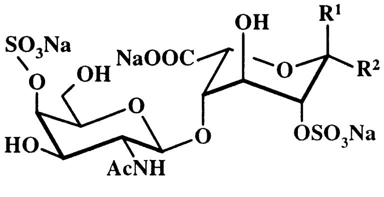
Several syntheses of DeS fragments have been reported, such as those of a monosulfated disaccharide [11,12], a disulfated disaccharide [13], as well as those of a hexasaccharide [14,15] containing three disulfated sequences. For the syntheses of these hexasaccharide species, the strategy was edicted by the encountered difficulties [15] to obtain an efficient β-interglycosidic linkage between a D-galactosamine donor and the 4-hydroxyl 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.



	R^1	R^2
1	H, OH	
2	OMe	H

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-*xylo*-dialdose 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-glucofuranose (**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.

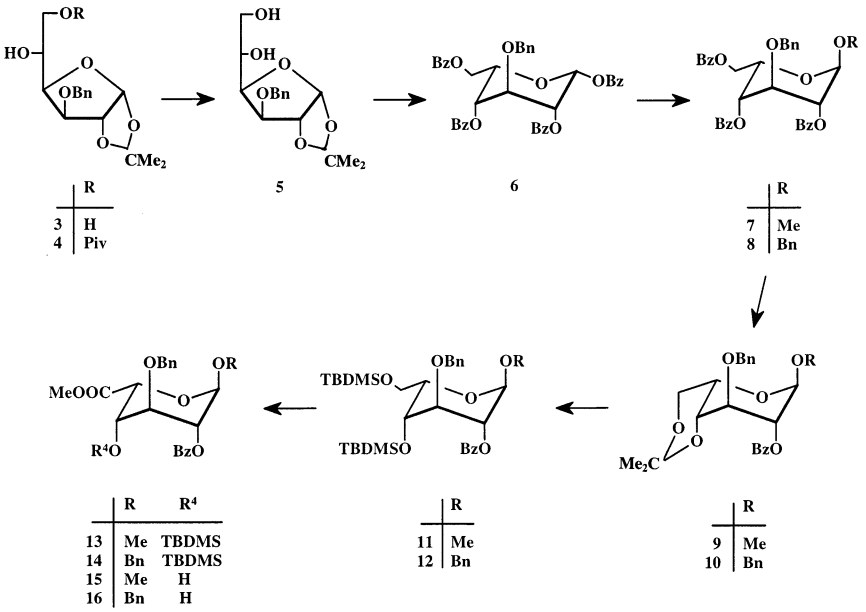
Treatment of **3** with pivaloyl chloride (1.5 equiv) in pyridine at 0 °C afforded the crystalline 6-*O*-pivaloyl derivative **4** in 85% yield, isolated by simple crystallization. Some dipivaloylated species were present in the mother liquors, but were easily recycled through transesterification. Trifluoromethanesulfonylation 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* → 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-*O*-benzyl-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 ^{1}H 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 L-iduronyl 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 2-methoxypropene 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 ^{1}H NMR spectra of the L-*ido* derivatives **8**–**16** (Table 1) showed, with the exception of **11** and **12**, long-range coupling constants ($J_{1,3}$

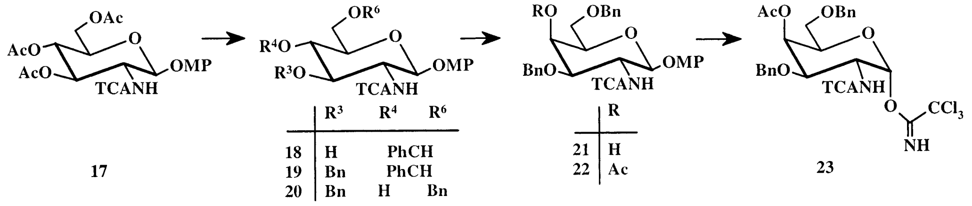
Table 1
^{1}H NMR data: carbohydrate ring protons for monosaccharide derivatives **4**–**6** and **8**–**16** [a]

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
$J_{1,3}$				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
$J_{2,3}$	~0	~0	3.0	3.0	4.2	4.0	3.3	5.2	2.5	2.7	2.4	2.5
$J_{2,4}$			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
$J_{3,4}$	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
$J_{4,5}$		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 $CDCl_3$.



Scheme 1.



Scheme 2.

Table 2
^{1}H 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
$J_{4,5}$	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
$J_{2,NH}$	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 $CDCl_3$.

and $J_{2,4}$) indicating a large predominance, if not the only one, of $^1C_4$ 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-*O*-acetyl-2-deoxy-2-trichloroacetamido-β-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*,*N*-dimethylformamide 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 ^{1}H NMR spectrum (Table 2). Acetylation of **21** gave **22**, which was submitted to oxidative removal of the anomeric 4-methoxyphenyl glycoside with ceric ammonium nitrate, followed by trichloroacetimidoylation with trichloroacetonitrile and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) to afford the target α-imidate **23** in 88% overall yield, the anomeric configuration of which was deduced from its ^{1}H 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 ^{1}H 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**, a rather unexpected species, since trichloroacetamide released by the glycosylation reaction is known [34] to be a rather poor nucleophile. However, an intramolecular rearrangement of the trichloroacetimidoyl 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 trioxide–trimethylamine 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 ^{1}H NMR spectra, recorded in deuterated methanol, of **29** and **30** (Table 3) and of their non-sulfated hydroxy acid precursors (details

Table 3
^{1}H NMR data: carbohydrate ring protons for disaccharide derivatives **25**–**30**, **1** and **2** [a]

Proton	**25**	**26**	**27**	**28**	**29** [b]	**30** [b]	**1** [c]	**2** [c]
H-1$^{\text{I}}$	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$^{\text{I}}$	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$^{\text{I}}$	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$^{\text{I}}$	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$^{\text{I}}$	4.83	4.88	4.83	4.86	4.53	4.56	4.52, 4.51	4.32
H-1$^{\text{II}}$	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$^{\text{II}}$	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$^{\text{II}}$	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$^{\text{II}}$	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$^{\text{II}}$	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$^{\text{II}}$	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$^{\text{II}}$	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				
$J_{2,\text{NH}}$	7.6	7.5	7.2	6.6				

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

[b] CD_3OD.

[c] D_2O.

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 ^{1}H (Table 3) and ^{13}C NMR data for **1** and **2** are in agreement with the expected structures. The coupling constants observed for the reducing methyl α-L-iduronate residue in **2** indicate a predominance of $^1C_4$ conformation, as reported [28] for a similar reducing moiety in a synthetic heparan sulfate fragment.

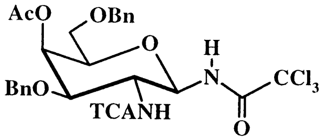
In conclusion, expeditious preparations of L-idose and D-galactosamine derivatives from D-*gluco* precursors are reported. A stereocontrolled and good-yielding coupling reaction with the low reactive 4-hydroxyl group of L-iduronic acid esters was achieved using the glycosyl donor **23**, exemplifying the efficiency of activated 2-deoxy-2-trichloroacetamido-D-*galacto* derivatives in syntheses of 1,2-*trans*-2-amino-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. ^{1}H and ^{13}C 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. 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).

*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 CH_2Cl_2

	R1	R2
1	H, OH	
2	OMe	H



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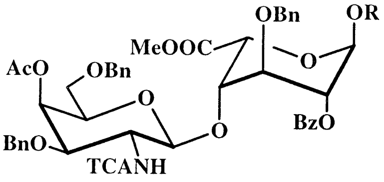
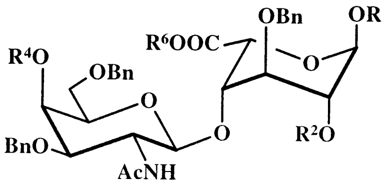


	R
25	Me
26	Bn



	R	R^2	R^4	R^6
27	Me	Bz	Ac	Me
28	Bn	Bz	Ac	Me
29	Me	SO_3Na	SO_3Na	Na
30	Bn	SO_3Na	SO_3Na	Na

(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 CH_2Cl_2 (50 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 **4** (18.47 g, 85%); mp 100–101 °C; $[\alpha]_D - 32°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 1); 7.30 (m, 5 H, Ph), 4.65 (ABq, 2 H, C*H*$_2$Ph), 1.47, 1.32 (2 s, 6 H, (C*H*$_3$)$_2$C), 1.21 (s, 9 H, (C*H*$_3$)$_3$C); ISMS: *m*/*z* 417, $[M + Na]^+$, 412, $[M + NH_4]^+$, 395, $[M + H]^+$. Anal. Calcd for $C_{21}H_{30}O_7$: 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 $NaHCO_3$, and water, dried ($MgSO_4$) and concentrated. The residue was eluted from a column (100 g) of silica gel with 6:1 → 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–CH_2Cl_2, and crystallized from EtOAc–petroleum ether to afford **5** (6.31 g, 72% from **4**); mp 84 °C, lit. 86–87 °C [27]; $[\alpha]_D - 58°$ (*c* 1, $CHCl_3$), lit. −61° [27]; ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 1); 7.40 (m, 5 H, Ph), 4.60 (ABq, 2 H, C*H*$_2$Ph), 3.05 (d, 1 H, *J* 2.5 Hz, *H*O-5), 2.12 (dd, 1 H, *J* 5.6 and 6.7 Hz, *H*O-6), 1.49, 1.34 (2 s, 6 H, (C*H*$_3$)$_2$C); ISMS: *m*/*z* 333, $[M + Na]^+$, 328, $[M + NH_4]^+$.

*1,2,4,6-Tetra-*O*-benzoyl-3-*O*-benzyl-β-*L*-idopyranose* (**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 CH_2Cl_2 (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 $NaHCO_3$ and water, dried ($MgSO_4$) 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**); $[\alpha]_D - 27°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 1); 8.10–7.10 (m, 25 H, Ph), 4.90 (s, 2 H, C*H*$_2$Ph); ISMS: *m*/*z* 709, $[M + Na]^+$, 704, $[M + NH_4]^+$, 687, $[M + H]^+$. Anal. Calcd for $C_{41}H_{34}O_{10}$: C, 71.71; H, 4.99. Found: C, 71.79; H, 4.98.

*Benzyl 2,4,6-tri-*O*-benzoyl-3-*O*-benzyl-α-*L*-idopyranoside* (**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 CH_2Cl_2 (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 Et_3N, and crystallized from the same mixture of solvents to give **8** (5.7 g, 70%); mp 113–114 °C; $[\alpha]_D - 5°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 1); 8.20–7.10 (m, 25 H, Ph), 4.83, 4.70 (2 ABq, 4 H, C*H*$_2$Ph); 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, 2-methoxypropene (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 $NaHCO_3$ and water, dried ($MgSO_4$) 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 CH_2Cl_2 (100 mL), washed with water, satd aq $NaHCO_3$, 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 Et_3N, and crystallized from the same mixture of solvents to give **9** (2.25 g, 75% from **7**); mp 110–111 °C; $[\alpha]_D$ − 29° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 1); 8.10–7.30 (m, 10 H, Ph), 4.74 (ABq, 2 H, C*H*$_2$Ph), 3.44 (s, 3 H, OC*H*$_3$), 1.47, 1.42 (2 s, 6 H, (C*H*$_3$)$_2$C); 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*-isopropylidene-α-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 Et_3N to afford amorphous **10** (2.53 g, 63%); $[\alpha]_D$ − 51° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 1); 8.10–7.20 (m, 15 H, Ph), 4.75, 4.70 (2 ABq, 4 H, C*H*$_2$Ph), 1.45, 1.42 (2 s, 6 H, (C*H*$_3$)$_2$C); 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-*O*-*tert*-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 × 10 mL) and toluene (2 × 10 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 ($MgSO_4$) 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%); $[\alpha]_D$ − 22° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 1); 8.10–7.10 (m, 10 H, Ph), 4.75 (ABq, 2 H, C*H*$_2$Ph), 3.45 (s, 3 H, OC*H*$_3$), 0.93, 0.76 (2 s, 18 H, (C*H*$_3$)$_3$C), 0.11, 0.09, − 0.08, − 0.25 (4 s, 12 H, C*H*$_3$Si); 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-*O*-*tert*-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° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 1); 8.10–7.20 (m, 15 H, Ph), 4.76, 4.70 (2 ABq, 4 H, C*H*$_2$Ph), 0.90, 0.78 (2 s, 18 H, (C*H*$_3$)$_3$C), 0.09, 0.05, − 0.03, − 0.16 (4 s, 12 H, C*H*$_3$Si); ISMS: *m/z* 716, $[M+Na]^+$, 711, $[M+NH_4]^+$, 586, $[M-OCH_2Ph]^+$. Anal. Calcd for $C_{39}H_{56}O_7Si_2$: 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 H_2SO_4 (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 CH_2Cl_2–MeOH) indicated complete disappearance of the starting material. The mixture was then poured into ice-cold water, and extracted with EtOAc (2 × 100 mL). The organic extracts were washed with water, dried ($MgSO_4$), and concentrated. The residue was eluted from a column (80 g) of silica gel with 15:1 CH_2Cl_2–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, Et_3N (0.62 mL, 4.5 mmol), and 4-dimethylaminopyridine (46 mg, 0.4 mmol) in anhyd CH_2Cl_2 (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 × 100 mL), washed with water, satd aq NH_4Cl and water, dried ($MgSO_4$) 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**); $[\alpha]_{\mathrm{D}} - 41°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 1); 8.15–7.30 (m, 10 H, Ph), 4.88 (ABq, 2 H, $C\mathit{H}_2Ph$), 3.79 (s, 3 H, $COOC\mathit{H}_3$), 3.50 (s, 3 H, $OC\mathit{H}_3$), 0.69 (s, 9 H, $(C\mathit{H}_3)_3C$), − 0.13, − 0.37 (2 s, 6 H, $C\mathit{H}_3Si$); ISMS: *m/z* 553, $[M + Na]^+$, 531, $[M + H]^+$, 499, $[M - OCH_3]^+$. Anal. Calcd for $C_{28}H_{38}O_8Si$: 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**); $[\alpha]_{\mathrm{D}} - 73°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 1); 8.0–7.20 (m, 15 H, Ph), 4.82, 4.77 (2 ABq, 4 H, $C\mathit{H}_2Ph$), 3.77 (s, 3 H, $COOC\mathit{H}_3$), 0.60 (s, 9 H, $(CH_3)_3C$), − 0.10, − 0.30 (2 s, 6 H, $C\mathit{H}_3Si$); ISMS: *m/z* 629, $[M + Na]^+$, 607, $[M + H]^+$, 499, $[M - OCH_2Ph]^+$. Anal. Calcd for $C_{34}H_{42}O_8Si$: 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 Bu_4NF (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 NH_4Cl, and water, dried ($MgSO_4$) 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%); $[\alpha]_{\mathrm{D}} - 19°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 1); 8.0–7.20 (m, 10 H, Ph), 4.84 (ABq, 2 H, $C\mathit{H}_2Ph$), 3.91 (s, 3 H, $COOC\mathit{H}_3$), 3.52 (s, 3 H, $OC\mathit{H}_3$), 2.85 (d, 1 H, *J* 11.5 Hz, *H*O-4); ^{13}C ($CDCl_3$): δ 170.04, 165.01 (C=O), 137.47–127.89 (aromatic C), 100.07 (C-1), 74.27 (C-5), 72.07 ($\mathit{C}H_2Ph$), 68.05, 67.57, 67.50 (C-2,3,4), 56.48 ($O\mathit{C}H_3$), 52.53 ($COO\mathit{C}H_3$); ISMS: *m/z* 439, $[M + Na]^+$, 417, $[M + H]^+$, 385, $[M - OCH_3]^+$. Anal. Calcd for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81. Found: C, 63.35; H, 5.89.

*Methyl (benzyl 2-*O*-benzoyl-3-*O*-benzyl-α-*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%); $[\alpha]_{\mathrm{D}} - 36°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 1); 8.0–7.20 (m, 15 H, Ph), 4.77, 4.75 (2 ABq, 4 H, $C\mathit{H}_2Ph$), 3.82 (s, 3 H, $COOC\mathit{H}_3$), 2.80 (d, 1 H, *J* 11.7 Hz, *H*O-4); ^{13}C ($CDCl_3$): 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 ($\mathit{C}H_2Ph$), 68.29, 67.94, 67.39 (C-2,3,4), 52.52 ($COO\mathit{C}H_3$); 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 Et_2O (500 mL) were added, and the mixture was stirred for 15 min at 0 °C. The solids were filtered off, and washed with Et_2O to give **18** as a white powder (19.2 g, 65%); mp 222–223 °C (from MeOH); $[\alpha]_{\mathrm{D}} + 1°$ (*c* 1, MeOH); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 7.50–6.80 (m, 9 H, Ph), 5.66 (s, 1 H, $PhC\mathit{H}$), 3.85 (s, 3 H, $OC\mathit{H}_3$), 2.85 (d, 1 H, *J* 2.9 Hz, *H*O-3); ISMS: *m/z* 541, $[M + Na]^+$, 519, $[M + H]^+$, 395, $[M - OC_6H_4OCH_3]^+$ for ^{35}Cl. 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 ($MgSO_4$) and concentrated. The solid residue was recrystallized from MeOH to give **19** (18.37 g, 82%); mp 261–262 °C; $[\alpha]_D + 4°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 7.50–6.80 (m, 14 H, Ph), 5.70 (s, 1 H, PhC*H*), 4.91 (ABq, 2 H, C*H*$_2$Ph), 3.84 (s, 1 H, OC*H*$_3$); ISMS: *m*/*z* 631, $[M + Na]^+$, 609, $[M + H]^+$, 485, $[M\text{-}OC_6H_4OCH_3]^+$ for ^{35}Cl. Anal. Calcd for $C_{29}H_{28}Cl_3NO_7$: 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 CH_2Cl_2 (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 $NaHCO_3$ 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 and crystallized from EtOAc–petroleum ether to afford **20** (4.43 g, 69%); mp 141–142 °C; $[\alpha]_D - 15°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 7.50–6.80 (m, 14 H, Ph), 4.88, 4.67 (2 ABq, 4 H, C*H*$_2$Ph), 3.83 (s, 3 H, OC*H*$_3$), 2.82 (d, 1 H, *J* 2.6 Hz, *H*O-4); ISMS: *m*/*z* 632, $[M + Na]^+$, 4.88, $[M - OC_6H_4OCH_3]^+$ for ^{35}Cl. Anal. Calcd for $C_{29}H_{30}Cl_3NO_7$: 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 CH_2Cl_2 (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 CH_2Cl_2 (100 mL), washed with water, brine and water, dried ($MgSO_4$), 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 × 100 mL). The combined extracts were washed with water, 5% aq HCl and water, dried ($MgSO_4$) and concentrated. The residue was crystallized from EtOAc–petroleum ether to afford **21** (4.06 g, 89%); mp 142–143 °C; $[\alpha]_D + 6.5°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 7.50–6.70 (m, 14 H, Ph), 4.64, 4.57 (2 ABq, 4 H, C*H*$_2$Ph), 3.75 (s, 3 H, OC*H*$_3$); ISMS: *m*/*z* 634, $[M + Na]^+$, 488, $[M - OC_6H_4OCH_3]^+$ for ^{35}Cl. 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 (Ac_2O in pyridine) of **21** (6.69 g, 10.9 mmol) followed by concentration of the mixture and crystallization of the residue from EtOAc–petroleum ether gave **22** (6.09 g, 85%); mp 144–145 °C; $[\alpha]_D + 13°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 7.40–6.70 (m, 14 H, Ph), 4.58, 4.53 (2 ABq, 4 H, C*H*$_2$Ph), 3.75 (s, 3 H, OC*H*$_3$), 2.10 (s, 3 H, Ac); ISMS: *m*/*z* 671, $[M + NH_4]^+$, 530, $[M - OC_6H_4OCH_3]^+$ for ^{35}Cl. 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-2-trichloroacetamido-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 ($MgSO_4$) 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, CCl_3CN (3 mL, 30 mmol) and DBU (0.11 mL, 0.74 mmol) in anhyd CH_2Cl_2 (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 Et_3N to give **23** as a white foam (1.94 g, 88% from **22**); $[\alpha]_D + 78°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 8.65 (s, 1 H, $C{=}N\mathit{H}$), 7.30 (m, 10 H, Ph), 4.59, 4.50 (2 ABq, 4 H, $C\mathit{H}_2Ph$), 2.10 (s, 3 H, Ac); ^{13}C ($CDCl_3$): 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 ($\mathit{C}Cl_3$), 73.80, 70.71 ($\mathit{C}H_2Ph$), 71.62, 70.77 (C-4,5), 67.35, 65.15 (C-6,3), 50.75 (C-2), 20.84 ($CO\mathit{C}H_3$); ISMS: *m*/*z* 714, $[M + Na]^+$, 530, $[M - CCl_3CONH]^+$ for ^{35}Cl. Anal. Calcd for $C_{26}H_{26}Cl_6N_2O_7$: 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→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 CH_2Cl_2 (7 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, 0.76 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 Et_3N to give first amorphous **24** (276 mg, 31% from **23**); $[\alpha]_D + 11.5°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 7.88 (d, 1 H, $J_{NH,1}$ 8.8 Hz, $NHCOCCl_3$), 7.30 (m, 10 H, Ph), 4.59, 4.51 (2 ABq, 4 H, CH_2Ph), 2.10 (s, 3 H, Ac); ^{13}C ($CDCl_3$): δ 170.18 (C=O), 164.14, 162.73 ($COCCl_3$), 137.38–128.22 (aromatic C), 92.49, 91.85 (CCl_3), 81.79 (C-1), 75.33, 74.38 (C-4,5), 73.93, 71.09 (CH_2Ph), 67.22, 64.75 (C-3,6), 52.30 (C-2), 20.96 ($COCH_3$). 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%); $[\alpha]_D - 11.5°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 3); 8.10–7.20 (m, 20 H, Ph), 4.74, 4.73, 4.40 (3 ABq, 6 H, $C\mathit{H}_2Ph$), 3.82 (s, 3 H, $COOC\mathit{H}_3$), 3.48 (s, 3 H, $OC\mathit{H}_3$), 1.62 (s, 3 H, Ac); ISMS: *m*/*z* 963, $[M + NH_4]^+$, 946, $[M + H]^+$ for ^{35}Cl. Anal. Calcd for $C_{46}H_{48}Cl_3NO_{14}$: C, 58.45; H, 5.12; N, 1.48. Found: C, 58.33; H, 5.23; N, 1.45.

*Methyl (4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-*D*-galactopyranosyl)-(1→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%); $[\alpha]_D - 27°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): 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, CH_2Ph), 3.80 (s, 3 H, $COOCH_3$), 1.60 (s, 3 H, Ac); ISMS: *m*/*z* 1039, $[M + NH_4]^+$ for ^{35}Cl. Anal. Calcd for $C_{52}H_{52}Cl_3NO_{14}$: 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-β-*D*-galactopyranosyl)-(1→4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-α-*L*-idopyranosid)uronate* (**27**).—A mixture of **25** (2.07 g, 2.2 mmol), Bu_3SnH (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 °C; $[\alpha]_D - 9°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 3); 8.10–7.20 (m, 20 H, Ph), 4.73, 4.51, 4.30 (3 ABq, 6 H, $C\mathit{H}_2Ph$), 3.81 (s, 3 H, $COOC\mathit{H}_3$), 3.47 (s, 3 H, $OC\mathit{H}_3$), 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-O-benzyl-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; $[\alpha]_D - 25°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 3); 8.10–7.20 (m, 25 H, Ph), 4.88–4.28 (m, 8 H, CH_2Ph), 3.77 (s, 3 H, $COOCH_3$), 2.0, 1.59 (2 s, 6 H, Ac); ISMS: *m*/*z* 941, $[M + Na]^+$, 811, $[M - OCH_2Ph]^+$. Anal. Calcd for $C_{52}H_{55}NO_{14}$: 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→4)-(sodium methyl 3-O-benzyl-2-O-sulfonato-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% H_2O_2 (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→9:1 CH_2Cl_2–MeOH to give the corresponding hydroxy acid (1.06 g, 90%); ^1H NMR (CD_3OD): δ 7.30 (m, 15 H, Ph), 4.82 (br s, 1 H, H-1$^{\mathrm{I}}$), 4.73–4.43 (m, 6 H, CH_2Ph), 4.48 (d, 1 H, $J_{4,5}$ 1.7 Hz, H-5$^{\mathrm{I}}$), 4.41 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1$^{\mathrm{II}}$), 4.10 (m, 2 H, H-2$^{\mathrm{I}}$,4$^{\mathrm{I}}$), 4.06 (dd, 1 H, $J_{2,3}$ 10.5 Hz, H-2$^{\mathrm{II}}$), 4.02 (m, 2 H, H-3$^{\mathrm{I}}$,4$^{\mathrm{II}}$), 3.61 (m, 3 H, H-5$^{\mathrm{II}}$,6a$^{\mathrm{II}}$,6b$^{\mathrm{II}}$), 3.46 (dd, 1 H, $J_{3,4}$ 3.0 Hz, H-3$^{\mathrm{II}}$), 3.37 (s, 3 H, OCH_3), 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→4:1 CH_2Cl_2–MeOH, then from a column (1.5 × 20 cm) of Sephadex SP C25 $[Na^+]$ with 9:5:1 CH_2Cl_2–MeOH–water to give amorphous **29** (590 mg, 65%); $[\alpha]_D$ −6° (*c* 1, MeOH); ^1H NMR (CD_3OD): carbohydrate ring protons (see Table 3); 7.30 (m, 15 H, Ph), 4.65–4.35 (m, 6 H, CH_2Ph), 3.37 (s, 3 H, OCH_3), 1.99 (s, 3 H, NAc). Anal. Calcd for $C_{36}H_{40}NNa_2O_{18}S_2$: 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→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 (CD_3OD): δ 7.30 (m, 20 H, Ph), 5.18 (br s, 1 H, H-1$^{\mathrm{I}}$), 4.80–4.40 (m, 8 H, CH_2Ph), 4.50 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1$^{\mathrm{II}}$), 4.47 (d, 1 H, $J_{4,5}$ 2.2 Hz, H-5$^{\mathrm{I}}$), 4.14 (m, 2 H, H-2$^{\mathrm{I}}$,4$^{\mathrm{I}}$), 4.12 (dd, 1 H, $J_{2,3}$ 10.6 Hz, H-2$^{\mathrm{II}}$), 3.99 (dd, 1 H, $J_{3,4}$ 3.0, $J_{4,5}$ 0.5 Hz, H-4$^{\mathrm{II}}$), 3.78 (m, 1 H, H-3$^{\mathrm{I}}$), 3.63 (m, 3 H, H-5$^{\mathrm{I}}$,6a$^{\mathrm{I}}$,6b$^{\mathrm{I}}$), 3.50 (dd, 1 H, H-3$^{\mathrm{II}}$), 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° (*c* 1, MeOH); ^1H NMR (CD_3OD): carbohydrate ring protons (see Table 3); 7.30 (m, 20 H, Ph), 4.95–4.40 (m, 8 H, CH_2Ph), 2.0 (s, 3 H, NAc). Anal. Calcd for $C_{42}H_{44}NNa_3O_{18}S_2$: 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-O-sulfonato-β-D-galactopyranosyl)-(1→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%); $[\alpha]_D$ −2.5° (*c* 1, equilibrium, water); ^1H NMR (D_2O, internal H_2O, δ_H 4.754): carbohydrate ring protons (see Table 3); 2.0, 1.99 (2 s, 3 H, NAc);^{13}C (D_2O, internal acetone, δ_C 30.45): δ 175.39, 175.29 (C=O), 103.13, 101.77 (C-1$^{\mathrm{II}}$), 92.78, 91.90 (C-1$^{\mathrm{I}}$), 78.39, 77.60 (C-4$^{\mathrm{I}}$), 75.81 (C-2$^{\mathrm{I}}$, C-4$^{\mathrm{II}}$), 74.48 (C-5$^{\mathrm{I}}$), 70.10, 68.70, 67.70 (C-3$^{\mathrm{I}}$, C-3$^{\mathrm{II}}$, C-5$^{\mathrm{II}}$), 60.97 (C-6$^{\mathrm{II}}$), 52.78 (C-2$^{\mathrm{II}}$), 22.71 ($COCH_3$). Anal. Calcd for $C_{14}H_{20}NNa_3O_{18}S_2$: 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-*O*-sulfonato-β-*D*-galactopyranosyl)-(1→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); ^{1}H NMR (D_2O, internal H_2O, δ_H 4.754): carbohydrate ring protons (see Table 3); 3.20 (s, 3 H, OCH_3), 2.04 (s, 3 H, NAc); ^{13}C (D_2O, internal acetone, δ_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 ($COCH_3$). Anal. Calcd for $C_{15}H_{22}NNa_3O_{18}S_2$: C, 28.26; H, 3.48; N, 2.20. Found: C, 27.92; H, 3.71; N, 2.08.

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