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Synthesis and anomeric stability of (1→6)-thiourea-linked pseudooligosaccharides

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Abstract

The synthesis of oligosaccharide mimics incorporating a thiourea intersaccharide bridge by coupling of mono- and disaccharide per-*O*-acetylated glycosyl isothiocyanates and methyl 6-amino-6-deoxy-α-D-glucopyranoside, is reported. An unexpected anomerization reaction was observed, however, for α- and β-D-mannopyranosylthioureido derivatives upon Zemplén deacetylation. Kinetics studies revealed that this anomerization process is base catalysed and strongly dependent upon reaction temperature and reaction time. The fully unprotected compounds could be obtained without epimerization by performing the last step at 0 °C. In all cases, the final pseudooligosaccharides were stable in water solution at room temperature in the absence of base.

Keywords: Sugar thioureas; Sugar isothiocyanates; Carbohydrate mimics; Oligosaccharide mimics; Anomerization

1. Introduction

The growing awareness of the role of oligosaccharides as carriers of biological information has spurred an aggressive effort towards the development of synthetic methodologies suitable for the construction of glycodrugs [1–3]. Assembly of monosaccharides through glycosidic linkages, as in the natural compounds, suffers from two major disadvantages, namely the complications associated with anomeric configuration control in glycoside bond-forming reactions and the biodegradability of oligosaccharide structures through the action of glycosidases. Replacement of the glycosidic oxygen atom by other achiral functional groups such as amide (carbopeptoids, saccharopeptides) [4–11] or phosphodiester (carbonucleotoids) [12], which can be generated in high yield without affecting the existing stereocenters, appears as a very attractive alternative. Thiourea-bridged oligosaccharide mimics [13–15], accessible through coupling reaction of readily available sugar isothiocyanates [16–18] and amino sugars, likewise comply with the above features. Recently, this strategy was implemented with

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the preparation of β-cyclodextrin-scaffolded glycoclusters containing (1→6)-intersaccharide thiourea bridges [19,20]. In the course of this work, an unprecedented anomerization reaction of α-D-mannopyranosylthiourea derivatives upon base treatment was observed. Since Zemplén deacetylation of multivalent α-D-mannopyranosylthioureas had previously been reported [21–24], several questions arose: (1) Whether the epimerization process was promoted by the cyclodextrin aglycon; (2) whether this is an intrinsic limitation to the synthesis of (1→6)-thiourea-tethered pseudooligosaccharides; or (3) whether it is a general aspect of the chemistry of fully unprotected glycosylthioureas. We have now investigated this problem by studying the anomeric stability of a series of thiourea-linked pseudooligosaccharides as well as simpler α- and β-D-mannopyranosylthioureas under various deacetylation reaction conditions.

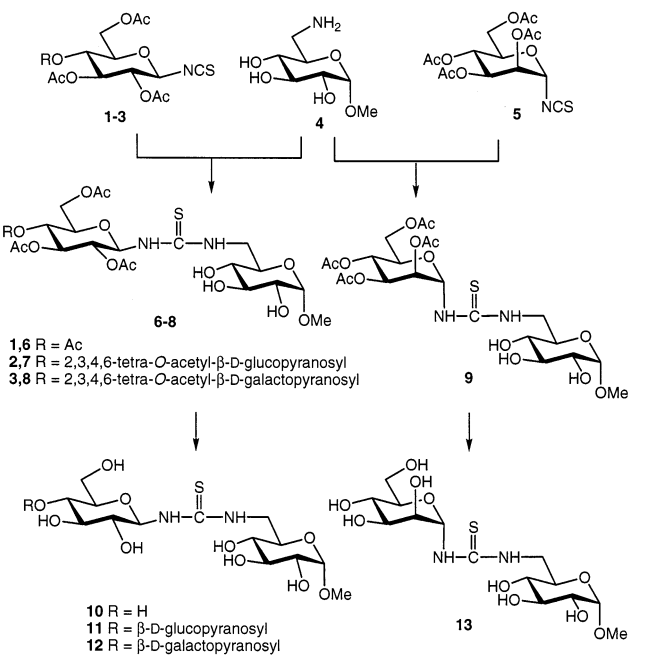
2. Results and discussion

Nucleophilic addition of methyl 6-amino-6-deoxy-α-D-glucopyranoside (**4**) [25] to per-*O*-acylated β-D-glucopyranosyl, β-cellobiosyl, β-lactosyl, and α-D-mannopyranosyl isothiocyanates (**1–3**, **5**) [16,26,27] in pyridine at room temperature afforded the corresponding partially protected adducts **6–9** in 85–90% yield (Scheme 1). As previously observed for the reaction of the same isothiocyanates with 6^{I}-amino-6^{I}-deoxy- and per(6-amino-6-deoxy)-β-cyclodextrin precursors [19], addition of the amino group to the central atom of the heteroallene group proceeded with total chemoselectivity and with no need for hydroxyl protection in the acceptor moiety. Since the anomeric C–N bond is not involved in formation of the intersaccharide thiourea bridge, the anomeric configuration of the glycosyl substituent in **6–9** matched that of the isothiocyanate precursor, as confirmed by ^{1}H and ^{13}C NMR data (Tables 1 and 2).

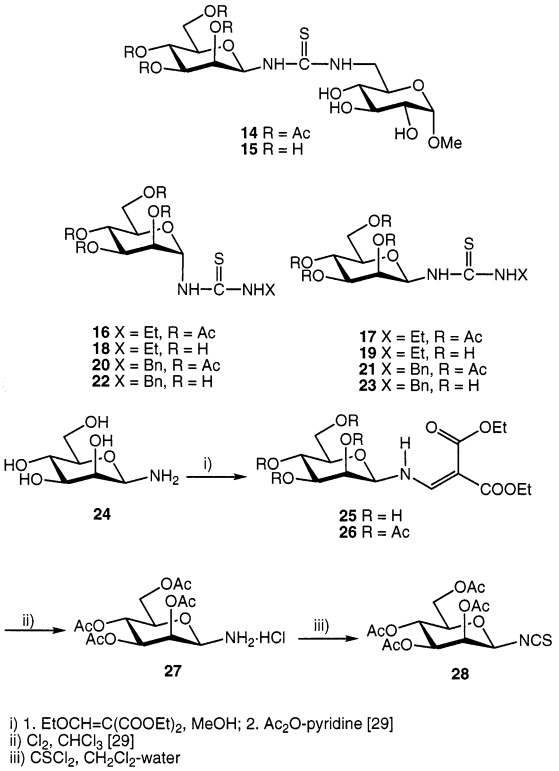
Conventional Zemplén deacetylation of the β-glycosylthioureido derivatives **6–8** led to the expected fully unprotected compounds **10** [13], **11**, and **12** with retention of the original configurational pattern (Scheme 1). However, under identical reaction conditions, the α-D-mannopyranosylthioureido isomer **9** experienced concomitant epimerization at the anomeric C-1′ center, leading to an inseparable mixture of diastereomeric pseudooligosaccharides. This result, in combination with our previous observation in the cyclodextrin series, discards an essential contribution of the aglyconic moiety in the anomerization process, pointing to a particular reactivity of mannopyranosylthiourea derivatives in alkaline medium.

In order to gain deeper insight into this problem, a series of α- and β-D-mannopyranosylthioureas was prepared by reaction of the respective per-*O*-acetylated α- (**5**) and β- (**28**) D-mannopyranosyl isothiocyanates with amino sugar **4**, ethylamine hydrochloride or benzylamine. The previously unreported 1,2-cis configured isothiocyanate **28** was obtained from β-D-mannopyranosylamine (**24**) [28] in four steps (20% overall yield) by transformation into the known enamine **26** [29], hydrolysis with chlorine in wet dichloromethane, and further isothiocyanation of the resulting amine hydrochloride **27** with thiophosgene (Scheme 2).

When compounds **14**, **16**, **17**, **20** and **21** were subjected to sodium methoxide-catalyzed



Scheme 1.



Scheme 2.

deacetylation, partial anomerization likewise occurred in both the α- and β-series. Yet, a puzzling dependence of the final relative proportion of anomers on the performer laboratory and hands, from almost undetectable to major presence of the opposite configuration at C-1, was evidenced, which probably accounted for different 'standard' Zemplén deacetylation protocols. To ascertain this point, the effects of a number of factors upon the outcome of the reaction were investigated, including substrate concentration, catalyst ratio, quality of methanol, temperature, reaction time, acidity of the resin, and time of contact of the resin with the reaction mixture.

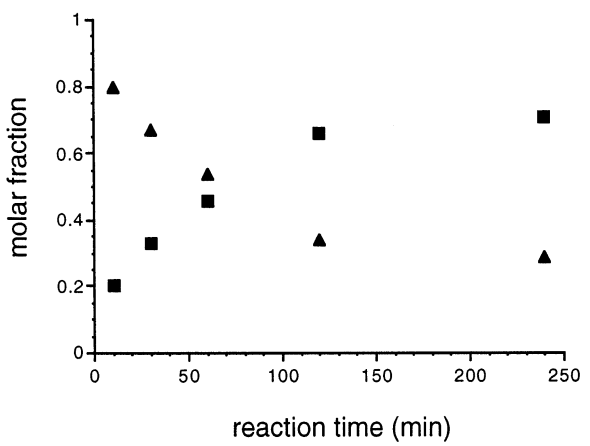


Fig. 1. Molar fractions (digital integration of ^{1}H signals at 500 MHz) of **18** (▲) and **19** (■) in the reaction mixture arising from deacetylation of **16** (0.02 M in CD_3OD) with $NaOCD_3$ (0.1 equiv per mol of acetate) at 300 K.

No definitive correlation was observed for different concentrations of the starting D-mannopyranosylthiourea (from 0.01 to 0.05 M) or sodium methoxide (from 0.1 to 0.5 equiv/mol of acetate). The results were also largely independent of the use of either absolute or commercial methanol and on the strong (Amberlite IR-120) or weakly acidic character (Amberlite IRC-50) of the resin that was used for neutralization after complete deprotection. When the deacetylation reaction of *N*-ethyl-*N*′-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)thiourea (**16**) was conducted at 30 °C in methanol-d_4 with deuterated sodium methoxide and with monitoring by ^{1}H NMR spectroscopy, the presence of the β anomer **19** was already detected after 10 min, with a 1:3 α/β thermodynamic equilibrium for **18** and **19** being achieved within 4 h (Fig. 1). An identical anomeric mixture was obtained starting from **17** after prolonged reaction times. We concluded, therefore, that the anomerization of D-mannopyranosylthioureas is a base-catalyzed process, ruling out an alternative acid-promoted mechanism at the resin surface. No changes in the composition of the neutralized mixtures occurred after 24 h in deuterium oxide or methanol-d_4 solution at room temperature[1].

Reaction temperature was found to exert a dramatic influence in the anomerization rate. Thus, at 0 °C no epimerization was observed after 1 h. At this temperature, deacetylation of acetylated D-mannopyranosylthiourea derivatives could be performed by using 0.02 M solutions in analytical grade methanol containing 0.5 equiv of sodium methoxide for 20 min. These conditions gave reproducible, virtually quantitative yields of the anomerically

[1] Partial anomerization occurred during the acquisition of ^{13}C NMR spectra for fully unprotected configurationally pure mannopyranosylthiourea derivatives in deuterium oxide solution at 70 °C overnight.

Table 1
^{1}H NMR data (500 MHz) for the new thiourea derivatives **6–9** and **11–23**

	Unit	Chemical shifts (δ)						
		H-1	H-2	H-3	H-4	H-5	H-6a	H-6b
6 [a,d]	I	5.04d	3.80dd	3.89t	3.54t	4.03m	4.25m	4.03m
	II	6.08d	5.38dd	5.67t	5.35t	4.35ddd	4.58dd	4.46dd
6 [b,d]	I	5.04d	3.48d	3.72t	3.24t	3.64dt	3.48m	3.48m
	II	5.68bs	5.04t	5.31t	4.98t	3.83ddd	4.28dd	4.09dd
7 [a,f]	I	5.30d	4.08dd	4.18t	3.81t	4.27m	4.73m	4.72m
	II	6.28d	5.58t	5.84t	4.55t	4.48m	5.01dd	4.74m
	III	5.32d	5.43t	5.78t	5.60t	4.51m	4.88dd	4.70m
7 [b,d]	I	4.72d	3.47dd	3.72t	3.22t	3.64ddd	3.67dd	3.45dd
	II	5.55m	4.94t	5.26t	3.85t	3.74ddd	4.43dd	4.23dd
	III	4.55d	4.91dd	5.15t	5.06t	3.68ddd	4.34dd	4.07dd
8 [a,f]	I	5.31d	4.07dd	4.18t	3.81t	4.27m	4.80m	4.80m
	II	6.28d	5.57t	5.83t	4.56t	4.48ddd	5.01dd	4.80m
	III	5.27dd	5.53dd	5.69dd	5.94d	4.80m	4.80m	4.80m
8 [b,c]	I	4.73d	3.47dd	3.71t	3.22bt	3.63dt	3.71m	3.45dd
	II	5.55m	4.94t	5.27t	3.88t	3.77m	4.40bd	4.27dd
	III	4.52d	5.10dd	4.98dd	5.35dd	3.89ddd	4.15dd	4.08dd
9 [a,f]	I	5.18d	3.93dd	4.04t	3.70t	4.20ddd	4.34m	4.12m
	II	6.27m	5.74m	5.74m	5.62t	4.48m	4.79dd	4.58dd
11 [a,f]	I	5.21d	3.97dd	4.08t	3.74t	4.20m	4.35m	4.20m
	II	5.75d	3.92t	4.15–4.07m	4.15–4.07m	4.15–4.07m	4.35dd	4.23dd
	III	4.94d	3.75dd	3.93t	3.84t	3.82ddd	4.33dd	4.15dd
12 [a,f]	I	5.19d	3.96dd	4.07t	3.72t	4.19m	4.35m	4.19m
	II	5.72bd	3.90t	4.06m	4.06m	4.10m	4.22dd	4.20dd
	III	4.86d	4.95dd	4.06dd	4.34d	4.12dd	4.18m	4.18m
13 [a,e]	I	5.37d	4.08dd	4.19t	4.84t	4.32m	4.45m	4.32m
	II	6.18m	4.55dd	4.24dd	4.19t	3.98ddd	4.41dd	4.32m
14 [a,e]	I	5.21d	3.97dd	4.08t	3.72t	4.20m	4.42m	4.20m
	II	6.46m	5.96dd	5.77dd	5.64t	4.50ddd	4.97dd	4.63dd
15 [a,e]	I	5.36d	4.11dd	4.22t	3.87t	4.30m	4.47m	4.30m
	II	6.11m	4.56dd	4.27dd	4.18t	4.01ddd	4.47dd	4.30m
16 [b,c]	I	5.30m	5.30m	5.25dd	5.20t	4.08ddd	4.26dd	4.15dd
17 [b,c]	I	5.90m	5.43dd	5.14dd	5.22t	3.82ddd	4.28dd	4.12dd
18 [a,g]	I	5.44bs	4.04m	3.83dd	3.65t	3.53m	3.86dd	3.74dd
19 [a,e]	I	5.75m	4.18m	3.91dd	3.80t	3.66ddd	4.09dd	3.92dd
20 [b,g]	I	5.38m	5.38m	5.35m	5.23t	4.10m	4.25dd	3.99dd
21 [b,c]	I	5.86bd	5.42dd	5.13dd	5.18t	3.78ddd	4.23dd	4.10dd
22 [a,e]	I	5.97m	4.45m	4.24m	4.12t	3.94m	4.17m	4.17m
23 [a,c]	I	5.77m	4.20m	3.92dd	3.83t	3.68ddd	4.11dd	3.95dd

Table 1 (Continued)

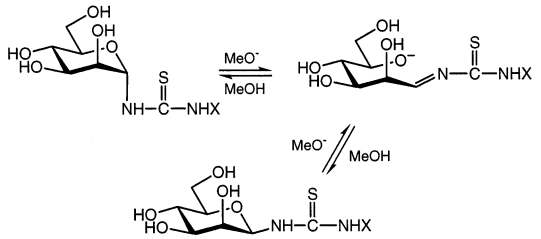
		Coupling constants (Hz)						
		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
6 [a,d]	I	3.7	9.5	9.5	9.5	–	–	–
	II	6.5	9.4	9.4	9.4	4.3	2.2	12.6
6 [b,d]	I	3.7	9.5	9.5	9.5	–	–	–
	II	9.4	9.4	9.4	9.4	4.3	2.2	12.6
7 [a,f]	I	3.9	9.4	9.4	9.4	–	–	–
	II	9.1	9.1	9.1	9.1	1.6	–	12.1
	III	7.9	9.2	9.2	9.2	–	–	–
7 [b,d]	I	3.8	9.6	9.6	9.6	3.2	4.5	–
	II	9.4	9.4	9.4	9.4	1.8	5.4	12.1
	III	7.9	9.3	9.3	9.3	4.4	2.4	12.4
8 [a,f]	I	3.9	9.8	9.8	9.8	–	–	–
	II	9.4	9.4	9.4	9.4	2.2	5.1	12.4
	III	7.9	10.3	3.3	0	–	–	–
8 [b,c]	I	3.7	9.4	9.4	9.4	2.4	3.6	–
	II	9.4	9.4	9.4	9.4	2.0	5.6	10.8
	III	7.9	10.3	3.4	0.9	6.2	7.5	11.1
9 [a,f]	I	3.8	9.4	9.4	9.4	2.8	6.5	–
	II	–	–	8.7	8.7	5.1	2.7	12.5
11 [a,f]	I	4.0	9.9	9.9	9.9	–	–	–
	II	9.1	9.1	–	–	0.8	2.0	12.7
	III	8.0	9.4	9.4	9.4	2.2	5.5	12.4
12 [a,f]	I	4.0	9.9	9.9	9.9	–	–	–
	II	9.0	9.0	–	–	1.2	2.0	11.8
	III	7.8	7.8	3.6	0	–	–	–
13 [a,e]	I	3.3	9.7	9.7	9.7	–	–	–
	II	2.3	3.3	9.5	9.5	2.5	4.8	12.3
14 [a,e]	I	3.8	9.3	9.3	9.3	–	–	–
	II	1.0	3.2	10.0	10.0	4.2	2.3	12.6
15 [a,e]	I	3.7	9.2	9.2	9.2	–	–	–
	II	1.3	3.1	9.6	9.6	2.0	5.6	12.2
16 [b,c]	I	–	3.0	8.8	8.8	6.2	2.5	12.3
17 [b,c]	I	1.0	3.2	10.0	10.0	5.4	2.3	12.3
18 [a,g]	I	–	3.2	9.6	9.6	2.1	6.6	12.3
19 [a,e]	I	–	3.2	9.3	9.3	2.2	5.8	12.3
20 [b,g]	I	–	–	9.2	9.2	6.0	2.0	12.2
21 [b,c]	I	1.0	3.1	9.9	9.9	5.7	2.5	12.3
22 [a,e]	I	–	–	9.5	9.5	–	–	–
23 [a,c]	I	–	2.8	9.7	9.7	1.9	5.8	12.2

[a] In D_2O.
[b] In $CDCl_3$.
[c] At 313 K.
[d] At 323 K.
[e] At 333 K.
[f] At 343 K.
[g] At 300 MHz.

Table 2
^{13}C NMR data (125.7 MHz) for the new thioureas **6–9** and **11–23**

	Unit	Chemical shifts (δ)					
		C-1	C-2	C-3	C-4	C-5	C-6
6 [a,d,f]	I	99.9	71.9	73.6	71.9	71.5	46.0
	II	82.9	71.3	74.2	69.0	73.3	62.7
6 [b,c]	I	99.6	70.5	73.9	71.0	70.6	45.0
	II	82.9	72.1	73.0	68.5	73.5	62.0
7 [a,e]	I	99.9	71.9	73.8	71.9	71.5	45.6
	II	82.5	72.0	74.5	76.4	73.5	63.0
	III	100.5	72.5	74.2	68.8	71.8	62.6
7 [b,d]	I	99.6	72.7	72.9	71.9	70.0	44.9
	II	82.7	70.6	72.2	76.0	74.8	61.8
	III	100.4	71.0	72.9	68.0	71.6	61.6
8 [a,e]	I	99.8	71.8	73.6	71.8	70.5	45.7
	II	82.3	73.2	74.2	75.8	74.5	63.0
	III	100.3	71.1	71.5	68.6	71.9	60.7
8 [b,c]	I	99.6	72.3	72.9	70.7	70.0	44.8
	II	82.8	71.2	72.2	75.8	74.8	61.9
	III	100.7	69.2	70.9	66.7	70.7	60.7
9 [a,e]	I	100.0	71.9	73.6	71.8	70.3	45.8
	II	80.3	69.8	69.5	67.2	70.2	62.7
9 [b,c]	I	99.7	72.1	73.4	72.1	69.5	45.6
	II	80.7	69.0	68.5	66.2	70.2	62.3
11 [a,e]	I	99.9	71.9	73.6	72.0	70.4	45.9
	II	84.0	72.6	76.7	79.2	75.7	60.9
	III	103.1	73.9	76.3	70.3	76.6	61.4
12 [a,e]	I [f]	83.6	71.6	73.2	71.6	70.0	44.9
	II	99.6	72.1	75.7 [g]	78.4	76.4	60.4
	III	103.2	71.3	72.9	68.9	75.5 [g]	61.4
13 [a,c]	I	101.8	73.0	75.4	73.8 [g]	71.9	48.1
	II	85.1	72.0	73.9 [g]	69.2	76.2	63.2
14 [a,d]	I	99.7	71.8	73.4	71.6	70.1	45.7
	II	81.1	70.5	72.3	66.2	73.3	62.7
15 [a,d]	I	102.4	74.4	76.0	74.2	72.5	48.3
	II	85.0	73.1	76.6	69.7	80.6	64.2
16 [b,c]	I	80.7	68.7	68.4	66.2	70.0	62.2
17 [b,c]	I	81.0	70.2	71.4	65.5	74.0	62.3
18 [a,e]	I	82.6	70.0	71.1	67.7	74.3	61.4
19 [a,d]	I	84.0	73.1	76.1	69.3	80.1	63.7
20 [b,c]	I	80.7	68.4	68.3	65.8	69.4	61.9
21 [b,c]	I	81.0	69.9	71.4	65.6	74.0	62.3
22 [a,d]	I	82.7	70.0	71.0	67.4	74.2	61.2
23 [a,c]	I	82.9	71.7	74.9	68.0	78.8	62.4

[a] In D_2O.
[b] In $CDCl_3$.
[c] At 313 K.
[d] At 333 K.
[e] At 343 K.
[f] At 75.5 MHz.
[g] Assignments may be reversed.



Scheme 3.

pure deacetylated compounds **13**, **15**, **18**, **19**, **22** and **23**. The anomeric configuration was confirmed in all cases by $J_{C\text{-}1,H\text{-}1}$ measurements (164–168 Hz for α- and 152–155 Hz for β-derivatives) [30].

At present, it is not clear why the *manno*-configured glycopyranosylthioureas anomerize upon treatment with base and the others do not. Probably, anomerization proceeds through an open-chain Schiff base-type intermediate, whose formation must be favored by the relatively acidic character of the glycosidic thiourea NH proton [31], following a mechanistic pattern analogous to that proposed for the anomerization of glycosylamines [28,32,33] (Scheme 3). One could expect that the electronic delocalization of π electrons in the thiourea ground state, resulting in a positive charge density at the NH region [34], would then favor the equatorial orientation of anomeric thioureido substituents by virtue of the reverse anomeric effect [35].

In conclusion, we have shown that coupling of per-*O*-acetylated glycosyl isothiocyanates and unprotected amino sugars, followed by catalytic deacetylation, provides a convenient access to thiourea-linked pseudooligosaccharides. The anomerization side reaction previously observed for D-mannopyranosylthiourea derivatives can be totally avoided by performing the last step at 0 °C. In all cases, the final compounds are configurationally stable in the absence of base.

3. Experimental

Materials and methods.—Methyl 6-amino-6-deoxy-α-D-glucopyranoside (**4**) was prepared from commercial grade methyl α-D-glucopyranoside in three steps, by direct replacement of the primary OH-6 by iodine, nucleophilic displacement by azide anion in DMF, and final Staudinger reduction of the 6-azido derivative with triphenylphosphine in dioxane–MeOH, followed by in situ hydrolysis of the resulting phosphinimine with ammonium hydroxide, as previously reported [25]. β-D-Mannopyranosylamine (**24**) [28] was prepared from D-mannose in 85% yield by treatment of a 0.2 M aq solution with ammoniun hydrogencarbonate and concentrated ammonia following the procedure reported by Lubineau et al. [36].

A Perkin–Elmer model 141 MC polarimeter and 1 dm tubes were used for measurement of specific rotations at 22 °C. Infrared spectra were recorded on a Bomem Michelson MB-120 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at 500 (125.7) and 300 (75.5) MHz with, respectively, Bruker 500 AMX and 300 AMX spectrometers. Chemical shifts are given in ppm with reference to tetramethylsilane as internal standard. Assignments of ^{1}H and ^{13}C signals were assisted by 2D COSY and HETCOR experiments. 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 thioglycerol, and the positive ions were separated and accelerated over a potential of 7 kV; NaI was added as cationizing agent. TLC was performed with E. Merck precoated TLC plates, Silica Gel 30F-245, with visualization 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). Microanalyses were performed by the Instituto de Investigaciones Químicas (CSIC, Sevilla).

General procedure for the preparation of partially protected (**6–9**, **14**) *and fully unprotected methyl 6-deoxy-6-glycosylthioureido-α-D-glucopyranoside derivatives* (**10–13**, **15**).—A solution of methyl 6-amino-6-deoxy-α-D-glucopyranoside [25] (**4**, 75 mg, 0.38 mmol) and the corresponding per-*O*-acetylglycopyranosyl isothiocyanate **1–3**, **5** [16,26,27] or **28** (0.38 mmol) in pyridine (2 mL) was stirred for 2 h at room temperature (rt). The solvent was evaporated and the residue was chromatographed (45:5:3 EtOAc–EtOH–H_2O) to afford the thiourea adducts **6–9** and **14**, re-

spectively. Subsequent Zemplén deacetylation of **6**–**8** (0.2 mmol) in MeOH (10 mL) was effected by treatment with methanolic NaOMe (0.1 equiv per mol of acetate) at rt for 3 h, giving the fully unprotected pseudooligosaccharides **10**–**12**. Under identical reaction conditions, compounds **9** and **14** led to a mixture of the α- and β-mannopyranosylthioureido derivatives **13** and **15**. Pure samples of **13** and **15** were obtained by performing the deacetylation step at 0 °C with 0.5 equiv of MeOH per mol of acetate and further neutralization (Amberlite IR-120 H^+) at the same temperature.

Methyl 6-deoxy-6-(2,3,4,6-tetra-O-*acetyl-β-*D-*glucopyranosylthioureido)-α-*D-*glucopyranoside* (**6**).—Yield: 202 mg (90%); $[\alpha]_D$ +27.3° (*c* 1.0, H_2O); R_f 0.49 (9:1 CH_2Cl_2–MeOH); NMR: ^1H (500 MHz, D_2O, 323 K) Table 1 and δ 3.63 (s, 3 H, O*Me*), 2.36, 2.35, 2.34, and 2.32 (4 s, each 3 H, 4 *Me*CO); ^1H (500 MHz, $CDCl_3$, 333 K) Table 1 and δ 7.28 (bs, 2 H, NH, N′H), 3.40 (s, 3 H, O*Me*), 2.04, 2.03, 2.00, and 1.98 (4 s, each 3 H, 4 *Me*CO); ^{13}C (125.7 MHz, D_2O, 323 K) Table 2 and δ 183.5 (C=S), 172.4, 172.3 (4 CO), 55.7 (OMe), 20.6 and 20.5 (4 *Me*CO); ^{13}C (125.7 MHz, $CDCl_3$, 313 K) Table 2 and δ 184.7 (C=S), 171.2, 170.8, 169.8, 169.6 (4 CO), 55.5 (OMe), and 20.7 (4 *Me*CO). Anal. Calcd for $C_{22}H_{34}N_2O_{14}S$: C, 45.36; H, 5.88; N, 4.81. Found: C, 45.25; H, 5.98; N, 4.72.

Methyl 6-deoxy-6-(2,3,6,2′,3′,4′,6′-hepta-O-*acetyl-β-cellobiosylthioureido)-α-*D-*glucopyranoside* (**7**).—Yield: 300 mg (89%); $[\alpha]_D$ −183.0° (*c* 1.1, CH_2Cl_2); R_f 0.34 (45:5:3 EtOAc–EtOH–water); NMR: ^1H (500 MHz, D_2O, 323 K) Table 1 and δ 4.07 (s, 3 H, O*Me*), 2.69, 2.68, 2.64, 2.63, 2.61, and 2.58 (7 s, each 3 H, 7 *Me*CO); ^1H (500 MHz, $CDCl_3$, 313 K) Table 1 and δ 6.95 (bs, 2 H, NH, N′H), 3.41 (s, 3 H, O*Me*), 2.11, 2.08 2.06, 2.03, 2.02, and 1.97 (7 s, each 3 H, 7 *Me*CO); ^{13}C (125.7 MHz, D_2O, 343 K) Table 2 and δ 184.5 (C=S), 174.1, 174.0, 173.4, 174.3, 173.2, 173.0, 172.8 (7 CO), 55.6 (OMe), 20.8, 20.7, 20.6, 20.5 and 20.4 (7 *Me*CO); ^{13}C (125.7 MHz, $CDCl_3$, 313 K) Table 2 and δ 184.7 (C=S), 171.2, 170.8, 169.8, 169.6 (4 CO), 55.5 (OMe), and 20.7 (4 *Me*CO); ^{13}C (125.7 MHz, $CDCl_3$, 313 K) Table 2 and δ 184.7 (C=S), 170.9, 170.7, 170.3, 170.0, 169.3, 169.1, 168.8 (7 CO), 55.4 (OMe), and 20.5 (7 *Me*CO); FABMS: *m*/*z* 893 (30%, $[M+Na]^+$). Anal. Calcd for $C_{34}H_{50}N_2O_{22}S$: C, 46.89; H, 5.78; N, 3.22. Found: C, 46.89; H, 5.75; N, 3.22.

Methyl 6-deoxy-6-(2,3,6,2′,3′,4′,6′-hepta-O-*acetyl-β-lactosylthioureido)-α-*D-*glucopyranoside* (**8**).—Yield: 287 mg (85%); $[\alpha]_D$ −120.3° (*c* 1.1, CH_2Cl_2); R_f 0.50 (45:5:3 EtOAc–EtOH–water); NMR: ^1H (500 MHz, D_2O, 343 K) Table 1 and δ 3.91 (s, 3 H, O*Me*), 2.73, 2.68, 2.66, 2.65, 2.64, 2.62, and 2.54 (7 s, each 3 H, 7 *Me*CO); ^1H (500 MHz, $CDCl_3$, 313 K) Table 1 and δ 7.06 (bs, 2 H, NH, N′H), 3.41 (s, 3 H, O*Me*), 2.11, 2.08, 2.06, 2.03, 2.02, and 1.97 (7 s, each 3 H, 7 *Me*CO); ^{13}C (125.7 MHz, D_2O, 343 K) Table 2 and δ 184.5 (C=S), 174.1, 174.0, 173.4, 174.3, 173.2, 173.0, 172.8 (7 CO), 55.6 (OMe), 20.8, 20.7, 20.6, 20.5 and 20.4 (7 *Me*CO); ^{13}C (125.7 MHz, D_2O, 343 K) Table 2 and δ 184.4 (C=S), 174.0, 173.7, 174.3, 173.2, 173.0, 172.8, 172.7 (7 CO), 55.5 (OMe), 20.6, 20.5 and 20.4 (7 *Me*CO); ^{13}C (125.7 MHz, $CDCl_3$, 313 K) Table 2 and δ 184.7 (C=S), 170.9, 170.7, 170.3, 170.0, 169.3, 169.1, 168.8 (7 CO), 55.4 (OMe), 20.7, 20.6, 20.4, and 20.3 (7 *Me*CO); FABMS: *m*/*z* 893 (100%, $[M+Na]^+$). Anal. Calcd for $C_{34}H_{50}N_2O_{22}S$: C, 46.89; H, 5.78; N, 3.22. Found: C, 46.72; H, 5.45; N, 3.22.

Methyl 6-deoxy-6-(2,3,4,6-tetra-O-*acetyl-α-*D-*mannopyranosylthioureido)-α-*D-*glucopyranoside* (**9**).—Yield: 196 mg (87%); $[\alpha]_D$ +69.0° (*c* 1.0, CH_2Cl_2); R_f 0.47 (45:5:3 EtOAc–EtOH–water); NMR: ^1H (500 MHz, D_2O, 343 K) Table 1 and δ 3.76 (s, 3 H, O*Me*), 2.58, 2.51, 2.50, and 2.45 (4 s, each 3 H, 4 *Me*CO); ^1H (500 MHz, $CDCl_3$, 313 K) Table 1 and δ 7.65 (bs, 1 H, NH), 7.29 (bs, 1 H, N′H), 3.41 (s, 3 H, O*Me*), 2.20, 2.15, 2.12, and 1.98 (4 s, each 3 H, 4 *Me*CO); ^{13}C (125.7 MHz, D_2O, 343 K) Table 2 and δ 183.9 (C=S), 174.1, 173.2, 173.1, 173.0 (4 CO), 55.7 (OMe), 20.7, 20.6, 20.5 and 20.4 (4 *Me*CO); ^{13}C (125.7 MHz, $CDCl_3$, 313 K) Table 2 and δ 184.3 (C=S), 170.6, 170.1, 169.9, 169.4 (4 CO), 55.4 (OMe), and 20.5 (4 *Me*CO); FABMS: *m*/*z* 605 (100%, $[M+Na]^+$). Anal. Calcd for $C_{22}H_{34}N_2O_{14}S$: C, 45.36; H, 5.88; N, 4.81. Found: C, 45.14; H, 5.71; N, 4.80.

Methyl 6-deoxy-6-(β-D-glucopyranosylthioureido)-α-D-glucopyranoside (**10**).—Yield: 80 mg (96%); $[\alpha]_D$ +42.5° (*c* 0.7, H_2O); lit. [13] $[\alpha]_D$ +42.8° (*c* 0.6, H_2O). The ^1H and ^{13}C NMR data were in full agreement with those reported in the literature [13].

Methyl 6-deoxy-6-(β-cellobiosylthioureido)-α-D-glucopyranoside (**11**).—Yield: 112 mg (98%); $[\alpha]_D$ +22.0° (*c* 0.7, H_2O); R_f 0.47 (2:1:1 BuOH–AcOH–water); NMR: ^1H (500 MHz, D_2O, 343 K) Table 1 and δ 3.82 (s, 3 H, O*Me*); ^{13}C (125.7 MHz, D_2O, 343 K) Table 2 and δ 184.2 (C=S), and 55.7 (OMe); FABMS: *m*/*z* 599 (10%, $[M+Na]^+$). Anal. Calcd for $C_{20}H_{36}N_2O_{15}S$: C, 41.66; H, 6.29; N, 4.86. Found: C, 41.45; H, 6.32; N, 4.70.

Methyl 6-deoxy-6-(β-lactosylthioureido)-α-D-glucopyranoside (**12**).—Yield: 110 mg (95%); $[\alpha]_D$ +34.0° (*c* 1.1, H_2O); R_f 0.42 (2:1:1 BuOH–AcOH–water); NMR: ^1H (500 MHz, D_2O, 343 K) Table 1 and δ 3.79 (s, 3 H, O*Me*); ^{13}C (75.5 MHz, D_2O, 313 K) Table 2 and δ 184.8 (C=S), and 55.5 (OMe); FABMS: *m*/*z* 599 (100%, $[M+Na]^+$). Anal. Calcd for $C_{20}H_{36}N_2O_{15}S$: C, 41.66; H, 6.29; N, 4.86. Found: C, 41.64; H, 6.17; N, 4.87.

Methyl 6-deoxy-6-(α-D-mannopyranosylthioureido)-α-D-glucopyranoside (**13**).—Yield: 80 mg (96%); $[\alpha]_D$ +116.4° (*c* 2.2, MeOH); R_f 0.51 (2:1:1 BuOH–AcOH–water); NMR: ^1H (500 MHz, D_2O, 333 K) Table 1 and δ 3.92 (s, 3 H, O*Me*); ^{13}C (125.7 MHz, D_2O, 313 K) Table 2 and δ 184.6 (C=S), 81.1 (C-1′, $J_{C\text{-}1',H\text{-}1'}$ 164.7 Hz), and 56.9 (OMe); FABMS: *m*/*z* 415 (20%, $[M+H]^+$). Anal. Calcd for $C_{14}H_{26}N_2O_{10}S$: C, 40.57; H, 6.32; N, 6.76. Found: C, 40.35; H, 6.19; N, 6.42.

Methyl 6-deoxy-6-(2,3,4,6-tetra-O-acetyl-β-D-mannopyranosylthioureido)-α-D-glucopyranoside (**14**).—Yield: 191 mg (85%); $[\alpha]_D$ −11.0° (*c* 0.5, CH_2Cl_2); R_f 0.41 (45:5:3 EtOAc–EtOH–water); NMR: ^1H (500 MHz, D_2O, 333 K) Table 1 and δ 3.81 (s, 3 H, O*Me*), 2.71, 2.56, 2.54, and 2.46 (4 s, each 3 H, 4 *Me*CO); ^{13}C (125.7 MHz, D_2O, 313 K) Table 2 and δ 184.2 (C=S), 174.0, 173.5, 173.3, 172.9 (4 CO), 55.6 (OMe), 20.6, 20.5, and 20.4 (4 *Me*CO); FABMS: *m*/*z* 605 (100%, $[M+Na]^+$). Anal. Calcd for $C_{22}H_{34}N_2O_{14}S$: C, 45.36; H, 5.88; N, 4.81. Found: C, 45.27; H, 5.66; N, 4.80.

Methyl 6-deoxy-6-(β-D-mannopyranosylthioureido)-α-D-glucopyranoside (**15**).—Yield: 82 mg (99%); $[\alpha]_D$ +40.7° (*c* 1.1, MeOH); R_f 0.53 (2:1:1 BuOH–AcOH–water); NMR: ^1H (500 MHz, D_2O, 333 K) Table 1 and δ 3.96 (s, 3 H, O*Me*); ^{13}C (125.7 MHz, D_2O, 323 K) Table 2 and δ 185.6 (C=S), 85.0 (C-1′, $J_{C\text{-}1',H\text{-}1'}$ 152.1 Hz), and 58.2 (OMe); FABMS: *m*/*z* 415 (100%, $[M+Na]^+$). Anal. Calcd for $C_{14}H_{26}N_2O_{10}S$: C, 40.57; H, 6.32; N, 6.76. Found: C, 40.34; H, 6.10; N, 6.41.

N-*Ethyl*-N′-*(α- and β-D-mannopyranosyl)-thioureas* (**16–19**).—To a solution of ethylamine hydrochloride (27 mg, 0.33 mmol) in water (5 mL), satd aq $NaHCO_3$ was added until pH 10. A solution of 2,3,4,6-tetra-*O*-acetyl-α(β)-D-mannopyranosyl isothiocyanate (**5** or **28**, 116 mg, 0.30 mmol) in CH_2Cl_2 (5 mL) was then added, and the biphasic reaction mixture was vigorously stirred for 30 min. The organic layer was separated, washed with water (2 × 5 mL), dried ($NaSO_4$), and concentrated, and the residue was purified by column chromatography using 1:1 EtOAc–hexanes as eluent to give thioureas **16** and **17**, respectively. Subsequent deacetylation was effected at 0 °C as described above to afford the fully unprotected mannopyranosylthioureas **18** and **19** in virtually quantitative yield.

N-*Ethyl*-N′-*(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)thiourea* (**16**). Yield: 115 mg (89%); $[\alpha]_D$ +124.5° (*c* 1.1 CH_2Cl_2); R_f 0.23 (1:1 EtOAc–hexanes); NMR: ^1H (500 MHz, $CDCl_3$, 313 K) Table 1 and δ 6.81 (bs, 1 H, NH), 6.72 (bs, 1 H, N′H), 3.60 (m, 2 H, CH_2CH_3), 2.13, 2.05, 2.03, 2.00 (4 s, each 3 H, 4 *Me*CO), and 1.22 (t, 3 H, $^3J_{H,H}$ 7.3 Hz, CH_2CH_3); ^{13}C (125.7 MHz, $CDCl_3$, 313 K) Table 2 and δ 183.8 (C=S), 170.2, 169.8, 169.5 (4 CO), 40.5 (CH_2CH_3), 20.6, 20.4, 20.3, 20.2 (4 *Me*CO), and 14.1 (CH_2CH_3); FABMS: *m*/*z* 457 (100%, $[M+Na]^+$) and 435 (50%, $[M+H]^+$). Anal. Calcd for $C_{17}H_{26}N_2O_9S$: C, 35.05; H, 4.50; N, 4.81. Found: C, 34.93; H, 4.31; N, 4.77.

N-*Ethyl*-N′-*(2,3,4,6-tetra-O-acetyl-β-D-mannopyranosyl)thiourea* (**17**). Yield: 110 mg (85%); $[\alpha]_D$ −16.0° (*c* 0.9, CH_2Cl_2); R_f 0.17 (1:1 EtOAc–hexanes); NMR: ^1H (500 MHz, $CDCl_3$, 313 K) Table 1 and δ 6.40 (bs, 1 H, NH), 5.90 (bs, 1 H, N'H), 3.47 (bs, 2 H,

CH_2CH_3), 2.22, 2.09 2.05, 1.98 (4 s, each 3 H, 4 *Me*CO), and 1.22 (t, 3 H, $^3J_{H,H}$ 7.5 Hz, CH_2CH_3); ^{13}C (125.7 MHz, $CDCl_3$, 313 K) Table 2 and δ 182.3 (C=S), 170.7, 170.6, 169.6 (4 CO), 39.4 (CH_2CH_3), 20.8, 20.7, 20.6, 20.4 (4 *Me*CO), and 13.8 (CH_2CH_3); FABMS: *m/z* 457 (100%, $[M+Na]^+$). Anal. Calcd for $C_{17}H_{26}N_2O_9S$: C, 35.05; H, 4.50; N, 4.81. Found: C, 35.05; H, 4.48; N, 4.61.

N-*Ethyl*-N′-*(α*-D-*mannopyranosyl)thiourea* (**18**). $[\alpha]_D$ +78.9° (*c* 1.0, MeOH); R_f 0.65 (2:1:1 BuOH–AcOH–water); NMR: ^1H (500 MHz, D_2O, 333 K) Table 1 and δ 3.90 (m, 2 H, CH_2CH_3), and 1.53 (t, 3 H, $^3J_{H,H}$ 7.0 Hz, CH_2CH_3); ^{13}C (125.7 MHz, D_2O, 333 K) Table 2 and δ 182.3 (C=S), 82.6 (C-1, $J_{C\text{-}1,H\text{-}1}$ 166.0 Hz), 40.5 (CH_2CH_3), and 13.8 (CH_2CH_3); FABMS: *m/z* 267 (100%, $[M+H]^+$). Anal. Calcd for $C_9H_{18}N_2O_5S$: C, 40.59; H, 6.81; N, 10.52. Found: C, 49.49; H, 6.69; N, 10.43.

N-*Ethyl*-N′-*(β*-D-*mannopyranosyl)thiourea* (**19**). $[\alpha]_D$ −3.1° (*c* 0.8, MeOH); R_f 0.72 (2:1:1 BuOH–AcOH–water); NMR: ^1H (500 MHz, D_2O, 333 K) Table 1 and δ 3.72 (m, 2 H, CH_2CH_3), and 1.37 (t, 3 H, $^3J_{H,H}$ 7.2 Hz, CH_2CH_3); ^{13}C (125.7 MHz, D_2O, 333 K) Table 2 and δ 183.8 (C=S), 84.0 (C-1, $J_{C\text{-}1,H\text{-}1}$ 153.0 Hz), 39.8 (CH_2CH_3), and 15.9 (CH_2CH_3); FABMS: *m/z* 289 (90%, $[M+Na]^+$), 267 (100%, $[M+H]^+$). Anal. Calcd for $C_9H_{18}N_2O_5S$: C, 40.59; H, 6.81; N, 10.52. Found: C, 40.37; H, 6.75; N, 10.33.

N-*Benzyl*-N′-*(α- and β*-D-*mannopyranosyl)-thioureas* (**20–23**).—To a solution of 2,3,4,6-tetra-*O*-acetyl-α(β)-D-mannopyranosyl isothiocyanate (**5** or **28**, 116 mg, 0.30 mmol) in CH_2Cl_2 (5 mL), benzylamine (33 μL, 0.30 mmol) was added. The reaction mixture was stirred for 15 min, then concentrated and purified by column chromatography (1:1 EtOAc–hexanes) to give thioureas **20** and **21**, respectively. Subsequent deacetylation was effected at 0 °C as described above to afford the fully unprotected mannopyranosylthioureas **22** and **23** in virtually quantitave yield.

N-*Benzyl*-N′-*(2,3,4,6-tetra*-O-*acetyl-α*-D-*mannopyranosyl)thiourea* (**20**). Yield: 184 mg (97%); $[\alpha]_D$ +70.9° (*c* 1.0, CH_2Cl_2); R_f 0.26 (1:1 EtOAc–hexanes); NMR: ^1H (300 MHz, $CDCl_3$) Table 1 and δ 7.36–7.17 (m, 7 H, Ph, NH, N′H), 4.76 (d, 2 H, $^3J_{H,H}$ 4.7 Hz, CH_2Ph), 2.15, 2.05, 2.02, and 1.88 (4 s, each 3 H, 4 *Me*CO); ^{13}C (75.5 MHz, $CDCl_3$) Table 2 and δ 184.3 (C=S), 170.4, 170.1, 169.5 (4 CO), 136.0, 128.7, 127.7, 127.5 (Ph), 49.4 (CH_2Ph), 20.6, 20.5, and 20.3 (4 *Me*CO); FABMS: *m/z* 519 (100%, $[M+Na]^+$). Anal. Calcd for $C_{22}H_{28}N_2O_9S$: C, 53.21; H, 5.68; N, 5.64. Found: C, 53.18; H, 5.55; N, 5.53.

N-*Benzyl*-N′-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*mannopyranosyl)thiourea* (**21**). Yield: 170 mg (91%); $[\alpha]_D$ −16.5° (*c* 1.0, CH_2Cl_2); R_f 0.31 (1:1 EtOAc–hexanes); NMR: ^1H (500 MHz, $CDCl_3$, 313 K) Table 1 and δ 7.36–7.26 (m, 5 H, Ph), 6.53 (bs, 1 H, NH), 6.35 (d, 1 H, $J_{1,N'H}$ 8.1 Hz, N′H), 4.65 (bs, 2 H, CH_2Ph), 2.12, 2.02, 1.99, and 1.96 (4 s, each 3 H, 4 *Me*CO); ^{13}C (125.7 MHz, $CDCl_3$, 313 K) Table 2 and δ 182.9 (C=S), 170.4, 170.3, 169.5 (4 CO), 136.0, 128.9, 127.9, 127.5 (Ph), 48.6 (CH_2Ph), 20.6, 20.4, 20.3, and 20.2 (4 *Me*CO); FABMS: *m/z* 519 (100%, $[M+Na]^+$). Anal. Calcd for $C_{22}H_{28}N_2O_9S$: C, 53.21; H, 5.68; N, 5.64. Found: C, 53.25; H, 5.58; N, 5.64.

N-*Benzyl*-N′-*(α*-D-*mannopyranosyl)thiourea* (**22**). $[\alpha]_D$ +37.0° (*c* 0.9, MeOH); R_f 0.75 (2:1:1 BuOH–AcOH–water); NMR: ^1H (500 MHz, D_2O, 333 K) Table 1 and δ 7.85–7.75 (m, 5 H, Ph), 5.25 and 5.14 (2 d, each 1 H, $^2J_{H,H}$ 15.0 Hz, CH_2Ph); ^{13}C (125.7 MHz, D_2O, 313 K) Table 2 and δ 182.5 (C=S), 138.1, 129.2, 127.9, 127.6 (Ph), 82.7 (C-1, $J_{C\text{-}1,H\text{-}1}$ 165.6 Hz), and 48.5 (CH_2Ph); FABMS: *m/z* (40%, $[M+Na]^+$), (100%, $[M+H]^+$). Anal. Calcd for $C_{14}H_{20}N_2O_5S$: C, 51.20; H, 6.14; N, 8.53. Found: C, 51.00; H, 6.05; N, 8.34.

N-*Benzyl*-N′-*(β*-D-*mannopyranosyl)thiourea* (**23**). $[\alpha]_D$ −8.0° (*c* 1.0, MeOH); R_f 0.80 (2:1:1 BuOH–AcOH–water); NMR: ^1H (500 MHz, D_2O, 313 K) Table 1 and δ 7.66–7.53 (m, 5 H, Ph), and 4.99 (m, 2 H, CH_2Ph); ^{13}C (125.7 MHz, D_2O, 313 K) Table 2 and δ 183.7 (C=S), 139.0, 130.2, 129.0, 128.6 (Ph), 82.9 (C-1, $J_{C\text{-}1,H\text{-}1}$ 155.2 Hz), and 49.2 (CH_2Ph); FABMS: *m/z* 351 (40%, $[M+Na]^+$), 329 (100%, $[M+H]^+$). Anal. Calcd for $C_{14}H_{20}N_2O_5S$: C, 51.20; H, 6.14; N, 8.53. Found: C, 51.03; H, 6.21; N, 8.30.

N-*(2,2-Diethoxycarbonylvinyl)-β*-D-*manno-pyranosylamine* (**25**).—Treatment of β-D-mannopyranosylamine (**24**, 0.496 g, 2.72 mmol) in dry MeOH (10 mL) with diethyl

ethoxymethylenemalonate (0.83 mL, 4.06 mmol) overnight, as reported [29], and column chromatography (45:5:3 EtOAc–H_2O–EtOH) of the resulting reaction mixture afforded **25** (0.75 g, 71%), mp 205–206 °C, $[\alpha]_D$ +81.1° (*c* 1, pyridine), R_f 0.46 (45:5:3 EtOAc–EtOH–water); lit. [29]: mp 207–209 °C, $[\alpha]_D$ +83° (pyridine); ^{13}C NMR (75.5 MHz, CD_3OD) δ 169.0 (C=O chelated), 167.8 (C=O free), 159.1 (=CH), 92.8 (C=), 87.2 (C-1), 79.9 (C-5), 75.3 (C-3), 71.9 (C-2), 67.9 (C-4), 62.8 (C-6), 61.0 (2 CH_2), and 14.7 (2 CH_3).

2,3,4,6-Tetra-O-*acetyl*-N-*(2,2-diethoxycarbonylvinyl)-β*-D-*mannopyranosylamine* (**26**).—Conventional acetylation of **25** (0.75 g, 2.1 mmol) with 1:1 Ac_2O–pyridine (10 mL) and column chromatography (1:1 EtOAc–hexanes) of the resulting product yielded **26** (0.67 g, 60%), mp 57–58 °C, $[\alpha]_D$ −23.1° (*c* 1.5, CH_2Cl_2), R_f 0.46 (1:1 EtOAc–hexanes); lit. [29]: mp 54–58 °C, $[\alpha]_D$ −47° ($CHCl_3$); NMR: ^1H (300 MHz, $CDCl_3$) δ 9.53 (dd, 1 H, $J_{1,NH}$ 9.2 Hz, $J_{=CH,\ NH}$ 13.1 Hz, NH), 7.99 (d, 1 H, =CH), 4.25, 4.17 (2 q, each 2 H, $^3J_{H,H}$ 7.0 Hz, CH_2CH_3), 5.45 (dd, 1 H, $J_{1,2}$ 1.4 Hz, $J_{2,3}$ 3.3 Hz, H-2), 5.23 (t, 1 H, $J_{3,4} = J_{4,5}$ 10.0 Hz, H-4), 5.10 (dd, 1 H, H-3), 4.83 (dd, 1 H, H-1), 4.26 (dd, 1 H, $J_{5,6a}$ 5.4 Hz, $J_{6a,6b}$ 12.4 Hz, H-6a), 4.18 (dd, 1 H, $J_{5,6b}$ 2.4 Hz, H-6b), 3.76 (ddd, 1 H, H-5), 2.20, 2.09, 2.04, 1.99 (4 s, each 3 H, 4 *Me*CO), 1.32, and 1.29 (2 t, each 3 H, 2 CH_2CH_3); ^{13}C (75.5 MHz, $CDCl_3$) δ 170.5, 170.1, 169.9, 169.4 (4 CO), 168.1 (C=O chelated), 165.2 (C=O free), 156.9 (=CH), 94.1 (=C), 84.3 (C-1), 73.9 (C-5), 70.9 (C-3), 69.0 (C-2), 64.8 (C-4), 62.1 (C-6), 20.7, 20.6, 20.5 (3 *Me*CO), 14.2, and 14.1 (2 CH_2CH_3).

2,3,4,6-Tetra-O-*acetyl-β*-D-*mannopyranosylamine hydrochloride* (**27**).—Through an ice-cooled solution of **26** (2.5 g, 4.83 mmol) in wet CH_2Cl_2 (20 mL) chlorine was bubbled until saturation. The reaction mixture was stirred for 30 min, then evaporated under reduced pressure and washed with diethyl ether to afford **27** in virtually quantitative yield, as seen by ^{13}C NMR spectroscopy. Compound **27**, isolated as a white amorphous solid, was used in subsequent reactions without further purification. FABMS: *m/z* 371 ($[M + Na - HCl]^+$); NMR: ^{13}C (125.7 MHz, $CDCl_3$) δ 170.8, 170.7, 169.8, 169.4 (4 CO), 78.5 (C-1), 74.8 (C-5), 71.0 (C-3), 67.5 (C-2), 65.2 (C-4), 61.7 (C-6), 21.2, 20.6, 20.5, and 20.4 (4 *Me*CO).

2,3,4,6-Tetra-O-*acetyl-β*-D-*mannopyranosyl isothiocyanate* (**28**).—To a mixture of 1:1 CH_2Cl_2–H_2O (40 mL) were added **27** (0.25 g, 0.65 mmol), $CaCO_3$ (195 mg, 3 equiv, 1.95 mmol) and $CsCl_2$ (0.077 mL, 1.5 eq, 1 mmol). The reaction mixture was vigorously stirred for 2 h and then filtered. The organic phase was separated, washed with water, and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by column chromatography using 1:2 EtOAc–hexanes as eluent to give **28** (128 mg, 50%); $[\alpha]_D$ −65.6° (*c* 1.0, CH_2Cl_2); R_f 0.55 (1:1 EtOAc–hexanes); IR (film) 2955, 2016, 1750, 1373, 1213, and 1090 cm^{-1}; NMR: ^1H (300 MHz, $CDCl_3$) δ 5.49 (dd, 1 H, $J_{1,2}$ 1.4, $J_{2,3}$ 3.3 Hz, H-2), 5.23 (t, 1 H, $J_{3,4} = J_{4,5}$ 10.0 Hz, H-4), 5.05 (dd, 1 H, H-3), 4.94 (d, 1 H, H-1), 4.25 (dd, 1 H, $J_{5,6a}$ 5.6, $J_{6a,6b}$ 12.4 Hz, H-6a), 4.18 (dd, 1 H, $J_{5,6b}$ 2.7 Hz, H-6b), 3.71 (ddd, 1 H, H-5); ^{13}C (75.5 MHz, $CDCl_3$) δ 171.3, 170.5, 169.8 (3 CO), 146.7 (N=C=S), 82.5 (C-1), 74.5 (C-5), 70.5 (C-3), 69.0 (C-2), 65.0 (C-4), 62.1 (C-6), 20.7, 20.6, 20.5 (4 *Me*CO); FABMS: *m/z* 412 (100%, $[M + Na]^+$). Anal. Calcd for $C_{15}H_{19}NO_9S$: C, 46.27; H, 4.92; N, 3.60. Found: C, 46.45; H, 4.83; N, 3.64.

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