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Unexpected stereochemical outcome of activated 4,6-*O*-benzylidene derivatives of the 2-deoxy-2-trichloroacetamido-D-*galacto* series in glycosylation reactions during the synthesis of a chondroitin 6-sulfate trisaccharide methyl glycoside

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Dedicated to Professor P. Sinaÿ on the occasion of his 62nd birthday.

Abstract

The synthesis of methyl (β-D-glucopyranosyluronic acid)-(1→3)-(2-acetamido-2-deoxy-6-*O*-sulfonato-β-D-galactopyranosyl)-(1→4)-(β-D-glucopyranosid)uronate trisodium salt, a chondroitin 6-sulfate trisaccharide derivative, is described. Loss of stereocontrol in glycosylation reactions involving activated 4,6-*O*-benzylidene derivatives of the 2-deoxy-2-trichloroacetamido-D-*galacto* series and D-glucuronic acid-derived acceptors was highlighted. This drawback was overcome through the use of phenyl 3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-2-trichloroacetamido-β-D-galactopyranoside, which afforded the desired β-linked disaccharide derivative in high yield with an excellent stereoselectivity. This later was submitted to acid-catalyzed methanolysis, followed by benzylidenation, and condensed with methyl 2,3,4-tri-*O*-benzoyl-1-*O*-trichloroacetimidoyl-α-D-glucopyranuronate to afford the expected trisaccharide derivative. Subsequent transformation of the *N*-trichloroacetyl group into *N*-acetyl, mild acid hydrolysis, selective O-sulfonation at C-6 of the amino sugar moiety, and saponification afforded the target molecule as its sodium salt in high yield.

Keywords: Glycosylation reactions; 2-Deoxy-2-trichloroacetamido-D-galactose derivatives; Chondroitin 6-sulfate trisaccharide

1. Introduction

Chondroitin sulfates belong to a family of structurally complex, microheterogeneous, linear polysaccharides called glycosaminoglycans (GAGs). Chondroitins are built from dimeric units composed of D-glucuronic acid (GlcA) and 2-acetamido-2-deoxy-D-galactose (GalNAc), namely [4)-β-D-Glc*p*A-(1→3)-β-D-Gal*p*NAc-(1→]$_n$, and contain, on average, one sulfate group per disaccharide unit either at C-4 or C-6 of the amino sugar moiety, but several types having sulfate(s) at various positions are known [1]. They are located on the cell surface and in the extracellular matrix, and are involved in numerous important bio-

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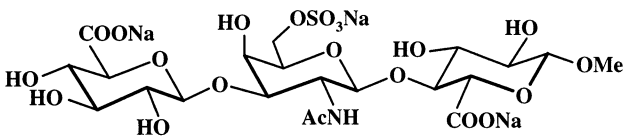
logical processes. In the case of chondroitin 6-sulfate, they, for example, play a role in inhibition of human C1q factor [2], could be a potent ligand for NKR-P_1 proteins of NK cells [3], and were found at increased levels in human colon carcinoma [4] or articular cartilage of older individuals [5]. In order to study these biological functions in more detail at the molecular level, and since it is quite difficult to get chemically pure fragments by chemical or enzymatic degradation, the availability of synthetic fragments is of prime importance.

Several syntheses of chondroitin 6-sulfate fragments have been reported, such as those of the basic reducing disaccharide [6], its methyl glycoside [7] or its 4-methoxyphenyl glycoside [8], or those of 4-methoxyphenyl glycosides of the tri- and tetrasaccharide [8]. In all these syntheses, monosaccharide synthons derived from D-galactosamine were used as the amino sugar moiety. We also reported [9] another approach based on selective inversion of the configuration at C-4 of a glucosamine-containing trisaccharide. We now report on the use and the unexpected stereochemical outcome of activated 4,6-*O*-benzylidene derivative of the 2-deoxy-2-trichloroacetamido-D-*galacto* series in the synthesis of chondroitin 6-sulfate trisaccharide methyl glycoside **1**.



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2. Results and discussion

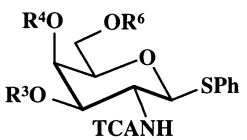
The preparation of D-galactosamine derivatives, which could serve initially as glycosyl donors and then as glycosyl acceptors after coupling, was first examined. We demonstrated [10] that 2-deoxy-2-trichloroacetamido-D-glucose derivatives are very efficient glycosyl donors for the synthesis of 1,2-*trans*-2-amino-2-deoxy-D-glucosides, and that the *N*-trichloroacetyl group in the products could be easily transformed into *N*-acetyl under neutral conditions. This method, which allows the direct glycosylation of the low-reactive 4-OH group of D-glucuronic acid derivatives [12], is particularly well suited for the construction of chondroitin fragments [9].

We first focused on the preparation of thioglycosides **4**–**6**. Treatment with benzaldehyde and trifluoroacetic acid of phenyl 2-deoxy-1-thio-2-trichloroacetamido-β-D-galactopyranoside (**2**), easily prepared [11] from the corresponding D-*gluco* analogue through a high-yielding three-step sequence, gave the crystalline 4,6-*O*-benzylidene derivative **3** in 90% yield. Temporary protection at O-3 was then achieved through chloroacetylation to give crystalline **4** in 75% yield, and silylation to give **5** in 92% yield. Acetylation of **2** with acetic anhydride–pyridine gave crystalline **6** in 92% yield (Scheme 1).

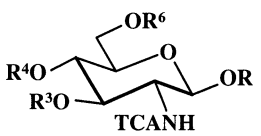
Another sequence was attempted starting from inexpensive D-glucosamine with a view to preparing the corresponding trichloroacetimidates. Treatment of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranose (**7**) [12] with 4-methoxyphenol and triflic acid afforded crystalline **8** in 87% yield, which was O-deacetylated with methanolic sodium methoxide to give quantitatively the crystalline triol **9**. Treatment of **9** with pivaloyl chloride in pyridine afforded the crystalline 3,6-di-*O*-pivaloyl derivative **10a** in 89% yield, along with its 4,6-isomer **10b** (9%). Inversion of configuration at C-4 was then achieved [11] through treatment of **10a** with triflic anhydride and pyridine in 1,2-dichloroethane at −15 °C, followed by addition of water and heating at 85 °C to give a mixture of 4,6- and 3,4-di-*O*-pivaloyl-D-*galacto* intermediates in a ~12:1 ratio (determined by integrated ^{1}H NMR, details not presented in Section 3), which was directly O-deacylated to give the crystalline triol **11** in 94% overall yield. Treatment of **11**, as described for **3**, gave the crystalline 4,6-*O*-benzylidene derivative **12** in 85% yield, which was then chloroacetylated at O-3 to afford **13** in 90% yield. Introduction of the trichloroacetimidoyl group at C-1 was then achieved by selective oxidative removal of the anomeric 4-methoxyphenyl group using ceric ammonium nitrate in toluene–acetonitrile–water [13], followed by treatment with trichloroacetonitrile and 1,8-diazabicyclo-

[5,4,0]-undec-7-ene (DBU) to give the crystalline α-imidate **14** in 61% overall yield. Acetylation of **11** gave crystalline **15** in 85% yield, which was similarly transformed into the crystalline α-imidate **16** in 70% overall yield. The physical data for **16** are in full agreement with those reported [14] for a derivative prepared from 2-amino-2-deoxy-D-galactose.

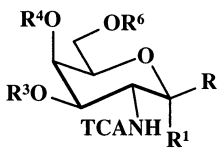
Coupling reactions that involved the donors **4**–**6**, **14** and **16** and the acceptors methyl (methyl 2,3-di-*O*-benzoyl-β-D-glucopyranosid)uronate (**19**) [9] and its 4-methoxyphenyl glycoside analogue **20** [10] were then studied (Table 1). Condensation of the thioglycoside **4** (1 equivalent) with the alcohol **20** in dichloromethane at room temperature in the presence of *N*-iodosuccinimide (NIS) and a catalytical amount of trimethylsilyl triflate afforded a mixture of β- (**21**) and α-linked (**25**) disaccharide derivatives in a ~3:1 ratio in 65% overall yield (Entry 1). Lowering the temperature (Entry 2), or varying the nature of the solvent (Entry 3) did not significantly change the product distribution. Condensation of **5**, bearing a bulky substituent at O-3, with **20** under the same conditions (Entry 5) afforded an inseparable mixture of disaccharides in which the α-linked isomer was predominant (determined by integrated ^{1}H NMR, details not presented in Section 3). Similar results were obtained when the imidate **14** and the alcohol **20** were condensed in dichloromethane (Entry 6) or toluene (Entry 7) under the catalysis of trimethylsilyl triflate. However, coupling of the O-acetylated thioglycoside **6** with **20** (Entry 8) or **19** (Entry 9), or coupling of the O-acetylated trichloroacetimidate **16** with **20** (Entry 10) afforded exclusively the crystalline β-linked disaccharide



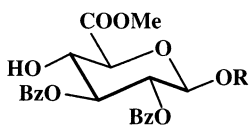
	R3	R4	R6
2	H	H	H
3	H	PhCH	
4	MCA	PhCH	
5	*t*BDMS	PhCH	
6	Ac	Ac	Ac



	R	R3	R4	R6
7	Ac	Ac	Ac	Ac
8	MP	Ac	Ac	Ac
9	MP	H	H	H
10a	MP	Piv	H	Piv
10b	MP	H	Piv	Piv



	R	R1	R3	R4	R6
11	OMP	H	H	H	H
12	OMP	H	H	PhCH	
13	OMP	H	MCA	PhCH	
14	H	$OC(NH)CCl_3$	MCA	PhCH	
15	OMP	H	Ac	Ac	Ac
16	H	$OC(NH)CCl_3$	Ac	Ac	Ac
17	OMe	H	MCA	PhCH	
18	OMe	H	Ac	Ac	Ac



	R
19	Me
20	MP

Scheme 1.

Table 1
Coupling reactions between donors **4**–**6**, **14** and **16** and acceptors **19** and **20**

Entry	Reactants	Catalyst [a]	Solvent [b]	Coupling [d]	β,α-ratio	Products
1	**4**+**20**	A	CH_2Cl_2	65	3:1	**21**, **25**
2	**4**+**20**	A	CH_2Cl_2 [c]	46	5:1	**21**, **25**
3	**4**+**20**	A	toluene	68	3:1	**21**, **25**
4	**4**+MeOH	A	CH_2Cl_2	74	β	**17**
5	**5**+**20**	A	CH_2Cl_2	80	1:2 [e]	
6	**14**+**20**	B	CH_2Cl_2	65	2:1	**21**, **25**
7	**14**+**20**	B	toluene	52	3:1	**21**, **25**
8	**6**+**20**	A	CH_2Cl_2	77	β	**22**
9	**6**+**19**	A	CH_2Cl_2	76	β	**23**
10	**16**+**20**	B	CH_2Cl_2	83	β	**22**
11	**16**+MeOH	B	CH_2Cl_2	94	β	**18**

[a] Catalysis with A, *N*-iodosuccinimide–trimethylsilyl triflate; B, trimethylsilyl triflate.
[b] Reactions at room temperature.
[c] Reaction at −20 °C.
[d] Yields (%) refer to isolated products.
[e] Determined by integrated ^{1}H NMR

derivatives **22** and **23** in 77, 76, and 83% yields, respectively. Surprisingly, with respect to the above results, coupling of **4** with methanol (Entry 4) gave exclusively the corresponding β-glycoside, as was the case with the imidate **16** (Entry 11).

Such an unexpected stereochemical outcome has still been reported [15] with activated 4,6-*O*-benzylidene derivatives of the 2-acetamido-2-deoxy-D-*galacto* series during a synthesis of the Thomsen–Friedenreich antigen. It was postulated that the 1,3-dioxolane ring system in the 4,6-*O*-benzylidene derivative prevented the participation of the 2-acetamido group. As a matter of fact, when donors **5** and **6** were treated with NIS–trimethylsilyl triflate for a short period in the absence of acceptor, the corresponding unstable silylated oxazoline **27** and the known [14] acetylated oxazoline **26** were isolated, respectively, as the major product, thus indicating that participation of the 2-trichloroacetamido group is quite effective in both cases. Comparison of the ^{1}H NMR spectra of **27** (Table 2) with those reported [14] for **26** showed very little differences (≤ 0.5 Hz) for the values of the $^3J_{H,H}$ coupling constants for H-1 to H-4, thus indicating that both oxazoline derivatives, which are assumed to be the major intermediates in the coupling reaction, have at least very similar conformations. It should be noted that coupling of the D-*gluco* analogue of **14** and **20** gave the corresponding β-linked disaccharide derivative in 89% yield [10]. Consequently, the loss of stereocontrol in the coupling reactions was apparently not due, as postulated, to a lack of anchimeric assistance of the 2-acylamido group, but more certainly to a mismatched pair formed in the transition state of the β-coupling caused by steric factors induced by the rigid 4(axial),6-dioxolane ring in the 4,6-*O*-benzylidene-D-*galacto* derivatives. Whether this phenomenon is general or not remains to be established (Scheme 2).

Since the amino sugar moiety could not be suitably protected before coupling, we tried to transform the easily available disaccharide derivative **23** into an acceptor having its 3′-OH group free, thus allowing further elongation at the non reducing end. Acid-catalyzed methanolysis [16] of **23** readily afforded the corresponding triol, which was treated directly with benzaldehyde and trifluoroacetic acid to give the crystalline acceptor **24** in 79% yield.

We have previously reported [17] that O-benzoylated derivatives of D-glucuronic acid activated through their corresponding trichloroacetimidates were very efficient donors for the preparation of β-D-glucuronides. Condensation of methyl 2,3,4-tri-*O*-benzoyl-1-*O*-trichloroacetimidoyl-α-D-glucopyranuronate **28** [9] (1.5 equivalents) with the alcohol **24** in the presence of trimethylsilyl triflate afforded

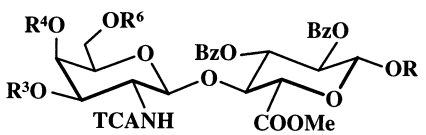
Table 2
^{1}H NMR data: carbohydrate ring protons for monosaccharide derivatives **3-6**, **8-15**, **17-18**, and **27** [a]

Proton	**3**	**4**	**5**	**6**	**8**	**9** [b]	**10a**	**10b**	**11** [b]	**12** [b]	**13**	**14**	**15**	**17**	**18**	**27**
H-1	5.04	5.18	5.40	4.92	5.05	4.91	4.99	5.26	4.87	5.02	5.36	6.59	5.10	4.86	4.61	6.48
$J_{1,2}$	10.0	10.0	10.0	10.0	8.5	8.0	8.5	8.5	8.5	8.0	8.5	3.5	8.5	8.5	8.5	6.0
H-2	3.75	4.09	3.69	4.15	4.15	3.50	4.18	4.25	4.00	3.92	4.35	4.94	4.30	4.09	4.05	4.23
$J_{2,3}$	10.0	10.0	10.0	10.5	10.0	10.0	10.0	10.0	10.0	10.0	10.0	11.0	10.5	10.0	11.0	7.5
H-3	4.10	5.51	4.54	5.27	5.37	3.65	5.45	3.68	3.50	4.05	5.59	5.49	5.39	5.53	5.32	3.80
$J_{3,4}$	3.5	3.5	3.5	3.5	9.5	9.0	9.0	9.0	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.0
H-4	4.20	4.40	4.09	5.37	5.15	3.15	3.55	4.84	3.68	4.15	4.47	4.48	5.40	4.40	5.35	4.18
$J_{4,5}$	1.0	1.0	1.0	1.0	9.5		9.0	9.5	1.0	1.0	1.0	1.0	1.0	1.0	1.0	2.5
H-5	3.57	3.68	3.57	3.93	3.80	3.15	3.75	3.81	3.40	4.05	3.66	3.94	4.01	3.60	3.92	3.88
$J_{5,6a}$	1.5	2.0	1.5	6.0	2.5		2.0	2.0			2.0	1.5	6.0	1.5	7.0	2.0
$J_{5,6b}$	1.5	2.0	1.5	7.0	5.0		6.0	6.0			2.0	1.5	6.0	1.5	7.0	2.0
H-6a	4.37	4.38	4.38	4.18	4.29	3.50	4.46	4.25	3.50	4.05	4.35	4.35	4.15	4.34	4.10	4.40
$J_{6a,6b}$	−12.5	−12.5	−12.5	−12.0	−12.0		−12.0	−12.0			−12.0	−12.0		−12.5		−12.5
H-6b	4.01	4.03	4.02	4.12	4.14	3.65	4.30	4.09	3.50	4.05	4.08	4.07	4.15	4.08	4.10	4.07
NH	6.81	6.64	6.78	6.75	6.80	8.77	7.24	7.01	8.70	8.78	6.81	6.80	6.79	7.01	6.85	
$J_{2,NH}$	8.0	8.5	7.5	8.5	7.5	9.0	9.0	7.0	9.0	9.0	8.0	9.0	8.0	8.0	8.5	

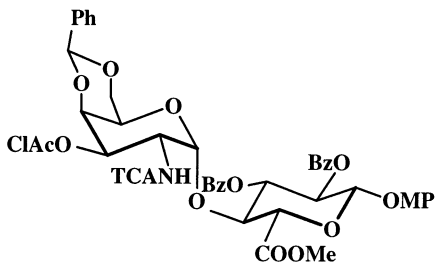
[a] Chemical shifts (δ, ppm) and coupling constants (J, in Hz) for solutions in $CDCl_3$, unless otherwise stated.
[b] $(CD_3)_2SO$.

the crystalline trisaccharide derivative **29** in 85% yield. The *N*-trichloroacetyl group in **29** was readily transformed into *N*-acetyl with tributyltin hydride and azobisisobutyronitrile (AIBN) to give the crystalline acetamide **30** in 82% yield. Treatment of **30** with aqueous acetic acid at 100 °C gave the crystalline diol **31** in 80% yield.

Preparation of the target molecule **1** was then achieved as follows. Treatment of the diol **31** with the sulfur trioxide–trimethylamine complex (3 equivalents) in *N*,*N*-dimethylformamide at 50 °C for 4 h, followed by ion-exchange chromatography, afforded the crystalline sodium salt **32** in 72% yield. Minor amounts of unreacted starting material and of the corresponding 4,6-disulfated derivative were also obtained, but easily separated from **32** by chromatography. These results were in accord with those previously reported [6], and no formation of imine-like products [8] coming from O-sulfonation of the tautomeric form of the amide was observed. Comparison of the NMR spectra of **32** and **31** showed for ^{1}H (Table 4) the expected [7] downfield shift (0.6 ppm) of the signals for



	R	R3	R4	R6
21	MP	MCA	PhCH	
22	MP	Ac	Ac	Ac
23	Me	Ac	Ac	Ac
24	Me	H	PhCH	



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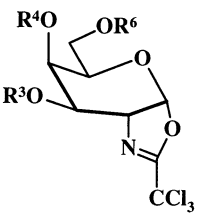
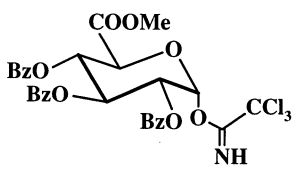


	R3	R4	R6
26	Ac	Ac	Ac
27	*t*BDMS	PhCH	



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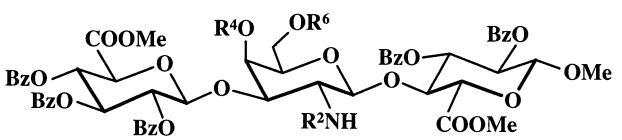

	R2	R4	R6
29	TCA	PhCH	
30	Ac	PhCH	
31	Ac	H	H
32	Ac	H	SO_3Na

Scheme 2.

Table 3
^{1}H NMR data: carbohydrate ring protons for disaccharide derivatives **21–25** [a]

Proton	**21**	**25**	**22**	**23**	**24**
H-1^{I}	5.23	5.30	5.22	4.65	4.66
$J_{1,2}$	7.0	7.0	7.0	7.0	7.0
H-2^{I}	5.57	5.61	5.58	5.35	5.34
$J_{2,3}$	9.0	9.0	9.0	9.5	9.0
H-3^{I}	5.76	5.78	5.71	5.64	5.67
$J_{3,4}$	9.0	9.0	9.0	9.5	9.0
H-4^{I}	4.52	4.77	4.41	4.29	4.34
$J_{4,5}$	9.0	9.0	9.0	9.5	9.0
H-5^{I}	4.25	4.34	4.22	4.12	4.14
H-1^{II}	5.07	5.37	4.95	4.91	4.86
$J_{1,2}$	8.0	3.5	8.5	8.5	8.0
H-2^{II}	4.15	4.72	3.97	3.94	3.87
$J_{2,3}$	11.0	11.0	10.5	11.0	11.0
H-3^{II}	5.22	5.24	5.09	5.09	3.81
$J_{3,4}$	3.5	3.5	3.5	3.5	3.5
H-4^{II}	4.18	4.39	5.13	5.11	3.97
$J_{4,5}$	1.0	1.0	1.0	1.0	1.0
H-5^{II}	3.33	3.75	3.71	3.69	3.24
$J_{5,6a}$	1.5	1.5	6.0	6.0	1.5
$J_{5,6b}$	1.5	1.5	7.5	7.0	1.5
H-6a^{II}	3.65	4.32	3.32	3.25	3.61
$J_{6a,6b}$	−12.0	−12.0	−11.5	−12.0	−12.5
H-6b^{II}	3.55	3.98	3.25	3.25	3.43
NH	6.78	6.62	6.68	6.74	7.00
$J_{2,NH}$	8.0	9.0	8.5	8.5	7.5

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

H-6a^{II} and H-6b^{II} in **32**, and for ^{13}C the expected [7] downfield shift (6.7 ppm) of the signal for C-6^{II} in **32**, respectively. Saponification of the ester groups was then achieved by treatment of **32** with lithium hydroperoxide in aqueous tetrahydrofuran at −5 °C [18], followed by methanolic sodium hydroxide to afford the target molecule **1** in 81% yield. The ^{1}H (Table 4) and ^{13}C NMR spectra of **1** are in full agreement with the expected structure, and in accord with those reported for synthetic trisaccharide derivatives [8,9] and polymeric chondroitin 6-sulfate [19].

In summary, unfavorable interactions in the transition state between 4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-D-*galacto*-derived glycosyl donors and D-glucuronic acid-derived acceptors may lead to a dramatic loss of stereoselectivity in the coupling reaction. However, this drawback should be overcome through the use of more flexible and less strerically hindered species, thus allowing the high-yielding preparation of a chondroitin 6-sulfate trisaccharide derivative.

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 25 °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. 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).

*Phenyl 4,6-*O*-benzylidene-2-deoxy-1-thio-2-trichloroacetamido-β-*D*-galactopyranoside* (**3**).—A mixture of phenyl 2-deoxy-1-thio-2-

trichloroacetamido-β-D-galactopyranoside (**2**) [11] (5.12 g, 12.2 mmol), benzaldehyde (40 mL), and CF_3COOH (2 mL) was stirred for 1.5 h at room temperature (rt). The solution was then cooled to 0 °C, and Et_3N (5 mL) was added. The mixture was then diluted with CH_2Cl_2 (250 mL), washed with water, dried ($MgSO_4$), and concentrated. The residue was eluted from a column (100 g) of silica gel with 1:1 → 2:1 EtOAc–petroleum ether, and crystallized from hot EtOH to give **3** (5.5 g, 90%); mp 167–168 °C; $[\alpha]_D$ −11° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 7.65–7.15 (m, 10 H, Ph), 5.52 (s, 1 H, PhC*H*), 2.75 (bs, 1 H, *H*O-3). Anal. Calcd for $C_{21}H_{20}Cl_3NO_5S{\cdot}H_2O$: C, 48.24; H, 4.24; N, 2.68. Found: C, 48.42; H, 4.19; N, 2.74.

Table 4
^1H NMR data: carbohydrate ring protons for trisaccharide derivatives **29–32** and **1** [a]

Proton	**29**	**30**	**31**	**32** [b]	**1** [c]
H-1^I	4.66	4.61	4.62	4.54	4.38
$J_{1,2}$	7.0	7.0	7.0	7.0	7.5
H-2^I	5.28	5.26	5.33	5.26	3.24
$J_{2,3}$	9.0	9.0	9.0	9.0	9.0
H-3^I	5.67	5.64	5.58	5.66	3.37
$J_{3,4}$	9.0	9.0	9.0	9.0	9.0
H-4^I	4.54	4.38	4.30	4.43	3.60
$J_{4,5}$	9.0	9.0	9.0	9.0	9.0
H-5^I	4.13	4.17	4.07	4.19	3.60
H-1^{II}	5.21	5.13	4.94	4.79	4.44
$J_{1,2}$	8.0	8.0	8.0	8.0	8.0
H-2^{II}	3.65	3.20	3.04	3.90	3.91
$J_{2,3}$	11.0	11.0	11.0	10.5	10.5
H-3^{II}	4.58	4.69	4.59	3.94	3.88
$J_{3,4}$	3.5	3.5	3.5	3.5	3.5
H-4^{II}	4.33	4.14	3.91	4.19	4.12
$J_{4,5}$	1.0	1.0	1.0	1.0	1.0
H-5^{II}	3.24	2.91	3.28	3.59	3.76
$J_{5,6a}$	1.0	1.0	5.0		
$J_{5,6b}$	1.5	1.0	6.0		
H-6a^{II}	3.92	3.74	3.15	3.75	4.12
*J*6a,6b	−12.0	−12.0			−12.0
H-6b^{II}	3.76	3.56	3.15	3.75	4.12
NH	7.04	5.51	5.37		
$J_{2,NH}$	7.0	7.0	6.0		
H-1^{III}	5.15	5.08	4.92	5.31	4.28
$J_{1,2}$	7.5	7.5	7.5	7.5	8.0
H-2^{III}	5.48	5.46	5.48	5.54	3.24
$J_{2,3}$	9.0	9.0	9.0	9.0	9.0
H-3^{III}	5.76	5.80	5.84	6.02	3.37
$J_{3,4}$	9.0	9.0	9.0	9.0	9.0
H-4^{III}	5.61	5.62	5.55	5.57	3.51
$J_{4,5}$	9.5	9.5	9.5	9.5	9.0
H-5^{III}	4.27	4.24	4.26	4.67	3.60

[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.

Phenyl 4,6-O-benzylidene-3-O-chloroacetyl-2-deoxy-1-thio-2-trichloroacetamido-β-D-galactopyranoside (**4**).—Chloroacetic anhydride (76 mg, 0.44 mmol) was added at 0 °C to a solution of **3** (0.15 g, 0.29 mmol) in anhyd CH_2Cl_2 (6 mL) and pyridine (0.6 mL), and the mixture was stirred for 1.5 h at this temperature. Ice-cold water (1 mL) was then added, and the mixture was diluted with CH_2Cl_2 (10 mL), washed with water, 5% aq $KHSO_4$, satd aq $NaHCO_3$, and water, dried ($MgSO_4$), and concentrated. The residue was eluted from a column (10 g) of silica gel with 1:1 EtOAc–petroleum ether, and crystallized from the same mixture of solvents to give **4** (129 mg, 75%); mp 209–210 °C; $[\alpha]_D$ +1° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 7.66–7.20 (m, 10 H, Ph), 5.49 (s, 1 H, PhC*H*), 3.98 (ABq, 2 H, COCH_2Cl). Anal. Calcd for $C_{23}H_{21}Cl_4NO_6S$: C, 47.52; H, 3.64; N, 2.41. Found: C, 47.72; H, 3.69; N, 2.49.

Phenyl 4,6-O-benzylidene-2-deoxy-3-O-tert-butyldimethylsilyl-1-thio-2-trichloroacetamido-β-D-galactopyranoside (**5**).—A mixture of **3** (80 mg, 0.16 mmol), imidazole (68 mg, 1 mmol), and *tert*-butyldimethylsilyl chloride (72 mg, 0.48 mmol) in dry DMF (2 mL) was stirred for 2 h at 80 °C, then cooled to 0 °C. Methanol (0.2 mL) was then added, and the mixture was diluted with CH_2Cl_2 (20 mL), washed with water, dried ($MgSO_4$), and concentrated. The residue was eluted from a column (10 g) of silica gel with 10:1 toluene–EtOAc to give amorphous **5** (90 mg, 92%); $[\alpha]_D$ +18° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 7.65–7.15 (m, 10 H, Ph), 5.49 (s, 1 H, PhC*H*), 0.82 (s, 9 H, (CH_3)$_3$C), 0.10 (s, 6 H, CH_3Si). Anal. Calcd for $C_{27}H_{34}Cl_3NO_5SSi$: C, 52.38; H, 5.54; N, 2.26. Found: C, 52.47; H, 5.50; N, 2.10.

Phenyl 3,4,6-tri-O-acetyl-2-deoxy-1-thio-2-trichloroacetamido-β-D-galactopyranoside (**6**).—Acetic anhydride (15 mL) was added at 0 °C to a solution of **2** (2.1 g, 15 mmol) in

pyridine (20 mL), and the mixture was stirred overnight at rt, then concentrated, and evaporated with toluene (3 × 20 mL). Crystallization of the residue from EtOAc–petroleum ether gave **6** (2.45 g, 92%); mp 151–152 °C; $[\alpha]_D$ −10° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 7.52–7.25 (m, 5 H, Ph), 2.10, 2.03, 1.97 (3 s, 9 H, Ac). Anal. Calcd for $C_{20}H_{22}Cl_3NO_8S$: C, 44.30; H, 4.08; N, 2.58. Found: C, 44.30; H, 4.08; N, 2.61.

4-Methoxyphenyl 3,4,6-tri-O-*acetyl-2-deoxy-2-trichloroacetamido-β*-D-*glucopyranoside* (**8**).—A mixture of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranose (**7**) [12] (5.0 g, 10 mmol), 4-methoxyphenol (2.5 g, 20 mmol), and 4 Å powdered molecular sieves (2.0 g) in anhyd CH_2Cl_2 (50 mL) was stirred for 1 h at rt under dry Ar, then cooled to 0 °C. Triflic acid (0.19 mL, 2 mmol) was added, and the mixture was stirred for 1.5 h at 0 °C and 1.5 h at rt. The mixture was then neutralized with solid $NaHCO_3$, diluted with CH_2Cl_2 (100 mL), washed with water, aq 2 M NaOH, and water, dried ($MgSO_4$), and concentrated. The residue was eluted from a column (100 g) of silica gel with 1:1 EtOAc–petroleum ether, and crystallized from the same mixture of solvents to give **8** (4.9 g, 87%); mp 176–177 °C; $[\alpha]_D$ −10° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 6.95–6.70 (m, 4 H, Ph), 3.72 (s, 3 H, OCH_3), 2.10, 2.05, 2.04 (3 s, 9 H, Ac). Anal. Calcd for $C_{21}H_{24}Cl_3NO_{10}$: C, 45.30; H, 4.34; N, 2.51. Found: C, 45.05; H, 4.35; N, 2.46.

4-Methoxyphenyl 2-deoxy-2-trichloroacetamido-β-D-*glucopyranoside* (**9**).—Methanolic NaOMe (0.1 M, 10 mL) was added to a solution of **8** (2.0 g, 3.6 mmol) in dry MeOH (30 mL), and the mixture was stirred for 2 h at rt, and was then deionized with Amberlite IR-120 (H^+) resin, filtered, and concentrated to give **9** as a white solid (1.52 g, 98%); mp 197–198 °C (from MeOH); $[\alpha]_D$ −5° (*c* 1, MeOH); ^1H NMR ($(CD_3)_2SO$): carbohydrate ring protons (see Table 2); 6.90 (m, 4 H, Ph), 5.15 (d, 1 H, O*H*), 5.12 (d, 1 H, O*H*), 4.61 (t, 1 H, *J* 6.0 Hz, *H*O-6), 3.63 (s, 3 H, OCH_3). Anal. Calcd for $C_{15}H_{18}Cl_3NO_7$: C, 41.83; H, 4.21; N, 3.25. Found: C, 42.08; H, 4.26; N, 3.27.

4-Methoxyphenyl 2-deoxy-3,6-di-O-*pivaloyl-2-trichloroacetamido-β*-D-*glucopyranoside* (**10a**) *and 4-methoxyphenyl 2-deoxy-4,6-di*-O-*pivaloyl-2-trichloroacetamido-β*-D-*glucopyranoside* (**10b**).—Pivaloyl chloride (2.0 mL, 15.6 mmol) was added dropwise at 0 °C to a solution of **9** (1.15 g, 2.6 mmol) in dry pyridine (80 mL), and the mixture was stirred for 5 h at rt, then diluted with CH_2Cl_2 (100 mL), washed with water, 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 to give first **10b** (0.14 g, 9%); mp 199–200 °C (from EtOAc–hexanes); $[\alpha]_D$ −2° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 6.85 (m, 4 H, Ph), 3.73 (s 3 H, OCH_3), 2.98 (d, 1 H, *J* 5.0 Hz, *H*O-3), 1.25, 1.15 (2 s, 18 H, (CH_3)$_3$C). Anal. Calcd for $C_{25}H_{34}Cl_3NO_9$: C, 50.13; H, 5.89; N, 2.34. Found: C, 50.23; H, 5.93; N, 2.34.

Next eluted was **10a** (1.38 g, 89%); mp 192–193 °C (from EtOAc–hexanes); $[\alpha]_D$ −23° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 6.82 (m, 4 H, Ph), 3.72 (s, 3 H, OCH_3), 3.30 (d, 1 H, *J* 6.0 Hz, *H*O-4), 1.25, 1.10 (2 s, 18 H, (CH_3)$_3$C). Anal. Calcd for $C_{25}H_{34}Cl_3NO_9$: C, 50.13; H, 5.89; N, 2.34. Found: C, 49.95; H, 5.81; N, 2.26.

4-Methoxyphenyl 2-deoxy-2-trichloroacetamido-β-D-*galactopyranoside* (**11**).—Triflic anhydride (0.24 mL, 1.4 mmol) was added dropwise at −15 °C to a solution of **10a** (0.6 g, 1 mmol) in dry 1,2-dichloroethane (10 mL) and dry pyridine (0.4 mL), and the mixture was stirred for 3 h at this temperature. Water (1 mL) was then added, and the mixture was stirred for 1.5 h at 85 °C, then cooled, diluted with CH_2Cl_2 (50 mL), washed with water, cold 5% aq HCl, satd aq $NaHCO_3$, and water, dried ($MgSO_4$), and concentrated. A solution of the residue in 2:1 petroleum ether–EtOAc was filtered through a pad (2 × 3 cm) of silica gel, and concentrated to give a mixture of 4,6- and 3,4-di-*O*-pivaloyl-D-*galacto* analogues of **10a** (572 mg, 95%) in a 12:1 ratio (integrated ^1H NMR).

A solution of the above isolated intermediates in MeOH (10 mL) was treated overnight at rt with methanolic NaOMe (1 M, 1 mL),

then deionized with Amberlite IR-120 (H^+) resin, filtered, and concentrated to give **11** as a white solid (406 mg, 94% from **10a**); mp 176–177 °C (from EtOAc–petroleum ether); $[\alpha]_D$ +7° (*c* 1, MeOH); ^{1}H NMR ($(CD_3)_2SO$): carbohydrate ring protons (see Table 2); 6.82 (m, 4 H, Ph), 4.82 (d, 1 H, *J* 6.0 Hz, O*H*), 4.71 (d, 1 H, *J* 4.0 Hz, O*H*), 4.68 (t, 1 H, *J* 5.0 Hz, *H*O-6), 3.63 (s, 3 H, OCH_3). Anal. Calcd for $C_{15}H_{18}Cl_3NO_7$: C, 41.83; H, 4.21; N, 3.25. Found: C, 41.75; H, 4.32; N, 3.17.

*4-Methoxyphenyl 4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-*D*-galactopyranoside* (**12**).—Compound **11** (1.1 g, 2.5 mmol) was treated as described for the preparation of **3** to give **12** (1.12 g, 85%); mp 223–224 °C (from EtOH); $[\alpha]_D$ −11° (*c* 1, pyridine); ^{1}H NMR ($(CD_3)_2SO$): carbohydrate ring protons (see Table 2); 7.50–6.80 (m, 9 H, Ph), 5.60 (s, 1 H, PhC*H*), 5.18 (d, 1 H, *J* 7.0 Hz, *H*O-3), 3.62 (s, 3 H, OCH_3). Anal. Calcd for $C_{22}H_{22}Cl_3NO_7$: C, 50.93; H, 4.27; N, 2.70. Found: C, 51.12; H, 4.33; N, 2.77.

*4-Methoxyphenyl 4,6-*O*-benzylidene-3-*O*-chloroacetyl-2-deoxy-2-trichloroacetamido-β-*D*-galactopyranoside* (**13**).—Compound **12** (1.85 g, 3.5 mmol) was treated as described for the preparation of **4**. The residue was eluted from a column (50 g) of silica gel with 1:1 EtOAc–petroleum ether to give amorphous **13** (1.9 g, 90%); $[\alpha]_D$ +14° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 7.50–6.80 (m, 9 H, Ph), 5.54 (s, 1 H, PhC*H*), 4.07 (ABq, 2 H, COCH_2Cl), 3.72 (s, 3 H, OCH_3). Anal. Calcd for $C_{24}H_{23}Cl_4NO_8$: C, 48.43; H, 3.89; N, 2.35. Found: C, 48.21; H, 3.95; N, 2.41.

*4,6-*O*-Benzylidene-3-*O*-chloroacetyl-2-deoxy-2-trichloroacetamido-1-*O*-trichloroacetimidoyl-α-*D*-galactopyranose* (**14**).—A mixture of **13** (1.0 g, 1.68 mmol) and ceric ammonium nitrate (7.0 g, 12.7 mmol) in 1:1.5:1 toluene–MeCN–water (52 mL) was vigorously stirred for 1 h at rt. The mixture was then diluted with EtOAc (150 mL), washed with water, brine, and water, dried ($MgSO_4$), and concentrated. The residue was eluted from a column (50 g) of silica gel with 1:1 EtOAc–petroleum ether to give the corresponding free hemiacetal (0.65 g, 71%).

A mixture of the above isolated hemiacetal, CCl_3CN (1.3 mL, 13 mmol), and DBU (40 μL, 0.25 mmol) in anhyd CH_2Cl_2 (6 mL) was stirred for 1 h at rt, then concentrated. The residue was eluted from a column (50 g) of silica gel with 2:1 petroleum ether–EtOAc containing 0.1% of Et_3N, and crystallized from EtOAc–hexanes to give **14** (0.65 g, 61% from **13**); mp 140–141 °C; $[\alpha]_D$ +113° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 8.80 (s, 1 H, C=N*H*), 7.40 (m, 5 H, Ph), 5.57 (s, 1 H, PhC*H*), 4.10 (ABq, 2 H, COCH_2Cl). Anal. Calcd for $C_{19}H_{17}Cl_7N_2O_5$: C, 36.02; H, 2.70; N, 4.42. Found: C, 35.82; H, 2.81; N, 4.21.

*4-Methoxyphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-β-*D*-galactopyranoside* (**15**).—A solution of **11** (988 mg, 2.29 mmol) in pyridine (10 mL) and Ac_2O (5 mL) was stirred overnight at rt, then concentrated, evaporated with toluene (3 × 10 mL), and crystallized from EtOAc–hexanes to give **15** (1.09 g, 85%); mp 145–146 °C; $[\alpha]_D$ −10° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 6.80 (m, 4 H, Ph), 3.73 (s, 3 H, OCH_3), 2.15, 2.05, 2.01 (3 s, 9 H, Ac). Anal. Calcd for $C_{21}H_{24}Cl_3NO_{10}$: C, 45.30; H, 4.34; N, 2.51. Found: C, 45.25; H, 4.26; N, 2.60.

*3,4,6-Tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-1-*O*-trichloroacetimidoyl-α-*D*-galactopyranose* (**16**).—Compound **15** (595 mg, 1 mmol) was treated as described for the preparation of **14**. The residue was eluted from a column (25 g) of silica gel with 2:1 petroleum ether–EtOAc containing 0.1% of Et_3N, and crystallized from EtOAc–hexanes to give **16** (416 mg, 70%); mp 89–90 °C, lit. 91–92 °C [14]; $[\alpha]_D$ +80° (*c* 1, $CHCl_3$), lit. +81° [14]; ^{13}C NMR ($CDCl_3$): δ 171.29, 170.11, 169.82, 162.02, 159.90 (C=O, C=N), 94.20 (C-1), 91.67 (CCl_3), 69.93, 69.28, 67.58, 66.71 (C-3, C-4, C-5, C-6), 49.61 (C-2), 20.49, 20.47, 20.43 (CO*C*H_3).

*Methyl 4,6-*O*-benzylidene-3-*O*-chloroacetyl-2-deoxy-2-trichloroacetamido-β-*D*-galactopyranoside* (**17**).—A mixture of **4** (50 mg, 86 μmol), NIS (25 mg, 115 μmol), 3 Å powdered molecular sieves (50 mg), and anhyd MeOH (35 μL, 0.86 mmol) in anhyd CH_2Cl_2 (1.5 mL) was stirred for 1 h at rt under dry Ar, then

cooled to 0 °C. A solution of Me_3SiOTf in toluene (1 M, 13 μL) was added, and the mixture was stirred for 1 h at 0 °C. Triethylamine (25 μL) was added, and the mixture was filtered, and concentrated. The residue was eluted from a column (5 g) of silica gel with 1:1 EtOAc–petroleum ether, and crystallized from the same mixture of solvents to give **17** (32 mg, 74%); mp 203–204 °C; $[\alpha]_D$ +34° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 7.40 (m, 5 H, Ph), 5.51 (s, 1 H, PhC*H*), 4.02 (ABq, 2 H, COCH_2Cl), 3.52 (s, 3 H, OCH_3). Anal. Calcd for $C_{18}H_{19}Cl_4NO_7$: C, 42.97; H, 3.80; N, 2.78. Found: C, 43.11; H, 4.02; N, 2.80.

Methyl 3,4,6-tri-O-acetyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranoside (**18**). —A mixture of **16** (238 mg, 0.4 mmol), 3 Å powdered molecular sieves (200 mg), and anhyd MeOH (0.16 mL, 4 mmol) in anhyd CH_2Cl_2 (3 mL) was stirred for 1 h at rt under dry Ar. A solution of Me_3SiOTf in toluene (1 M, 58 μL) was added, and the mixture was stirred for 1 h at rt. Triethylamine (0.1 mL) was added, and the mixture was filtered, and concentrated. The residue was eluted from a column (10 g) of silica gel with 5:4 petroleum ether–EtOAc to give **18** (175 mg, 94%); mp 122–123 °C (from EtOAc–hexanes); $[\alpha]_D$ +16° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 3.49 (s, 3 H, OCH_3), 2.15, 2.01, 1.95 (3 s, 9 H, Ac). Anal. Calcd for $C_{15}H_{20}Cl_3NO_9$: C, 38.77; H, 4.34; N, 3.01. Found: C, 38.63; H, 4.31; N, 3.05.

Methyl (4,6-O-benzylidene-3-O-chloroacetyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranosyl)-(1→4)-(4-methoxyphenyl 2,3-di-O-benzoyl-β-D-glucopyranosid)uronate (**21**) *and methyl (4,6-O-benzylidene-3-O-chloroacetyl-2-deoxy-2-trichloroacetamido-α-D-galactopyranosyl)-(1→4)-(4-methoxyphenyl 2,3-di-O-benzoyl-β-D-glucopyranosid)uronate* (**25**).—A mixture of **4** (76 mg, 0.13 mmol), methyl (4-methoxyphenyl 2,3-di-*O*-benzoyl-β-D-glucopyranosid)uronate (**20**) [10] (69 mg, 0.13 mmol), NIS (40 mg), and 4 Å powdered molecular sieves (100 mg) in anhyd CH_2Cl_2 (1.5 mL) was stirred for 1 h at rt under dry Ar. A solution of Me_3SiOTf in toluene (1 M, 16 μL) was added, and the mixture was stirred for 1 h. Triethylamine (25 μL) was added, and the mixture was filtered, and concentrated. The residue was eluted from a column (10 g) of silica gel with 6:1 toluene–EtOAc to give first **21** (65 mg, 50%); mp 175–176 °C (from EtOAc–hexanes); $[\alpha]_D$ +18° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 3); 8.0–6.75 (m, 19 H, Ph), 5.25 (s, 1 H, PhC*H*), 3.97 (ABq, 2 H, COCH_2Cl), 3.71 (s, 6 H, COOCH_3, OCH_3). Anal. Calcd for $C_{45}H_{41}Cl_4NO_{16}$: C, 54.34; H, 4.25; N, 1.41. Found: C, 54.04; H, 4.27; N, 1.30.

Next eluted was **25** (25 mg, 15%); $[\alpha]_D$ +93° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 3); 7.95–6.85 (m, 19 H, Ph), 5.53 (s, 1 H, PhC*H*), 4.05 (ABq, 2 H, COCH_2Cl), 3.75 (s, 6 H, COOCH_3, OCH_3). Anal. Calcd for $C_{45}H_{41}Cl_4NO_{16}$: C, 54.34; H, 4.25; N, 1.41. Found: C, 54.12; N, 4.32; N, 1.29.

Methyl (3,4,6-tri-O-acetyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranosyl)-(1→4)-(4-methoxyphenyl 2,3-di-O-benzoyl-β-D-glucopyranosid)uronate (**22**).—A mixture of **6** (408 mg, 0.75 mmol) and **20** (340 mg, 0.65 mmol) was treated as described for the preparation of **21**. The residue was eluted from a column (40 g) of silica gel with 6:1 toluene–EtOAc to give **22** (470 mg, 77%); mp 128–129 °C (from EtOAc–hexanes); $[\alpha]_D$ −10° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 3); 8.0–6.82 (m, 14 H, Ph), 3.72, 3.71 (2 s, 6 H, COOCH_3, OCH_3), 1.98, 1.95, 1.92 (3 s, 9 H, Ac). Anal. Calcd for $C_{42}H_{42}Cl_3NO_{18}$: C, 52.81; H, 4.43; N, 1.43. Found: C, 52.64; H, 4.49; N, 1.53.

Methyl (3,4,6-tri-O-acetyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranosyl)-(1→4)-(methyl 2,3-di-O-benzoyl-β-D-glucopyranosid)uronate (**23**).—A mixture of **6** (0.4 g, 0.74 mmol) and methyl (methyl 2,3-di-*O*-benzoyl-β-D-glucopyranosid)uronate (**19**) [9] (276 mg, 0.64 mmol) was treated as described for the preparation of **21**. The residue was eluted from a column (50 g) of silica gel with 3:1 toluene–EtOAc to give **23** (421 mg, 76%); mp 120–121 °C (from EtOAc–hexanes); $[\alpha]_D$ −5° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 3); 8.0–7.10 (m, 10 H, Ph), 3.80 (s, 3 H, COOCH_3), 3.49 (s, 3 H, OCH_3), 2.10, 2.07, 2.05 (3 s, 9 H, Ac).

Anal. Calcd for $C_{36}H_{38}Cl_3NO_{17}$: C, 50.10; H, 4.41; N, 1.62. Found: C, 50.00; H, 4.54; N, 1.49.

*Methyl (4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-*D*-galactopyranosyl)-(1→4)-(methyl 2,3-di-*O*-benzoyl-β-*D*-glucopyranosid)uronate* (**24**).—A solution of AcCl (0.2 mL) in anhyd MeOH (5 mL) was added to a solution of **23** (422 mg, 0.5 mmol) in anhyd CH_2Cl_2 (5 mL), and the mixture was stirred for 24 h at rt, then deionized with Dowex 1X2-400 (OH^-) resin, filtered, concentrated, and dried, to give the corresponding triol (360 mg).

The crude residue was treated as described for the preparation of **3**. The residue was eluted from a column (50 g) of silica gel with 1:1 → 3:1 EtOAc–petroleum ether to give **24** (327 mg, 79%); mp 191–192 °C (from EtOAc–hexanes); $[\alpha]_D$ −12° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): carbohydrate ring protons (see Table 3); 8.10–7.0 (m, 15 H, Ph), 5.27 (s, 1 H, PhC*H*), 3.85 (s, 3 H, COOCH_3), 3.50 (s, 3 H, OCH_3), 2.64 (d, 1 H, *J* 10.0 Hz, *H*O-3^{II}). Anal. Calcd for $C_{37}H_{35}Cl_3NO_{14}$: C, 53.93; H, 4.28; N, 1.70. Found: C, 53.97; H, 4.37; N, 1.56.

*2-Trichloromethyl-4,5-dihydro-(4,6-*O*-benzylidene-1,2-dideoxy-3-*O*-tert-butyldimethylsilyl-α-*D*-galactopyranoso)[2,1-d]-1,3-oxazole* (**27**).—A mixture of **5** (50 mg, 80 μmol), NIS (37 mg, 0.16 mmol), and 4 Å powdered molecular sieves (50 mg) in anhyd CH_2Cl_2 (1.5 mL) was stirred for 1 h at rt under dry Ar. A solution of Me_3SiOTf in toluene (1 M, 25 μL) was added, and the mixture was stirred for 10 min. Triethylamine (30 μL) was added, and the mixture was filtered, and concentrated. The residue was eluted from a column (5 g) of silica gel with 6:1 petroleum ether–EtOAc containing 0.5% of Et_3N to give unstable **27** (14 mg, 34%); $[\alpha]_D$ +50° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): carbohydrate ring protons (see Table 2); 7.40 (m, 5 H, Ph), 5.59 (s, 1 H, PhC*H*), 0.95 (s, 9 H, (CH_3)$_3$C), 0.15 (s, 6 H, (CH_3)$_2$Si). No satisfactory elemental analysis could be obtained for this unstable derivative.

*Methyl (methyl 2,3,4-tri-*O*-benzoyl-β-*D*-glucopyranosyluronate)-(1→3)-(4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-*D*-galactopyranosyl)-(1→4)-(methyl 2,3-di-*O*-benzoyl-β-*D*-glucopyranosid)uronate* (**29**).—A mixture of **24** (0.2 g, 0.24 mmol), methyl 2,3,4-tri-*O*-benzoyl-1-*O*-trichloroacetimidoyl-α-*D*-glucopyranuronate (**28**) [9] (0.23 g, 0.36 mmol), and 4 Å powdered molecular sieves (0.2 g) in anhyd toluene (10 mL) was stirred for 45 min at rt under dry Ar. A solution of Me_3SiOTf in toluene (1 M, 0.11 mL) was added, and the mixture was stirred for 2 h. Triethylamine (0.25 mL) was added, and the mixture was filtered, and concentrated. The residue was eluted from a column (25 g) of silica gel with 5:1 toluene–EtOAc containing 0.2% of Et_3N to give **29** (274 mg, 85%); mp 215–216 °C (from EtOAc–petroleum ether); $[\alpha]_D$ +14° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): carbohydrate ring protons (see Table 4); 7.95–7.10 (m, 30 H, Ph), 5.32 (s, 1 H, PhC*H*), 3.80, 3.60 (2 s, 6 H, COOCH_3), 3.45 (s, 3 H, OCH_3). Anal. Calcd for $C_{65}H_{58}Cl_3NO_{23}$: C, 58.81; H, 4.40; N, 1.05. Found: C, 58.75; H, 4.38; N, 1.10.

*Methyl (methyl 2,3,4-tri-*O*-benzoyl-β-*D*-glucopyranosyluronate)-(1→3)-(2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-*D*-galactopyranosyl)-(1→4)-(methyl 2,3-di-*O*-benzoyl-β-*D*-glucopyranosid)uronate* (**30**).—A mixture of **29** (1.0 g, 0.75 mmol), Bu_3SnH (1.2 mL, 3.4 mmol), and AIBN (100 mg) in dry benzene (40 mL) and *N*,*N*-dimethylacetamide (2 mL) was stirred for 1 h at rt under a stream of dry Ar, then heated for 2 h at 80 °C, cooled, and concentrated. The residue was stirred with petroleum ether (20 mL) for 1 h at 0 °C, and the precipitate was filtered off, washed with petroleum ether, and crystallized from EtOAc–petroleum ether to give **30** (775 mg, 82%); mp 220–221 °C; $[\alpha]_D$ +14° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): carbohydrate ring protons (see Table 4); 7.93–7.18 (m, 30 H, Ph), 5.27 (s, 1 H, PhC*H*), 3.75, 3.56 (2 s, 6 H, COOCH_3), 3.45 (s, 3 H, OCH_3), 1.70 (s, 3 H, NAc); ISMS: *m*/*z* 1225, $[M+H]^+$. Anal. Calcd for $C_{65}H_{61}NO_{23}$: C, 63.77; H, 5.02; N, 1.14. Found: C, 63.88; H, 4.95; N, 1.10.

*Methyl (methyl 2,3,4-tri-*O*-benzoyl-β-*D*-glucopyranosyluronate)-(1→3)-(2-acetamido-2-deoxy-β-*D*-galactopyranosyl)-(1→4)-(methyl 2,3-di-*O*-benzoyl-β-*D*-glucopyranosid)uronate* (**31**).—A mixture of **30** (0.17 g, 0.14 mmol) and AcOH (5 mL) was stirred at 100 °C.

Water (2 mL) was then added dropwise, and the mixture was stirred for 30 min at 100 °C, cooled, concentrated, evaporated with water (3 × 10 mL), and toluene (2 × 10 mL). The residue was eluted from a column (15 g) of silica gel with 1:1 CH_2Cl_2–EtOAc to give **31** (126 mg, 80%); mp 188–189 °C (from EtOAc–hexanes); $[\alpha]_D$ +12° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): carbohydrate ring protons (see Table 4); 7.95–7.20 (m, 25 H, Ph), 3.71, 3.58 (2 s, 6 H, COOCH_3), 3.45 (s, 3 H, OCH_3), 2.55 (d, 1 H, *J* 3.0 Hz, *H*O-4^{II}), 1.90 (1 H, *H*O-6^{II}), 1.33 (s, 3 H, NAc); ^{13}C ($CDCl_3$): δ 172.37, 167.84, 167.08, 165.65, 165.54, 165.22, 165.18, 164.72 (C=O), 133.61–128.36 (aromatic C), 102.11, 101.51, 98.56 (C-1^I, C-1^{II}, C-1^{III}), 78.05, 77.56, 76.54, 75.61, 74.18, 72.80, 72.35, 71.81, 71.42, 71.26, 69.84 (C-2^I, C-2^{III}, C-3^I, C-3^{III}, C-4^I, C-4^{III}, C-5^I, C-5^{III}, C-3^{II}, C-4^{II}, C-5^{II}), 61.96 (C-6^{II}), 57.38, 54.62 (2 COO*C*H_3, O*C*H_3), 52.99 (C-2^{II}), 22.95 (CO*C*H_3); ISMS: *m*/*z* 1137, $[M+H]^+$. Anal. Calcd for $C_{58}H_{59}NO_{23}\cdot 2\,H_2O$: C, 59.33; H, 5.40; N, 1.19. Found: C, 59.21; H, 5.33; N, 1.18.

*Methyl (methyl 2,3,4-tri-*O*-benzoyl-β-*D*-glucopyranosyluronate)-(1→3)-(sodium 2-acetamido-2-deoxy-6-*O*-sulfonato-β-*D*-galactopyranosyl)-(1→4)-(methyl 2,3-di-*O*-benzoyl-β-*D*-glucopyranosid)uronate* (**32**).—A mixture of **31** (0.25 g, 0.22 mmol) and sulfur trioxide–trimethylamine complex (91 mg, 0.66 mmol) in anhyd DMF (9 mL) was stirred for 4 h at 50 °C under dry Ar, then cooled. Methanol (0.25 mL) was then added, and the mixture was concentrated. The residue was eluted from a column (20 g) of silica gel with 8:1 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 **32** (196 mg, 72%); mp 196–198 °C (from $CHCl_3$–petroleum ether); $[\alpha]_D$ −3° (*c* 1, MeOH); ^1H NMR (CD_3OD): carbohydrate ring protons (see Table 4); 8.0–7.15 (m, 25 H, Ph), 3.89, 3.62 (2 s, 6 H, COO*C*H_3), 3.41 (s, 3 H, O*C*H_3), 1.32 (s, 3 H, NAc); ^{13}C (CD_3OD): δ 174.14, 170.46, 170.36, 168.13, 167.56, 167.40, 167.34, 167.23 (C=O), 135.49–130.20 (aromatic C), 103.88, 103.57, 103.28 (C-1^I, C-1^{II}, C-1^{III}), 82.65, 78.19, 76.36, 74.94, 74.62, 74.46, 74.02, 73.68, 72.14 (C-2^I, C-2^{III}, C-3^I, C-3^{III}, C-4^I, C-4^{III}, C-5^I, C-5^{III}, C-3^{II}, C-4^{II}, C-5^{II}), 68.70 (C-6^{II}), 58.21, 54.49, 54.38 (COO*C*H_3, O*C*H_3), 52.98 (C-2^{II}), 23.40 (CO*C*H_3). Anal. Calcd for $C_{58}H_{52}NNaO_{26}S\cdot H_2O$: C, 55.64; H, 4.35; N, 1.12. Found: C, 55.32; H, 4.61; N, 1.05.

*Sodium (sodium β-*D*-glucopyranosyluronate)-(1→3)-(sodium 2-acetamido-2-deoxy-6-*O*-sulfonato-β-*D*-galactopyranosyl)-(1→4)-(methyl β-*D*-glucopyranosid)uronate* (**1**).—A solution of **32** (267 mg, 0.22 mmol) in 7:3 THF–water (10 mL) was treated at −5 °C with 30% H_2O_2 (1.1 mL) and LiOH (1 M, 2.2 mL), and the mixture was stirred for 2 h at this temperature and 16 h at rt, then cooled to 0 °C. Methanol (8 mL) and NaOH (4 M, 1.4 mL) were added, and the mixture was stirred for 8 h at rt, then diluted with water (3 mL), and treated with Amberlite IR-120 (H^+) resin to pH 3 (pH meter control), filtered, and concentrated. The residue was stirred for 1 h at 0 °C with abs EtOH (10 mL), and the solids were filtered off and washed with cold abs EtOH. The residue was eluted from a column (12 g) of silica gel with 4:3:3 EtOAc–MeOH–water, then taken up in water (5 mL). The pH of the solution was brought to 6.5 with diluted NaOH (pH meter control), and the solution was filtered, and freeze-dried to give **1** as an amorphous hygroscopic powder (130 mg, 81%); $[\alpha]_D$ −17° (*c* 1, H_2O); ^1H NMR (D_2O, internal H_2O): carbohydrate ring protons (see Table 4); 3.43 (s, 3 H, OCH_3), 1.98 (s 3 H, NAc); ^{13}C (D_2O, internal acetone): δ 176.01, 175.32, 174.85 (C=O), 104.45 (C-1^{III}), 103.65 (C-1^{II}) 101.72 (C-1^I), 81.70 (C-4^I), 80.29 (C-3^{II}), 76.95, 76.45 (C-5^I, C-5^{III}), 75.65 (C-3^{III}), 74.45 (C-5^{II}), 73.06 (C-3^I), 72.97, 72.87 (C-2^I, C-2^{III}), 67.89, 67.70 (C-4^{II}, C-6^{II}), 57.60 (O*C*H_3), 51.23 (C-2^{II}), 22.88 (CO*C*H_3). Anal. Calcd for $C_{21}H_{30}NNa_3O_{21}S$: C, 34.29; H, 4.12; N, 1.90. Found: C, 33.91; H, 4.32; N, 1.79.

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