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Synthesis of glycosyl(thio)ureido sugars via carbodiimides and their conformational behaviour in water

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Abstract

The preparation of sugar ureas and thioureas by nucleophilic addition of water or hydrogen sulfide, respectively, to sugar-derived carbodiimides has been examined. Acetic acid efficiently catalysed the formation of ureas, whereas silica gel was found to be a more convenient catalyst in the case of the thioxo analogues. The procedures have been exploited in the development of an amine- and isocyanate-free synthesis of urea- and thiourea-tethered pseudooligosaccharides via the corresponding glycosylcarbodiimido sugars. The fully unprotected compounds adopted, preferentially, the (*Z*,*Z*) configuration at the pseudoamide bonds in water solution.

Keywords: Sugar ureas; Sugar thioureas; Sugar carbodiimides; Oligosaccharide mimics; Pseudooligosaccharides

1. Introduction

Glycosylureido sugars are found in nature as constituents of the glycocynnamoylspermidines [1,2], a unique group of broad-spectrum aminoglycoside antibiotics isolated from *Nocardia* bacteria [3,4]. Although this family of pseudooligosaccharides, having a urea intersaccharide bridge as the main structural feature, have been known for more than 20 years, the chemical synthesis of structurally related fragments has never been reported before, probably because of the lack of suitable synthetic methodologies compatible with the polyfunctionality of carbohydrates. The recorded examples of synthetic compounds having two monosaccharide frameworks joined through a urea bridge are limited to symmetric *N*,*N*′-bis(glycosyl) derivatives [5].

Thiourea-linked pseudooligosaccharides, both symmetric and unsymmetric, have been previously prepared by the coupling reaction of sugar isothiocyanates and amino sugars [6–18]. A parallel synthetic scheme using isocyanates is, however, problematic. First, the synthesis of isocyanates involves highly toxic phosgene or phosgene substitutes and they are themselves hazardous to work with [19]. Secondly, whereas isothiocyanates exhibit a total chemoselectivity towards amino groups in the presence of hydroxyl groups [14–18], using

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the much more reactive isocyanates implies *O*-selective protection at the amino sugar counterpart. If acyl protecting groups are required, inter- and intra-molecular O → N acyl migration may seriously impede the final yield, a drawback already encountered in the thioxo series [7,8,13].

We now report a synthesis of glycosylureido and glycosylthioureido sugars that avoids the use of sugar-derived isocyanates and amines using sugar carbodiimides as the key intermediates. The methodology is compatible with acyl and acetal *O*-protecting groups. A conformational study of the fully unprotected (thio)urea-tethered pseudooligosaccharides in aqueous solution is included.

2. Results and discussion

We have previously shown [20,21] that the reaction of O-protected azidodeoxysugars **1**–**3** with isothiocyanates in the presence of triphenylphosphine provides an efficient access to unsymmetric sugar carbodiimides, probably through transient triazenophosphorane intermediates [21]. Further transformation of the carbodiimide adducts into the corresponding ureas was first optimised on the methylcarbodiimido sugars **4a**–**6a**. Addition of water to a solution of the carbodiimides in toluene in the presence of acetic acid resulted in clean reactions to give **7a**–**9a** in quantitative yield. The same protocol applied to the pseudodi- and pseudotrisaccharides **4b**,**c**–**6b**,**c** afforded the per-O-protected *N*′-(β-D-glucopyranosyl)- and *N*′-(β-cellobiosyl)ureido derivatives (**7b**–**9b** and **7c**–**9c**, respectively). Completion of the reaction was confirmed by the disappearance of the ν_{NCN} absorption (2150–2135 cm^{-1}) in the IR spectra of the reaction mixtures.

Since a main concern during the isolation of the carbodiimide precursors is the formation of ureas by the action of moisture [21], the one-pot transformation of azides into ureas by reaction with the corresponding triphenyl phosphine–isothiocyanate system and in situ addition of water–acetic acid to the preformed carbodimide was found advantageous. Using this procedure, overall yields above 85% were achieved for the **1**–**3** → **7a**,**b**,**c**–**9a**,**b**,**c** conversion. Sequential Zemplén deacetylation and trifluoroacetic acid-catalysed acetal hydrolysis, when appropriate, afforded the fully unprotected target derivatives **10a**,**d**,**e**–**12a**,**d**,**e**. The IR, MS, microanalytical, ^1H (Table 1) and ^{13}C NMR data (Table 2) fully agreed with the proposed structures (Scheme 1).

Our next interest was to implement this strategy for the access to the thioxo analogues. No reaction was observed after bubbling dry hydrogen sulfide through a solution of the carbodiimides **4a**–**6a** in toluene, whereas addition of acetic acid resulted in incomplete conversions after prolonged reaction times. Moreover, formation of the corresponding ureas became a significant side reaction under these conditions.

The observation that silica gel was able to catalyse water addition to the carbodiimide group during TLC or column chromatography separations prompted us to check it as a catalyst for the analogous addition of hydrogen sulfide. When the reaction was carried out at 0 °C in the presence of activated silica gel, total consumption of the starting material **4a**–**6a** occurred after 5–6 h, with isolated yields on the target thioureas **13a**–**15a** ranging from 86 to 90%. The methodology was further validated by the preparation of the (1 → 6)-thiourea-linked pseudodisaccharides **13b**–**15b** from the corresponding glucosylcarbodiimido sugars **4b**–**6b**. After the deprotection steps, the fully unprotected 6-deoxy-6-methylthioureido sugars (**16a**–**18a**) and the known [17] 6-deoxy-6-[*N*′-(β-D-glucopyranosyl)]thioureido derivatives (**16d**–**18d**) were obtained in high yield (Scheme 2).

The ^1H (Table 1) and ^{13}C NMR spectra (Table 2) of compounds **13a**,**b**–**18a**,**b** recorded at 300 K exhibited broad signals indicative of the existence of slow rotating processes around the NH–C(=S) bonds. A better resolution was achieved at 313 K. The presence of the thiourea functional group was confirmed by the characteristic ^{13}C resonance of the thiocarbonyl group ($\delta_{C=S}$ 184–179.1 ppm), whereas the $^4C_1$ (D) conformation and β-anomeric configuration of the glycosylthioureido substituent was evident from the $^3J_{H,H}$ values around the pyranose ring.

Table 1
^{1}H NMR data for the new urea and thiourea derivatives **7a**–**c** to **9a**–**c**, **10a**,**d**,**e** to **12a**,**d**,**e**, **13a**,**b** to **15a**,**b** and **16a**–**18a**

	Unit	Chemical shifts (δ)						
		H-1	H-2	H-3	H-4	H-5	H-6a	H-6b
7a [a,c]	I	5.51d	4.30dd	4.59dd	4.23dd	3.92ddd	3.56dd	3.18dd
7b [a,c]	I	5.51d	4.31dd	4.60dd	4.19dd	3.85m	3.60bd	3.20dd
	II	5.16t	4.91t	5.30t	5.06t	3.82ddd	4.29dd	4.07dd
7c [b,c]	I	5.48d	4.29dd	4.58dd	4.16dd	3.82bd	3.54m	3.17bdd
	II	5.05t	4.79t	5.25t	3.53t	3.68ddd	4.43dd	4.09dd
	III	4.48d	4.91t	5.12t	5.05t	3.63ddd	4.35dd	4.02dd
8a [b,c]	I	5.97d	4.55d	4.17d	4.25d	3.60ddd	3.53bd	3.26dd
8b [b,c]	I	5.91d	4.49d	4.14d	4.15dd	3.54m	3.45m	3.17m
	II	5.10t	4.82t	5.23t	4.98t	3.76ddd	4.24dd	4.00dd
8c [b,c]	I	5.97d	4.55d	4.18d	4.20dd	3.60td	3.51bs	3.24ddd
	II	5.07t	4.80t	5.25dd	3.74t	3.69ddd	4.44dd	4.12dd
	III	4.49d	4.91dd	5.13t	5.06t	3.65ddd	4.36dd	4.02dd
9a [a,c]	I	4.90d	4.83dd	5.46t	4.91t	3.86m	3.48bd	3.29dd
9b [b,c]	I	4.89d	4.78dd	5.42t	4.81t	3.82dd	3.46bdd	3.24bdd
	II	5.12t	4.86t	5.28t	5.0t	3.78ddd	4.28dd	4.04dd
9c [b,c]	I	4.80d	4.79dd	5.44t	4.90m	3.83m	3.47m	3.24m
	II	5.05t	4.82t	5.27t	3.75t	3.68ddd	4.43dd	4.11dd
	II	4.49d	4.90m	5.12t	5.06t	3.64ddd	4.36dd	4.02dd
10a [b,d]	Iα	5.07d	3.61dd	3.67dd	3.77bd	3.90ddd	3.20dd	3.09dd
	Iβ	4.38d	3.31dd	3.43dd	3.71d	3.51ddd	3.22dd	3.12dd
10d [b,d]	Iα	5.10d	3.65dd	3.70dd	3.82d	3.96m	3.28m	3.16m
	Iβ	4.41d	3.34t	3.49dd	3.76d	3.57m	3.31dd	3.19m
	II	4.69d	3.25t	3.40t	3.24t	3.36m	3.74bd	3.59m
10e [a,c]	Iα	5.63d	4.19dd	4.23dd	4.35dd	n.a. [g]	n.a. [g]	n.a. [g]
	Iβ	4.94d	3.89m	4.01dd	4.29d	n.a. [g]	n.a. [g]	n.a. [g]
	II	4.90d	3.72dd	3.849m	3.82t	3.89m	4.30da	4.12dd
	III	5.22d	3.79t	4.07t	4.01t	4.06m	4.32d	4.18da
11a [b,d]	Iα	5.12d	3.44dd	3.61t	3.21t	3.73ddd	3.40dd	3.26dd
	Iβ	4.53d	3.14dd	3.39t	3.22t	3.26m	3.46dd	3.22dd
11d [b,d]	Iα	5.06d	3.38dd	3.55t	3.16t	3.70ddd	3.41dd	3.24dd
	Iβ	4.48d	3.08dd	3.24t	3.16t	3.22m	3.47dd	3.19dd
	II	4.69d	3.23t	3.40t	3.21t	3.35m	3.74bd	3.56dd
11e [a,d]	Iα	5.57d	3.89dd	4.07t	3.647t	3.90m	4.22m	3.76dd
	Iβ	4.95d	3.68t	3.85t	3.60dd	3.83m	3.98da	3.74m
	II	5.22d	3.78t	4.00m		4.06m	3.21da	4.17da
	III	4.89d	3.71dd	3.89t	3.80t	3.87m	4.29da	4.11dd
12a [b,d]	I	4.62d	3.38dd	3.49t	3.15t	3.47ddd	3.40dd	3.12dd
12d [b,d]	I	4.66d	3.22dd	3.51t	3.17t	3.52m	3.47dd	3.42dd
	II	4.70d	3.26t	3.40t	3.21t	3.36ddd	3.74dd	3.57dd
12e [b,d]	I	4.64d	3.41dd	3.51t	3.15d	3.44ddd	3.42dd	3.21dd
	II	4.37d	3.18dd	3.36t	3.28t	3.34m	3.78bd	3.59dd
	III	4.72d	3.25t	3.51t	3.14dd	3.46m	3.79bd	3.66bdd
13a [a,c,e]	I	5.44d	4.25dd	4.55dd	4.20dd	4.08m	3.90m	3.39ddd

Table 1 (Continued)

	Unit	Chemical shifts (δ)						
		H-1	H-2	H-3	H-4	H-5	H-6a	H-6b
13b [a,c,e]	I	5.50d	4.30dd	4.59dd	4.19dd	3.94m	3.45m	
	II	5.54m	4.96t	5.29t	5.05t	3.83ddd	4.29dd	4.08dd
14a [a,c,e]	I	5.97d	4.56d	4.20d	4.28dd	3.70td	3.76m	3.52ddd
14b [a,c,e]	I	5.97d	4.57d	4.25–4.19m		3.66m	3.49m	
	II	5.65bt	4.94t	5.34t	5.05t	3.84ddd	4.30dd	4.10dd
15a [a,c,e]	I	4.94d	4.83dd	5.48t	4.90t	3.98ddd	3.93ddd	3.59dt
15b [a,c,e]	I	4.94d	4.81dd	5.46t	4.84t	3.94m	3.70–3.30m	
	II	5.72dd	4.96t	5.44t	5.08t	3.83ddd	4.31dd	4.09dd
16a [b,d,e]	Iα	5.43d	3.99dd	4.03dd	4.15bd	4.40bt	3.95m	3.78m
	Iβ	4.75d	3.667dd	3.82dd	4.10bd	4.04m	3.95m	3.78m
17a [b,d,f]	Iα	5.45d	3.77dd	3.94t	3.55t	4.17ddd	3.17sa	
	Iβ	4.86d	3.47dd	3.72t	3.56t	3.80ddd	3.17sa	
18a [b,d,e]	I	5.51d	4.27d	4.38t	4.03t	4.47ddd	4.58dd	4.37dd

		Coupling constants (Hz)						
		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
7a [a,c]	I	5.0	2.4	7.9	1.8	3.7	8.6	14.2
7b [a,c]	I	4.9	2.4	7.8	1.6		9.3	13.7
	II	9.4	9.4	9.4	9.4	4.0	1.9	12.4
7c [b,c]	I	4.9	2.4	7.9	1.5		8.0	12.0
	II	9.6	9.6	9.6	9.6	1.4	4.4	12.1
	III	8.5	8.5	8.5	8.5	4.3	2.1	12.5
8a [b,c]	I	3.6	0	3.8	7.0		6.9	14.2
8b [b,c]	I	3.7	0	4.2				
	II	9.5	9.5	9.5	9.5	4.2	2.0	12.4
8c [b,c]	I	3.7	0	3.9	7.0	3.6	7.0	13.1
	II	9.4	9.4	8.9	8.9	1.8	4.5	12.2
	III	7.8	9.2	9.2	9.2	4.3	2.3	12.4
9a [a,c]	I	3.6	9.7	9.7	9.7		5.6	14.4
9b [b,c]	I	3.5	9.8	9.8	9.8	4.6	6.0	15.1
	II	9.5	9.5	9.5	9.5	4.3	2.0	12.5
9c [b,c]	I	3.6	10.1	10.1				
	II	9.4	9.4	9.4	9.4	1.7	5.6	12.2
	II	8.0	9.3	9.3	9.3	4.3	2.2	12.5
10a [b,d]	Iα	3.8	10.4	3.2	0	5.8	7.8	14.4
	Iβ	8.0	9.7	3.4	0	5.6	7.8	14.4
10d [b,d]	Iα	3.7	9.3	3.2	0			
	Iβ	7.8	7.8	3.1	0	5.8		10.3
	II	9.2	9.2	9.2	9.2			10.5
10e [a,c]	Iα	4.5	10.0	3.9	0			
	Iβ	7.9	9.8	3.9	0			
	II	8.0	7.8	9.0	9.0		5.4	12.4
	III	9.3	9.3	9.3	9.3			12.3

Table 1 (Continued)

	Unit	Coupling constants (H_2)						
		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
11a [b,d]	Iα	3.8	9.6	9.6	9.6	3.5	6.3	14.2
	Iβ	8.0	9.2	9.2	9.2	2.5	6.2	14.4
11d [b,d]	Iα	3.7	9.5	9.5	9.5	2.5	5.4	14.1
	Iβ	8.1	9.2	9.2	9.2	1.8	7.9	14.2
	II	9.1	9.1	9.1	9.1		4.6	12.5
11e [a,d]	Iα	4.2	9.0	9.0	9.0		5.7	14.5
	Iβ	8.1	8.1	8.1	9.2			14.0
	II	9.2	9.2					12.5
	III	8.0	9.0	9.0	9.0		5.5	12.6
12a [b,d]	I	3.8	9.6	9.6	9.6	2.6	7.0	12.6
12d [b,d]	I	3.2	9.3	9.3	9.3	2.7	3.8	14.5
	II	9.3	9.3	9.3	9.3	2.1	5.5	12.3
12e [b,d]	I	3.4	9.2	9.2	10.1	4.5	6.4	14.5
	II	8.0	9.3	9.3	9.3		5.3	12.6
	III	9.3	9.3	9.3	8.2			12.1
13a [a,c,e]	I	5.0	2.4	7.9	1.8		8.2	14.1
13b [a,c,e]	I	5.0	2.3	7.9	1.6			
	II	9.5	9.5	9.5	9.5	4.3	2.0	12.4
14a [a,c,e]	I	3.7	0	4.0	4.4	7.1	7.1	12.7
14b [a,c,e]	I	3.7	0					
	II	9.5	9.5	9.5	9.5	4.4	2.2	12.4
15a [a,c,e]	I	3.7	9.8	9.8	9.8	2.7	5.9	14.5
15b [a,c,e]	I	4.2	9.8	9.8	9.8			
	II	9.4	9.4	9.4	9.4	4.7	2.2	12.4
16a [b,d,e]	Iα	3.7	10.3	3.2	0	6.4	6.4	
	Iβ	7.9	10.0	3.5	0			
17a [b,d,e]	Iα	3.8	9.8	9.8	9.8	6.4	3.0	
	Iβ	8.4	8.8	8.8	8.8	6.6	2.8	
18a [a,d,f]	I	3.7	9.7	9.7	9.7	2.6	6.7	13.7

[a] At 300 MHz.
[b] At 500 MHz.
[c] In $CDCl_3$.
[d] In D_2O.
[e] At 313 K.
[f] At 343 K.
[g] Not assigned.

The efficiency of this methodology to prepare fully acylated derivatives such as **12b**,**c** and **15b** is noteworthy. Previous attempts to obtain **15b** by coupling of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate [7,22] and methyl 2,3,4-tri-*O*-acetyl-6-amino-6-deoxy-α-D-glucopyranoside [23] resulted in extensive acyl migration to the more basic primary amino group.

Conformational data on ureido and thioureido sugars in solution are scarce and limited to O-protected derivatives in organic solvents [8,9,11,13,24–27]. In order to determine the conformational properties of these

Table 2
^{13}C NMR data for the new urea and thiourea derivatives **7a–c** to **9a–c**, **10a**,**d**,**e** to **12a**,**d**,**e**, **13a**,**b** to **15a**,**b** and **16a–18a**

	Unit	Chemical shifts (δ)					
		C-1	C-2	C-3	C-4	C-5	C-6
7a [a,c]	I	96.1	70.5	70.6	71.4	67.1	40.8
7b [a,c]	I	96.1	70.4	70.6	70.9	66.9	40.6
	II	80.1	71.4	72.8	68.1	72.9	61.7
7c [b,c]	I	96.0	70.4	70.6	71.4	67.0	40.6
	II	80.0	70.6	72.3	76.1	73.7	61.8
	III	100.5	71.4	72.8	67.6	72.3	61.4
8a [b,c]	I	106.1	83.7	74.8	80.3	71.4	42.9
8b [b,c]	I	106.3	83.8	74.9	79.9	71.4	42.9
	II	80.5	73.0	73.0	68.3	70.5	61.8
8c [b,c]	I	106.3	83.7	73.9	80.0	71.4	42.5
	II	80.5	72.8	70.7	76.2	74.8	61.8
	III	100.5	71.4	72.3	67.7	71.8	61.5
9a [a,c]	I	96.2	70.2	69.2	69.8	68.1	39.8
9b [b,c]	I	96.6	70.5	69.9	69.3	68.3	40.1
	II	80.2	70.9	72.9	68.0	73.1	61.8
9c [b,c]	I	96.5	70.8	69.1	69.7	67.8	40.3
	II	79.9	70.6	72.2	76.2	73.9	61.8
	II	100.5	71.4	72.8	67.7	71.8	61.4
10a [b,d]	Iα	92.4	69.0	69.2	69.4	68.3	40.4
	Iβ	96.5	71.9	72.8	68.9	73.6	40.4
10d [b,d]	Iα	92.2	68.8	69.2	69.4	68.2	40.0
	Iβ	96.4	71.7	72.6	68.6	73.3	40.0
	II	80.9	76.4	77.0	69.0	71.8	60.5
10e [a,c]	Iα	91.8	68.2	68.6	68.9	67.8	39.6
	Iβ	96.0	71.3	72.2	68.4	72.8	39.6
	II	80.4	72.6	74.6	78.1	75.0	60.1
	III	102.0	71.2	75.4	68.9	75.5	59.4
11a [b,d]	Iα	92.0	71.5	72.5	70.9	70.3	40.7
	Iβ	95.8	74.7	75.3	70.7	74.1	40.7
11d [b,d]	Iα	92.0	71.4	72.4	70.9	70.1	40.4
	Iβ	95.8	74.4	75.3	70.7	74.1	40.4
	II	80.9	76.5	77.0	69.3	71.9	60.6
11e [a,d]	Iα	91.6	71.0	72.0	70.5	69.6	40.1
	Iβ	95.4	74.0	74.6	69.6	73.6	40.1
	II	80.4	72.6	74.9	77.8	75.0	59.4
	III	102.0	71.2	75.4	68.9	75.5	60.1
12a [b,d]	I	99.4	71.3	73.2	70.8	71.6	40.9
12d [b,d]	I	99.2	71.1	73.0	70.3	71.3	40.5
	II	81.1	76.7	77.1	69.5	72.0	60.7
12e [b,d]	I	99.1	71.0	72.8	70.2	71.2	40.4
	II	80.9	73.1	75.0	78.2	75.4	59.9
	III	102.5	71.7	75.8	69.4	75.9	60.5
13a [a,c,e]	I	96.1	70.4[c]	70.5[c]	71.4	66.4	44.8
13b [a,c,e]	I	96.1	70.4	70.5	70.5	66.2	45.2
	II	82.6	71.2	72.7	68.1	73.9	61.6
14a [a,c,e]	I	106.3	83.9	74.9	80.0	71.3	46.8
14b [a,c,e]	I	106.4	83.9	75.0	80.3	72.7	46.7
	II	83.1	71.2	72.7	68.3	73.3	61.6
15a [a,c,e]	I	96.8	70.9	69.7	69.8	68.2	44.8
15b [a,c,e]	I	96.6	70.6	69.6	69.5	68.4	44.5
	II	82.8	70.8	72.8	67.7	73.3	61.7
16a [b,d,e]	Iα	92.5	68.4	69.1	69.5	68.5	44.5
	Iβ	96.6	71.9	72.7	68.9	73.0	44.5
17a [b,d,e]	Iα	91.8	71.2	72.2	71.0	69.7	44.6
	Iβ	95.6	73.9	75.1	70.6	73.9	44.6
18a [b,d,e]	I	102.4	74.4	76.2	73.1	74.4	48.0

[a] At 75.5 MHz.
[b] At 125.5 MHz.
[c] In $CDCl_3$.
[d] In D_2O.
[e] At 313 K.

families of pseudooligosaccharides in water solution, NMR experiments for the methyl 6-deoxy-6-[*N*′-β-D-glucopyranosyl(thio)ureido]-α-D-glucopyranosides (**15d** and **18d**) were recorded in 9:1 H_2O–D_2O mixtures. A NOESY spectrum at 10 °C showed intense-cross-peaks for the NH/NH′ and NH′/H-2 resonances. These data strongly support a major (*Z*,*Z*) configuration at the pseudoamide bonds and the anti relative disposition between the H-1 and N′H protons (Fig. 1(A)).

The anti-*Z* conformational arrangement at the glycosidic segment is in agreement with previous data on carbohydrate derivatives bearing a pseudoamide group at a secondary position, both in organic solvents [8,9,11] and in the solid state [28,29]. A similar confirmation has also been recently reported for the *N*-glycosylamide segment of (1→6)-linked saccharopeptides [30]. In contrast, the *E*-disposition has been shown to be favoured for NH–(C=S) bonds located at the primary C-6 position in chloroform-*d* solution, due to intramolecular hydrogen-bonding stabilisation [11,13,22,24]. The strong preference for the 1,3-parallel disposition of the (thio)urea NH protons in water is, probably, a consequence of the formation of three-centred intermolecu-

lar hydrogen bonds, with the oxygen atom of a water molecule acting as acceptor (Fig. 1(B)). Related supramolecular structures involving urea or thiourea derivatives and oxygen ligands have previously been characterised [31,32].

In summary, we have developed a mild and efficient method to prepare glycosyl-(thio)ureido sugars via carbodiimide intermediates. The synthetic scheme involves readily available azidodeoxy sugars [33] and glycosyl isothiocyanates [34,35] as starting materials, avoiding hazardous isocyanate and amine reagents. The method is particularly attractive for the preparation of acylated derivatives, since the O→N acyl migration problems associated to acylated amino sugars are prevented. The fully unprotected pseudooligosaccharides were found to be stable and to exist in the major (*Z*,*Z*) rotameric form in water solution.

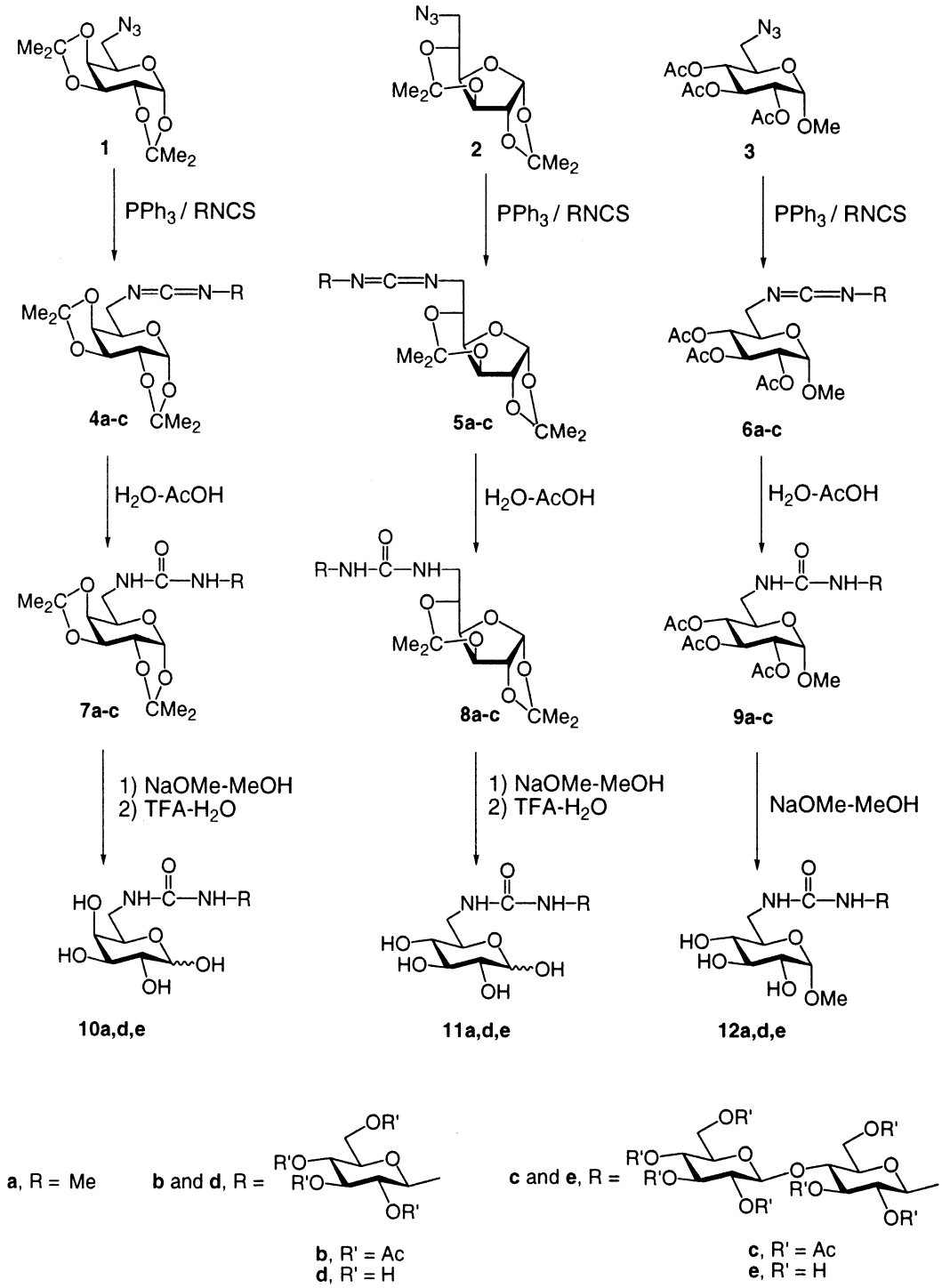
3. Experimental

General methods.—A Perkin–Elmer model 141 MC polarimeter and 1 dm tubes were used for measurement of specific rotations. IR spectra were recorded on a Bomem Michelson MB-120 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at 500 (125.7), 400 (100.6) and 300 (75.5) MHz with, respectively, Bruker 500 AMX and DRX, 400 DRX and 300 AMX spectrometers. Chemical shifts are given in ppm with reference to Me_4Si as internal standard. Assignments of ^{1}H and ^{13}C signals were assisted by 2D COSY, 1D TOCSY and HETCOR experiments. 2D NOESY experiments were carried out at 500 MHz and 283 K, with a mixing time of 400 ms. FAB mass spectra were obtained with a Kratos MS-80 RFA instrument. The operating conditions were the following: the primary beam consisted of Xe atoms with a maximum energy of 8 keV; the samples were dissolved in *m*-nitrobenzyl alcohol, and the positive ions were separated and accelerated over a potential of 7 kV; NaI was added as cationising agent. TLC was performed with E. Merck precoated TLC plates, Silica Gel $30F_{245}$, with visualisation by UV light and by charring with 10% H_2SO_4. Column chromatography was carried out with Silica Gel 60 (E. Merck, 230–400 mesh). Deacetylations were carried out using the Zemplén technique (catalytic NaOMe in MeOH). Hydrolysis of acetal protecting groups were effected by treatment with 9:1 TFA–water in a rotatory evaporator for 10 min. The fully unprotected compounds were purified by gel permeation chromatography (GPC) using Sephadex G-10 (Pharmacia-Abersham) as stationary phase and eluting with 1:1 MeOH–water. Microanalyses were performed by the Instituto de Investigaciones Químicas (CSIC, Seville).

General procedure for the preparation of sugar ureas.—(a) From sugar carbodiimides: To a solution of the corresponding carbodiimido sugar **4a**–**c**, **5a**–**c** or **6a**–**c** [21] (0.5 mmol) in toluene (3 mL) was added glacial acetic acid (0.1 mL) and water (0.05 mL). The reaction mixture was stirred at room temperature (rt) for 15 min, then concd and the residue purified by column chromatography using the eluent indicated in each case for the R_f value, to give **7a**–**c**, **8a**–**c** or **9a**–**c**, respectively, as amorphous solids in 96–99% yield.

(b) One-pot preparation of ureas from sugar azides: to a solution of the corresponding 6-azido-6-deoxy sugar **1**–**3** [36] (0.5 mmol) and methyl, 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl [25], or 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-β-cellobiosyl isothiocyanate [37] (0.55 mmol) in toluene (3 mL) was added triphenylphosphine (0.55 mmol) in toluene (3 mL). The mixture was stirred for 45 min at rt and then acetic acid (0.1 mL) and water (0.05 mL) were added. After stirring for 15 min, the reaction mixture was concd and the residue purified by column chromatography as above. By this procedure, yields above 85% based on the starting azide were obtained in all cases.

6-Deoxy-1,2:3,4-di-O-*isopropylidene-6-(*N′-*methylureido)*-α-D-*galactopyranose* (**7a**).—Yield: 153 mg (97%); $[\alpha]_D^{22}$ −36.9° (*c* 1.2, CH_2Cl_2); R_f (EtOAc) 0.40; IR (KBr): ν_{max} 3347, 2988, 2936, 1632, 1582, 1383, 1254, 1211, 1071 and 1003 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): Table 1 and δ 5.02 (bs, 2 H, 2 NH), 2.75 (s, 3 H, N′Me), 1.50 1.44, 1.34 and 1.32 (4 s, each 3 H, 4 Me); ^{13}C NMR (75.5 MHz, $CDCl_3$): Table 2 and δ 168.1 (CO urea), 109.2,



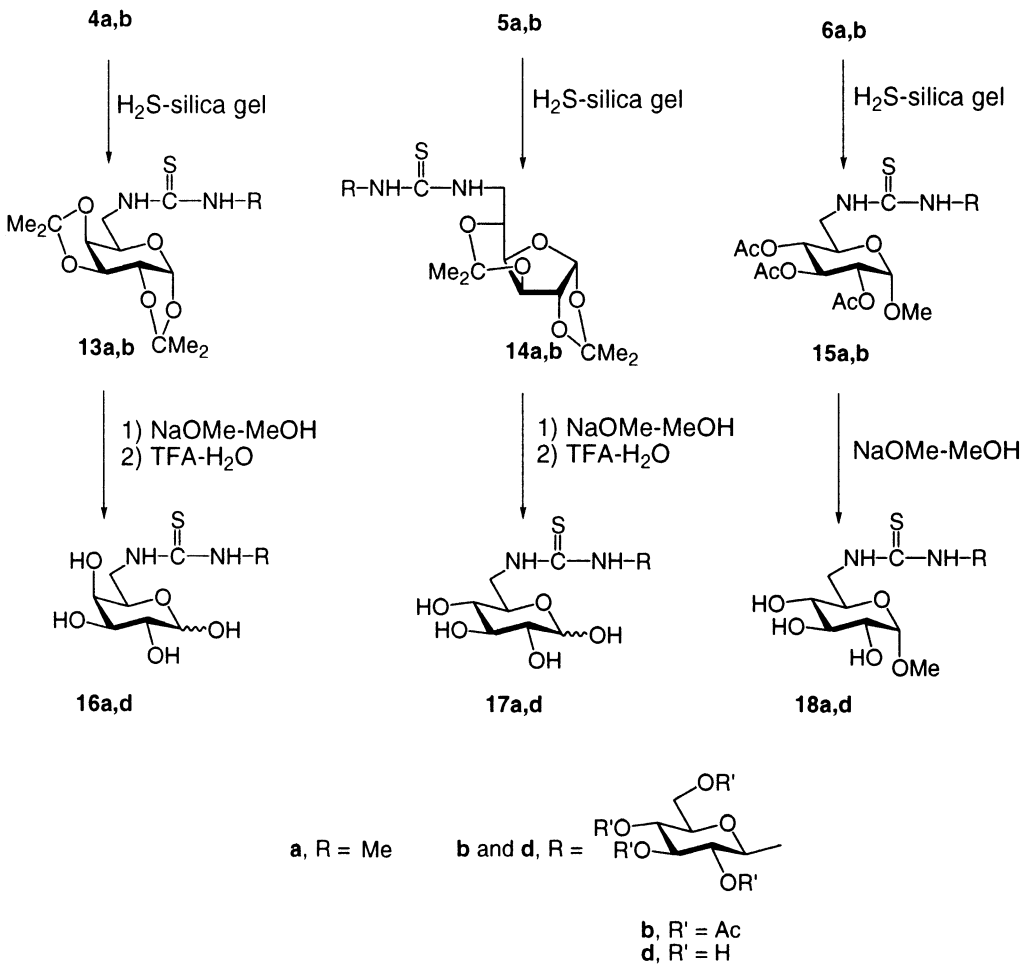
Scheme 1.

108.7 (2 CMe_2), 27.9 (MeN), 27.0 (2 C), 26.9 and 25.9 (4 Me); FABMS: *m/z* 339 (100%, $[M + Na]^+$) and 317 (80, $[M + H]^+$). Anal. Calcd for $C_{14}H_{24}N_2O_6$: C, 53.15; H, 7.65; N, 8.85. Found: C, 53.08; H, 7.99; N, 8.83.

*6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-[*N′*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-ureido]-α-*D*-galactopyranose* (**7b**).—Yield: 304 mg (96%); $[\alpha]_D^{22}$ −21.5° (*c* 1.1, CH_2Cl_2); R_f (3:1 CCl_4–acetone) 0.28; IR (KBr): ν_{max} 3370, 2988, 2938, 1753, 1659, 1562, 1377, 1229 and 1067 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): Table 1 and δ 5.48 (bs, 1 H, N′H), 5.19 (bs, 1 H, NH), 2.08, 2.06, 2.03, 2.02 (4 s, each 3 H,

4 Ac), 1.45, 1.44, 1.34 and 1.33 (4 s, each 3 H, 4 Me); ^{13}C NMR (75.5 MHz, $CDCl_3$): Table 2 and δ 170.8, 170.6, 169.5, 169.3 (4 CO ester), 156.4 (CO urea), 109.3, 108.7 (2 CMe_2), 27.5 (2 C), 25.9, 25.8, (4 Me) and 20.5 (4 C, 4 *Me*CO); FABMS: m/z 655 (100%, $[M+Na]^+$). Anal. Calcd for $C_{27}H_{40}N_2O_{15}$: C, 51.26; H, 6.37; N, 4.43. Found: C, 51.46; H, 6.37; N, 4.47.

6-Deoxy-6-[N′-(2,3,6,2′,3′,4′,6′-hepta-O-acetyl-β-cellobiosyl)ureido]-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (**7c**).—Yield: 451 mg (98%); $[\alpha]_D^{22}$ −21.5° (*c* 0.9, CH_2Cl_2); R_f (3:1 CCl_4–acetone) 0.22; IR (KBr): ν_{max} 3389, 2940, 1753, 1650, 1377, 1229 and 1040 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): Table 1 and δ 5.41 (bd, 1 H, $J_{1',N'H}$ 9.5 Hz, N′H), 5.21 (bs, 1



Scheme 2.

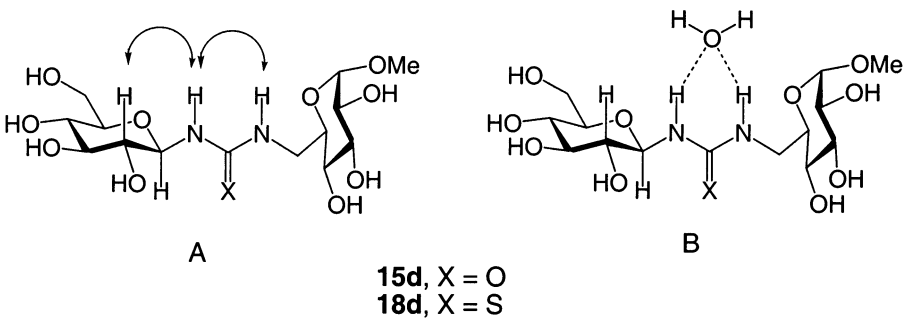


Fig. 1. (A) Preferred conformation at the (thio)urea region for the pseudodisaccharides **15d** and **18d** in 9:1 H_2O–D_2O showing the observed NOE contacts; (B) probable stabilization of the *Z*,*Z* rotamer at the pseudoamide bonds by formation of three-centered hydrogen bonds with water molecules.

H, NH), 2.10, 2.08, 2.02, 2.01, 2.00, 1.99, 1.97 (7 s, each 3 H, 7 Ac), 1.47, 1.42, 1.31 and 1.30 (4 s, each 3 H, 4 Me); ^{13}C NMR (75.5 MHz, $CDCl_3$): Table 2 and δ 171.0, 170.4, 170.1, 169.3, 169.2, 168.9, 169.1 (7 CO ester), 156.3 (CO urea), 109.3, 108.7 (2 CMe_2), 25.8 (2 C), 24.8, 24.1 (4 Me), 20.7, 20.6, 20.5 and 20.4 ($MeCO$); FABMS: m/z 943 (100%, $[M+Na]^+$). Anal. Calcd for $C_{39}H_{56}N_2O_{23}$: C, 50.87; H, 6.13; N, 3.04. Found: C, 50.83; H, 6.28; N, 3.04.

*6-Deoxy-1,2:3,5-di-*O*-isopropylidene-6-(*N′*-methylureido)-α-*D*-glucofuranose* (**8a**).—Yield: 155 mg (98%); $[\alpha]_D^{22}$ +14.0° (*c* 1.1, CH_2Cl_2); R_f (3:1 CCl_4–acetone) 0.23; IR (KBr): ν_{max} 3364, 2988, 2936, 1643, 1574, 1221, 1167 and 1003 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): Table 1 and δ 5.15 (bs, 2 H, 2 NH), 2.73 (s, 3 H, N′Me), 1.46, 1.32, 1.31 and 1.30 (4 s, each 3 H, 4 Me); ^{13}C NMR (125.5 MHz, $CDCl_3$): Table 2 and δ 159.3 (CO urea), 112.0 (CMe_2 dioxolane), 100.7 (CMe_2 dioxane) [38], 26.8 (MeN), 26.9, 26.7, 24.0 and 23.3 (4 Me); FABMS: m/z 339 (100%, $[M+Na]^+$). Anal. Calcd for $C_{14}H_{24}N_2O_6$: C, 53.15; H, 7.65; N, 8.85. Found: C, 53.14; H, 7.59; N, 8.85.

*6-Deoxy-1,2:3,5-di-*O*-isopropylidene-6-[*N′*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-ureido]-α-*D*-glucofuranose* (**8b**).—Yield: 310 mg (98%); $[\alpha]_D^{22}$ +6.9° (*c* 1.1, CH_2Cl_2); R_f (3:1 CCl_4–acetone) 0.27; IR (KBr): ν_{max} 3383, 2991, 2943, 1753, 1697, 1562, 1230 and 1035 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): Table 1 and δ 5.87 (bs, 1 H, N′H), 3.37 (bs, 1 H, NH), 1.99, 1.97, 1.95, 1.93 (4 s, each 3 H, 4 Ac), 1.40, 1.29, 1.25 and 1.24 (4 s, each 3 H, 4 Me); ^{13}C NMR (125.5 MHz, $CDCl_3$): Table 2 and δ 170.8, 170.7, 169.9, 169.7 (4 CO ester), 156.8 (CO urea), 112.2 (CMe_2 dioxolane), 101.0 (CMe_2 dioxane) [38], 27.1, 26.5, 23.9, 23.8, (4 Me), 20.8, 20.7, 20.6 and 20.5 (4 $MeCO$); FABMS: m/z 655 (100%, $[M+Na]^+$). Anal. Calcd for $C_{27}H_{40}N_2O_{15}$: C, 51.26; H, 6.37; N, 4.43. Found: C, 51.14; H, 6.44; N, 4.42.

*6-Deoxy-6-[*N′*-(2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-β-cellobiosyl)ureido]-1,2:3,5-di-*O*-isopropylidene-α-*D*-glucofuranose* (**8c**).—Yield: 442 mg (96%); $[\alpha]_D^{22}$ −2.2° (*c* 0.8, CH_2Cl_2); R_f (3:1 CCl_4–acetone) 0.25; IR (KBr): ν_{max} 3389, 2928, 2857, 1753, 1645, 1377, 1231 and 1038 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): Table 1 and δ 5.45 (bs, 1 H, N′H), 4.92 (s, 1 H, NH), 2.10, 2.08, 2.07, 2.05, 2.04, 2.00, 1.97 (7 s, each 3 H, 7 Ac), 1.34, 1.30, 1.27 and 1.24 (4 s, each 3 H, 4 Me); ^{13}C NMR (75.5 MHz, $CDCl_3$): Table 2 and δ 171.1, 170.4, 170.1 (2 C), 169.3, 169.2, 168.9, (7 CO ester), 156.4 (CO urea), 112.2 (CMe_2 dioxolane), 100.9 (CMe_2 dioxane) [38], 29.6, 29.2, 27.0, 26.4 (4 Me), 20.7, 20.6, 20.5 and 20.4 ($MeCO$); FAMBS m/z 943 (100%, $[M+Na]^+$). Anal. Calcd for $C_{39}H_{56}N_2O_{23}$: C, 50.87; H, 6.13; N, 3.04. Found: C, 51.20; H, 5.84; N, 3.15.

*Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-(*N′*-methylureido)-α-*D*-glucopyranoside* (**9a**).—Yield: 180 mg (96%); $[\alpha]_D^{22}$ +96.0° (*c* 1.0, CH_2Cl_2); R_f (1:1 CCl_4–acetone) 0.41; IR (KBr): ν_{max} 3347, 2942, 1751, 1651, 1568, 1373, 1227 and 1045 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): Table 1 and δ 3.39 (s, 3 H, OMe), 2.75 (s, 3 H, N′Me), 2.08, 2.06 and 2.00 (3 s, each H, 3 Ac); ^{13}C NMR (125.5 MHz, $CDCl_3$): Table 2 and δ 170.1 (2 C), 169.8 (3 CO ester), 158.9 (CO urea), 55.0 (OMe), 29.8 (MeN) and 20.4 (3 C, 3 $MeCO$); FABMS: m/z 399 (100%, $[M+Na]^+$). Anal. Calcd for $C_{15}H_{24}N_2O_9$: C, 47.87; H, 6.43; N, 7.44. Found: C, 47.63; H, 6.29; N, 7.63.

*Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-[*N′*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-ureido]-α-*D*-glucopyranoside* (**9b**).—Yield: 336 mg (97%); $[\alpha]_D^{22}$ +61.0° (*c* 0.8, CH_2Cl_2); R_f (1:1 CCl_4–acetone) 0.64; IR (KBr): ν_{max} 3406, 2960, 2851, 1753, 1648, 1560, 1228 and 1035 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): Table 1 and δ 5.45 (bs, 1 H, N′H), 5.15 (t, 1 H, $J_{6a,NH} = J_{6b,NH}$ 6.1 Hz, NH), 3.35 (s, 3 H, OMe), 2.06, 2.04 (2 C), 2.01, 1.99, 1.98 and 1.95 (6 s, each 3 H, 7 Ac); ^{13}C NMR (125.5 MHz, $CDCl_3$): Table 2 and δ 171.3, 170.7, 170.4, 170.1, 170.0, 169.9, 169.7, (7 CO ester), 156.3 (CO urea), 55.5 (OMe), 20.7 (2 C) y 20.6 (5 C) (7 $MeCO$); FABMS: m/z 715 (100%, $[M+Na]^+$). Anal. Calcd for $C_{28}H_{40}N_2O_{18}$: C, 48.55; H, 5.82; N, 4.04. Found: C, 48.14; H, 5.74; N, 4.29.

*Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-[*N′*-(2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-β-cellobiosyl)-ureido]-α-*D*-glucopyranoside* (**9c**).—Yield: 485 mg (99%); $[\alpha]_D^{22}$ +40.4° (*c* 1.1, CH_2Cl_2); R_f (1:1 EtOAc–petroleum ether) 0.15; IR (KBr):

ν_{max} 3407, 3135, 2957, 1755, 1646, 1562, 1377, 1229 and 1040 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): Table 1 and δ 5.47 (bs, 1 H, N′H), 5.08 (bs, 1 H, NH), 3.36 (s, 3 H, OMe), 2.10, 2.07, 2.06, 2.03, 2.02, 2.01, 2.00, 1.99, 1.98 and 1.97 (10 s, each H, 10 MeCO); ^{13}C NMR (125.5 MHz, $CDCl_3$): Table 2 and δ 171.4, 170.4, 170.1 (2 C), 169.9 (2 C), 169.8, 169.3, 169.2, 168.9 (10 CO ester), 156.0 (CO urea), 55.3 (OMe), 20.9, 20.8, 20.6 (2 C), 20.5 and 20.4 (*Me*CO); FABMS: *m/z* 1003 (100%, $[M + Na]^+$). Anal. Calcd for $C_{40}H_{56}N_2O_{26}$: C, 48.98; H, 5.75; N, 2.87. Found: C, 49.01; H, 5.81; N, 2.87.

*6-Deoxy-6-(*N′*-methylureido)-*D*-galacto-pyranose* (**10a**).—Deacetalation of **7a** (0.126 g, 0.4 mmol) and purification of the crude product by GPC yielded **10a** (92 mg, 98%) as a white foam after freeze-drying from an aqueous solution; $[\alpha]_D^{22}$ +43.4° (*c* 1.3, H_2O); R_f (1:1 CH_2Cl_2–MeOH) 0.70; α:β ratio 1:1.8 (H-1 integration); ^1H NMR (500 MHz, D_2O): Table 1 and δ 2.52 (s, 3 H, N′Me); ^{13}C NMR (75.5 MHz, D_2O): Table 2 and δ 159.4 (CO urea) and 26.4 (MeN); FABMS: *m/z* 259 (100%, $[M + Na]^+$). Anal. Calcd for $C_8H_{16}N_2O_6$: C, 40.68; H, 6.83; N, 11.86. Found: C, 40.79; H, 6.68; N, 11.91.

*6-Deoxy-6-[*N′*-(β-*D*-glucopyranosyl)ureido]-*D*-galactopyranose* (**10d**).—Zemplén deacetylation of **7b** (0.253 g, 0.4 mmol) followed by acetal hydrolysis and purification of the crude product by GPC yielded **10d** (149 mg, 97%) as a white foam after freeze-drying from an aqueous solution; $[\alpha]_D^{22}$ +16.5° (*c* 0.8, H_2O); R_f (2:1:1 BuOH–AcOH–H_2O) 0.28; α:β ratio 1:2 (H-1 integration); ^1H NMR (500 MHz, D_2O): Table 1; ^{13}C NMR (100.6 MHz, D_2O): Table 2 and δ 159.5 (CO urea); FABMS: *m/z* 407 (50%, $[M + Na]^+$). Anal. Calcd for $C_{13}H_{24}N_2O_{11}$: C, 40.62; H, 6.29; N, 7.29. Found: C, 40.60; H, 6.22; N, 7.33.

*6-Deoxy-6-[*N′*-(β-cellobiosyl)ureido]-*D*-galactopyranose* (**10e**).—Zemplén deacetylation of **7c** (0.368 g, 0.4 mmol) followed by acetal hydrolysis and purification of the crude product by GPC yielded **10e** (196 mg, 90%) as a white foam after freeze-drying from an aqueous solution; $[\alpha]_D^{22}$ +16.5° (*c* 0.9, H_2O); R_f (2:1:1 BuOH–AcOH–H_2O) 0.24; α:β ratio 1:1.8 (H-1 integration); ^1H NMR (500 MHz, D_2O): Table 1; ^{13}C NMR (125.5 MHz, D_2O): Table 2 and δ 159.0 (CO urea); FABMS: *m/z* 569 (100%, $[M + Na]^+$). Anal. Calcd for $C_{19}H_{34}N_2O_{16}$: C, 41.76; H, 6.27; N, 5.13. Found: C, 42.04; H, 6.22; N, 5.14.

*6-Deoxy-6-(3-methylureido)-*D*-gluco-pyranose* (**11a**).—Deacetalation of **8a** (0.126 g, 0.4 mmol) and purification of the crude product by GPC yielded **11a** (92 mg, 98%) as a white foam after freeze-drying from an aqueous solution; $[\alpha]_D^{22}$ +43.4° (*c* 1.6, H_2O); R_f (1:1 CH_2Cl_2–MeOH) 0.67; α:β ratio 1:1.9 (H-1 integration); ^1H NMR (500 MHz, D_2O): Table 1 and δ 2.60 (s, 3 H, N′Me); ^{13}C NMR (125.5 MHz, D_2O): Table 2 and δ 161.2 (CO urea) and 26.3 (MeN); FABMS: *m/z* 259 (100%, $[M + Na]^+$). Anal. Calcd for $C_8H_{16}N_2O_6$: C, 40.68; H, 6.83; N, 11.86. Found: C, 40.79; H, 6.81; N, 11.89.

*6-Deoxy-6-[*N′*-(β-*D*-glucopyranosyl)ureido]-*D*-glucopyranose* (**11d**).—Zemplén deacetylation of **8b** (0.253 g, 0.4 mmol) followed by acetal hydrolysis and purification of the crude product by GPC yielded **11d** (149 mg, 97%) as a white foam after freeze-drying from an aqueous solution; $[\alpha]_D^{22}$ +15.5° (*c* 2.0, H_2O); R_f (2:1:1 BuOH–AcOH–H2O) 0.23; α:β ratio 1:2.5 (H-1 integration); ^1H NMR (500 MHz, D_2O): Table 1; ^{13}C NMR (100.6 MHz, D_2O): Table 2 and δ 161.1 (CO urea); FABMS: *m/z* 407 (50%, $[M + Na]^+$). Anal. Calcd for $C_{13}H_{24}N_2O_{11}$: C, 40.62; H, 6.29; N, 7.29. Found: C, 40.62; H, 6.25; N, 7.32.

*6-Deoxy-6-[*N′*-(β-cellobiosyl)ureido]-*D*-glucopyranose* (**11e**).—Zemplén deacetylation of **8c** (0.368 g, 0.4 mmol) followed by acetal hydrolysis and purification of the crude product by GPC yielded **11e** (186 mg, 85%) as a white foam after freeze-drying from an aqueous solution; $[\alpha]_D^{22}$ +5.0° (*c* 1.0, H_2O); R_f (2:1:1 BuOH-AcOH–H_2O) 0.18; α:β ratio 1:1. (H-1 integration); ^1H NMR (500 MHz, D_2O): Table 1; ^{13}C NMR (125.5 MHz, D_2O): Table 2 and δ 159.6 (CO urea); FABMS: *m/z* 569 (70%, $[M + Na]^+$). Anal. Calcd for $C_{19}H_{34}N_2O_{16}$: C, 41.76; H, 6.27; N, 5.13. Found: C, 41.65; H, 6.24; N, 5.13.

*Methyl 6-deoxy-6-(*N′*-methylureido)-α-*D*-glucopyranoside* (**12a**).—Zemplén deacetylation of **9a** (0.150 g, 0.4 mmol) and purification of the crude product by GPC yielded **12a** (96

mg, 96%) as a white foam after freeze-drying from an aqueous solution; $[\alpha]_D^{22}$ +95.2° (*c* 1.0, H_2O); R_f (2:1:1 BuOH–AcOH–H_2O) 0.48; ^1H NMR (500 MHz, D_2O): Table 1 and δ 3.23 (s, 3 H, OMe) and 2.60 (s, 3 H, N′Me); ^{13}C NMR (75.5 MHz, D_2O): Table 2 and δ 161.6 (CO urea), 55.1 (OMe) and 26.7 (MeN); FABMS: *m*/*z* 273 (100%, $[M+Na]^+$). Anal. Calcd for $C_9H_{18}N_2O_6$: C, 43.19; H, 7.25; N, 11.19. Found: C, 43.25; H, 7.54; N, 11.19.

*Methyl 6-deoxy-6-[*N′*-(β-*D*-glucopyranosyl)ureido]-α-*D*-glucopyranoside* (**12d**).—Zemplén deacetylation of **9b** (0.277 g, 0.4 mmol) and purification of the crude product by GPC yielded **12d** (146 mg, 92%) as a white foam after freeze-drying from an aqueous solution; $[\alpha]_D^{22}$ +71.7° (*c* 1.2, H_2O); R_f (2:1:1 BuOH–AcOH–H_2O) 0.21; ^1H NMR (500 MHz, D_2O): Table 1 and δ 3.29 (OMe); ^{13}C NMR (75.5 MHz, D_2O): Table 2 and δ 159.8 (CO urea) and 55.0 (OMe); FABMS: *m*/*z* 421 (100%, $[M+Na]^+$). Anal. Calcd for $C_{14}H_{26}N_2O_{11}$: C, 42.21; H, 6.58; N, 7.03. Found: C, 42.31; H, 6.42; N, 7.08.

*Methyl 6-deoxy-6-[*N′*-(β-cellobiosyl)-ureido]-α-*D*-glucopyranoside* (**12e**).—Zemplén deacetylation of **9c** (0.392 g, 0.4 mmol) and purification of the crude product by GPC yielded **12e** (186 mg, 83%) as a white foam after freeze-drying from an aqueous solution; $[\alpha]_D^{22}$ +34.1° (*c* 0.8, H_2O); R_f (2:1:1 BuOH–AcOH–H_2O) 0.10; ^1H NMR (500 MHz, D_2O): Table 1 and δ 3.24 (OMe); ^{13}C NMR (125.5 MHz, D_2O): Table 2 and δ 159.7 (CO urea) and 54.9 (OMe); FABMS: *m*/*z* 583 (60%, $[M+Na]^+$). Anal. Calcd for $C_{20}H_{36}N_2O_{16}$: C, 42.86; H, 6.47; N, 5.00. Found: C, 42.76; H, 6.49; N, 4.99.

General procedure for the preparation of sugar thioureas from sugar carbodiimides.—Dry ($CaCl_2$) H_2S was bubbled through a suspension of the corresponding carbodiimide **4a**,**b**–**6a**,**b** (1 mmol) and activated silica gel (0.7 g) in toluene (8 mL) at 0 °C for 5–6 h. The reaction mixture was then concentrated and the residue was extracted with EtOAc (2 × 5 mL), the organic solution was concd and the residue purified by column chromatography with the eluent indicated in each case to give **13a**,**b**–**16a**,**b** as amorphous solids.

*6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-(*N′*-methylthioureido)-α-*D*-galactopyranose* (**13a**).—Yield: 299 mg (90%); $[\alpha]_D^{22}$ −45.9° (*c* 1.0, CH_2Cl_2); R_f (2:1 EtOAc–petroleum ether) 0.54; UV (CH_2Cl_2): 246 nm (ε_{mM} 8.1); IR (KBr): 3360, 3268, 2986, 2936, 1561, 1381, 1213 and 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 313 K) Table 1 and δ 6.54 (bq, 1 H, $J_{N'H,Me}$ 4.8 Hz, N′H), 6.40 (bt, $J_{NH,6a} = J_{NH,6b}$ 4.4 Hz, NH), 2.91 (d, 3 H, MeN), 1.46, 1.38, 1.28 and 1.26 (4 s, each 3 H, 4 Me); ^{13}C NMR (75.5 MHz, $CDCl_3$, 313 K): Table 2 and δ 183.1 (CS), 109.2, 108.8 (2 CMe_2), 30.4 (MeN), 25.8, 25.7, 24.7 and 24.1 (4 Me); FABMS: *m*/*z* 355 (100%, $[M+Na]^+$) and 333 (30, $[M+H]^+$). Anal. Calcd for $C_{14}H_{24}N_2O_5S$: C, 50.58: H, 7.28; N, 8.43; S, 9.64. Found: C, 50.52; H, 7.33; N, 8.44; S, 9.61.

*6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-[*N′*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-thioureido]-α-*D*-galactopyranose* (**13b**).—Yield: 421 mg (65%); $[\alpha]_D^{22}$ −29.9° (*c* 1.0, CH_2Cl_2); R_f (1:1 EtOAc–petroleum ether) 0.46; UV (CH_2Cl_2): 254 nm (ε_{mM} 16.6); IR (KBr): 3370, 2982, 2942, 1757, 1537, 1379, 1223 and 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 313 K): Table 1 and δ 6.82 (bs, 1 H, N′H), 6.65 (bs, 1 H, NH), 2.07, 2.05, 2.02, 2.00 (4 s, each H, 4 Ac), 1.49 (s, 3 H, Me), 1.42 (s, 3 H, Me) and 1.31 (2 s, each 3 H, 2 Me); ^{13}C NMR (75.5 MHz, $CDCl_3$, 313 K): Table 2 and δ 183.9 (CS), 171.2, 170.6, 169.8, 169.5 (4 CO), 109.4 (CMe_2), 108.8 (CMe_2), 26.9, 26.8, 24.8, 24.1 (2 CMe_2), 20.6 (2 C) and 20.4 (4 C, 4 *Me*CO); FABMS: *m*/*z* 671 (100%, $[M+Na]^+$) and 649 (35, $[M+H]^+$). Anal. Calcd for $C_{27}H_{40}N_2O_{14}S$: C, 49.99; H, 6.22; N, 4.32; S, 4.94. Found: C, 50.06; H, 6.27; N, 4.32; S, 4.67.

*6-Deoxy-1,2:3,5-di-*O*-isopropylidene-6-(*N′*-methylthioureido)-α-*D*-glucofuranose* (**14a**).—Yield: 288 mg (87%); $[\alpha]_D^{22}$ +6.3° (*c* 0.9, CH_2Cl_2); R_f (2:1 EtOAc–petroleum ether) 0.51; UV (CH_2Cl_2): 258 nm (ε_{mM} 2.3); IR (KBr): 3324, 2986, 2936, 1557, 1377, 1219 and 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 313 K): Table 1 and δ 6.55 (bs, 1 H, NH), 6.16 (bs, 1 H, NH), 3.00 (d, 3 H, $J_{Me,NH}$ 4.8 Hz, MeN), 1.47, 1.35, 1.34 and 1.31 (4 s, each 3 H, 4 Me); ^{13}C NMR (75.5 MHz, $CDCl_3$, 313 K): Table 2 and δ 183.7 (CS), 112.3 (CMe_2 dioxolane), 101.1 (CMe_2 dioxane) [38], 30.9

(MeN), 27.0, 26.4, 24.1 and 23.8 (4 Me); FABMS: m/z 355 (90%, $[M+Na]^+$) and 333 (50, $[M+H]^+$). Anal. Calcd for $C_{14}H_{24}N_2O_5S$: C, 50.58; H, 7.28; N, 8.43; S, 9.64. Found: C, 50.69; H, 7.35; N, 8.40; S, 9.60.

*6-Deoxy-1,2:3,5-di-*O*-isopropylidene-6-[*N′*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-thioureido]-α-*D*-glucofuranose* (**14b**).—Yield: 453 mg (70%); $[\alpha]_D^{22}$ −5.9° (*c* 1.0, CH_2Cl_2); R_f (1:1 EtOAc–petroleum ether) 0.45; UV (CH_2Cl_2): 257 nm (ε_{mM} 28.1); IR (KBr) 3335, 2993, 2939, 1757, 1547, 1377, 1219 and 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 313 K): Table 1 and δ 7.00 (bs, 1 H, N′H), 6.46 (bs, 1 H, NH), 2.06, 2.05, 2.02, 2.01 (4 s, each 3 H, 4 Ac), 1.48, 1.40, 1.35 and 1.32 (4 s, each 3 H, 4 Me); ^{13}C NMR (75.5 MHz, $CDCl_3$, 313 K): Table 2 and δ 184.4 (CS), 170.9, 170.3, 169.6, 169.4 (4 CO), 112.4 (*C*Me$_2$ dioxolane), 101.4 (*C*Me$_2$ dioxane) [38], 27.1, 26.4, 23.9, 23.8 (2 C*Me$_2$*), 20.6, 20.5 and 20.4 (4 *Me*CO); FABMS: m/z 671 (100%, $[M+Na]^+$) and 649 (65, $[M+H]^+$). Anal. Calcd for $C_{27}H_{40}N_2O_{14}S$: C, 49.99; H, 6.22; N, 4.32; S, 4.94. Found: C, 49.74; H, 6.07; N, 4.35; S, 4.98.

*Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-(*N′*-methylthioureido)-α-*D*-glucopyranoside* (**15a**).—Yield: 337 mg (86%); $[\alpha]_D^{22}$ +124.0° (*c* 0.7, CH_2Cl_2); R_f (3:1 EtOAc–petroleum ether) 0.16; UV (CH_2Cl_2): 250 nm (ε_{mM} 9.9); IR (KBr): 3383, 3298, 1753, 1561, 1227 and 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 313 K): Table 1 and δ 6.29 (q, 1 H, $J_{N'H,Me}$ 4.8 Hz, N′H), 6.10 (t, 1 H, $J_{6a,NH} = J_{6b,NH}$ 5.9 Hz, NH), 3.40 (s, 3 H, OMe), 3.00 (d, 3 H, MeN), 2.07, 2.06 and 1.99 (3 s, 9 H, 3 MeCO); ^{13}C NMR (75.5 MHz, $CDCl_3$, 313 K): Table 2 and δ 182.0 (CS), 170.2, 170.1, 169.8 (3 CO), 55.5 (OMe), 30.6 (MeNH), 20.6 and 20.5 (2C) (3 *Me*CO); FABMS: m/z 393 (100%, $[M+H]^+$). Anal. Calcd for $C_{15}H_{24}N_2O_8S$: C, 45.91; H, 6.16; N, 7.14; S, 8.17. Found: C, 45.95; H, 5.98; N, 7.11; S, 8.38.

*Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-[*N′*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-thioureido]-α-*D*-glucopyranoside* (**15b**).—Yield: 439 mg (62%); $[\alpha]_D^{22}$ +67.0° (*c* 0.9, CH_2Cl_2); R_f (1:1 EtOAc–petroleum ether) 0.35; UV (CH_2Cl_2): 255 nm (ε_{mM} 11.0); IR (KBr): 3368, 2955, 1748, 1537, 1371, 1230 and 1043 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 313 K): Table 1 and δ 6.80 (bs, 1 H, N′H), 6.60 (m, 1 H, NH), 3.39 (s, 3 H, OMe), 2.08, 2.06, 2.05, 2.02, 2.01, 2.00 and 1.98 (7 s, each 3 H, 7 Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$, 313 K): Table 2 and δ 184.5 (CS), 171.2, 170.4, 170.0, 169.9, 169.7, 169.6, 169.4 (7 CO), 55.6 (OMe), 20.5 and 20.4 (7 MeCO); FABMS: m/z 731 (85%, $[M+Na]^+$) and 709 (20, $[M+H]^+$). Anal. Calcd for $C_{28}H_{40}N_2O_{17}S$: C, 47.45; H, 5.69; N, 3.95; S, 4.52. Found: C, 47.47; H, 5.75; N, 3.97; S, 4.51.

*6-Deoxy-6-(*N′*-methylthioureido)-*D*-galactose* (**16a**).—Deacetalation of **13a** (0.133 g, 0.4 mmol) and purification of the crude product by GPC yielded **16a** (98 mg, 98%) as a white foam after freeze-drying from an aq soln; $[\alpha]_D^{22}$ +46.8° (*c* 0.9, H_2O); R_f (45:5:3 EtOAc–EtOH–H_2O) 0.23; α:β ratio 1:1.7 (H-1 integration); UV (H_2O): 236 nm (ε_{mM} 9.9); ^1H NMR (500 MHz, D_2O, 313 K): Table 1 and δ 3.01 (s, 3 H, MeN); ^{13}C NMR (75.5 MHz, D_2O, 313 K): Table 2 and δ 179.9 (CS) and 30.4 (MeN); FABMS: m/z 275 (100%, $[M+Na]^+$). Anal. Calcd for $C_8H_{16}N_2O_5S$: C, 38.08; H, 6.39; N, 11.10; S, 12.71. Found: C, 38.02; H, 6.50; N, 11.12; S, 12.72.

*6-Deoxy-6-[*N′*-(β-*D*-glucopyranosyl)-thioureido]-*D*-galactopyranose* (**16d**).—Zemplén deacetylation of **13b** (0.259 g, 0.4 mmol) followed by acetal hydrolysis and purification of the crude product by GPC yielded **16d** (152 mg, 95%) as a white foam after freeze-drying from an aqueous solution; $[\alpha]_D^{22}$ +28.0° (*c* 1.0, H_2O); lit. [11] $[\alpha]_D$ +28.6° (*c* 1.0, H_2O). The ^1H and ^{13}C NMR data were in full agreement with those reported in the literature [11].

*6-Deoxy-6-(3-methylthioureido)-*D*-glucopyranose* (**17a**).—Deacetalation of **14a** (0.133 g, 0.4 mmol) and purifica-tion of the crude product by GPC yielded **17a** (97 mg, 96%) as a white foam after freeze-drying from an aqueous solution; $[\alpha]_D^{22}$ +30.6° (*c* 0.8, H_2O); R_f (45:5:3 EtOAc–EtOH–H_2O) 0.24; α:β ratio 1:1.8 (H-1 integration); UV (H_2O): 236 nm (ε_{mM} 5.6); ^1H NMR (500 MHz, D_2O, 313 K): Table 1; ^{13}C NMR (125.5 MHz, D_2O, 313 K): Table 2 and δ 180.1 (CS) and 31.1 (MeN); FABMS: m/z 275 (90%, $[M+Na]^+$). Anal. Calcd for $C_8H_{16}N_2O_5S$: C, 38.08; H, 6.39; N, 11.10; S, 12.71. Found: C, 38.25; H, 6.37; N, 11.10; S, 12.78.

6-Deoxy-6-[N′-(β-D-glucopyranosyl)thioureido]-D-glucopyranose (**17d**).—Zemplén deacetylation of **14b** (0.259 g, 0.4 mmol) followed by acetal hydrolysis and purification of the crude product by GPC yielded **17d** (155 mg, 97%) as a white foam after freeze-drying from an aqueous solution; $[\alpha]_D^{22}$ −64.5° (*c* 0.9, H_2O); lit. [11] $[\alpha]_D$ −65.8° (*c* 1.0, H_2O). The ^1H and ^{13}C NMR data were in full agreement with those reported in the literature [11].

Methyl 6-deoxy-6-(3-methylthioureido)-α-D-glucopyranoside (**18a**).—Zemplén deacetylation of **15a** (0.157g, 0.4 mmol and purification of the crude product by GPC yielded **18a** (102 mg, 96%) as a white foam after freeze-drying from an aq soln; $[\alpha]_D^{22}$ +88.0° (*c* 0.9, H_2O); R_f (4:1 CH_2Cl_2–MeOH) 0.25; UV (H_2O): 234 nm (ε_{mM} 12.6); ^1H NMR (300 MHz, D_2O, 343 K): Table 1 and δ 4.11 (s, 3 H, NMe) and 3.67 (s, 3 H, OMe); ^{13}C NMR (75.5 MHz, D_2O, 313 K): Table 2 and δ 179.1 (CS), 58.1 (OMe) and 33.4 (MeN); FABMS: *m/z* 289 (100%, $[M+Na]^+$) and 267 (10, $[M+H]^+$). Anal. Calcd for $C_9H_{18}N_2O_5S$: C, 40.59; H, 6.81; N, 10.52; S, 12.04. Found: C, 40.60; H, 6.70; N, 10.41; S, 12.04.

Methyl 6-deoxy-6-[N′-(β-D-glucopyranosyl)thioureido]-α-D-glucopyranoside (**18d**).—Zemplén deacetylation of **15b** (0.283 g, 0.4 mmol) followed by acetal hydrolysis and purification of the crude product by GPC yielded **18d** (155 mg, 94%) as a white foam after freeze-drying from an aq soln; $[\alpha]_D^{22}$ +37.0° (*c* 1.0, H_2O); lit. [11] $[\alpha]_D$ +37.7° (*c* 0.9, H_2O). The ^1H and ^{13}C NMR data were in full agreement with those reported in the literature [11].

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