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Synthesis of α- and β-Glycosyl Isothiocyanates via Oxazoline Intermediates

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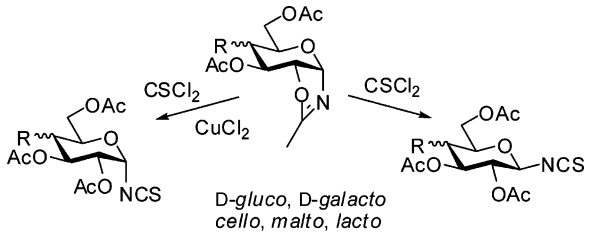

A practical synthesis of acylated glycosyl isothiocyanates from sugar oxazolines, by reaction with thiophosgene, is reported. In the absence of any additive, the reaction is governed by the reverse anomeric effect, leading to the equatorially oriented isothiocyanate. However, in the presence of copper(II) chloride, the reaction proceeds preferentially with retention of the configuration at the anomeric center, providing the axial anomer as the major product. Noteworthy, this strategy allows accessing per-*O*-acetylated glycopyranosyl isothiocyanates with 1,2-cis relative configuration (e.g., the α-anomer in the D-gluco and D-galacto series), a problem that was outside the scope of previous methodologies.

Sugar isothiocyanates rank among the most versatile synthetic intermediates in carbohydrate chemistry. The isothiocyanate group plays a pivotal role in the preparation of a broad series of functional groups such as amide, isonitrile, carbodiimide, and *N*-thiocarbonyl derivatives allowing, simultaneously, the covalent attachment of a quite unrestricted variety of structures to the saccharide moiety.[1] Thus, glycosyl isothiocyanates have been profusely used to construct a battery of *N*-nucleoside and glycosylaminoheterocycles,[1,2] the *N*-glycopeptide linkage present in natural *N*-glycoproteins,[1,3] the cyclic isourea group of trehazoloid glycosidase inhibitors,[1,4] or the thiourea bridge in multivalent glycoconjugates,[1,5] to cite just a few examples.

Several efficient general methods for the introduction of the isothiocyanate functionality at the anomeric position of mono- and oligosaccharides are currently at hand. Most of them rely on either the isothiocyanation reaction of a glycosylamine[1,6] (e.g., **1**) or the nucleophilic displacement of an anomeric leaving group, commonly from a glycosyl halide (e.g., **2** or **4**) by isothiocyanate anion.[1,7] The first approach leads to the corresponding β-glycosyl isothiocyanate (e.g., **3**β) by virtue of the reverse anomeric effect (Scheme 1, a).[8] The second method yields the 1,2-*trans* compound (e.g, the **3**β in the case of a D-glucopyranosyl derivative) or a mixture of the α and β anomers (e.g, the **5**α and **5**β) depending on the participating (Scheme 1, b) or nonparticipating character of the neighboring group (Scheme 1, c). In the frame of a project aiming at developing thiourea-linked glycooligomers for the specific binding of oligonucleotides,[9] we were interested in accessing glycosyl isothiocyanates having the α-configuration in the D-gluco and D-galacto series. The corresponding per-*O*-benzyl ether protected derivatives have previously been obtained from the corresponding glycosyl halides.[7c] However, separation from the β-anomer was rather troublesome, and moreover, further hydrogenolysis of the benzyl groups in the presence of thiocarbonyl functionalities became exceedingly problematic. Using instead ester protection would imply the axial orientation of the NCS groups and a cis-relative disposition with respect to the vicinal *O*-acyl group, a problem that is outside the scope of the above methodologies.[10]

Here, we report a general method for the synthesis of glycosyl isothiocyanates based on the ring-opening reaction of glycosylamine-derived oxazoline precursors (e.g., **6**) with thiophosgene (Scheme 1, c). The transformation proceeds to give the target isothiocyanate while regenerating an acetoxy group at the vicinal carbon atom. The stereochemical outcome of the reaction depends on the nature of the starting sugar template, but it can be tuned to

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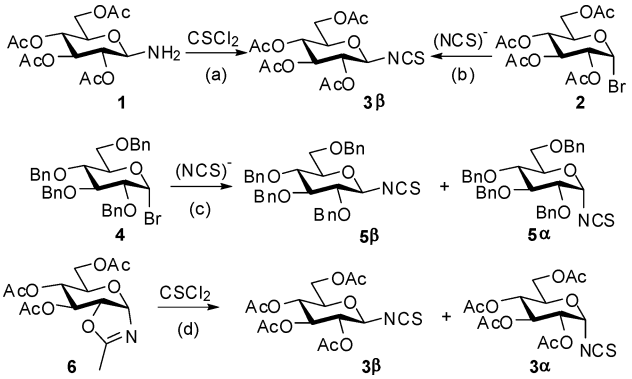
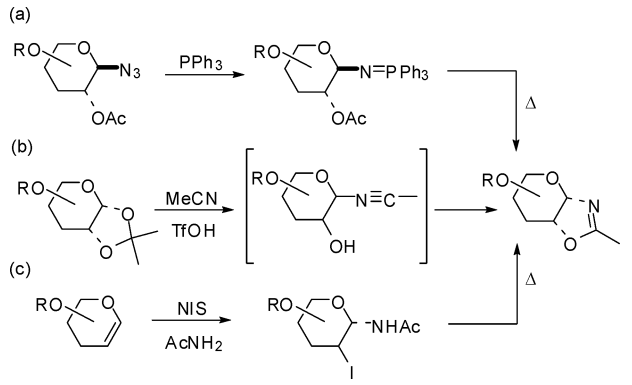
SCHEME 1. Synthetic Routes to Glycosyl Isothiocyanates



SCHEME 2. Synthetic Strategies for the Preparation of Glycooxazolines

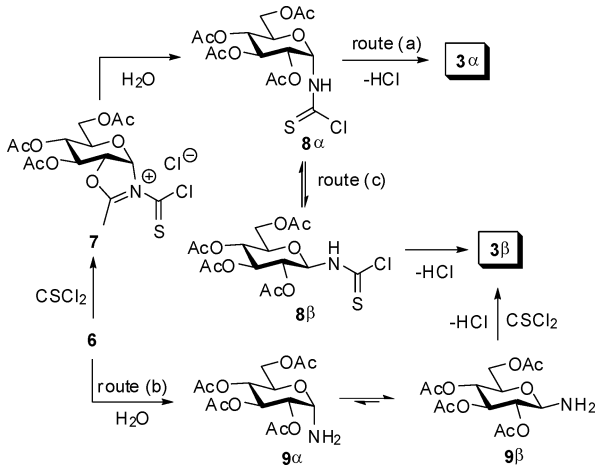


favor the elusive axial−equatorial cis-relative disposition of the isothiocyanate and acyloxy groups (e.g., **3**α). Noteworthy, the acylated glycosyl isothiocyanate anomers can be readily separated by column chromatography, which is an important difference of practical importance as compared with per-*O*-benzyl derivatives.

There have been numerous reports on the synthesis and reactivity of glycooxazolines having the oxygen atom linked to the anomeric carbon atom (C-1 in aldoses).[11] In sharp contrast, the synthetic potential of the *N*-glycosyl positional isomers has been much less explored. Recently, several approaches for the synthesis of this type of sugar derivatives from readily available starting materials, such as glycosyl azides, acetal-protected monosaccharides, or glycals, have been reported, involving intramolecular condensation of glycosylphosphinimes with vicinal ester groups (Scheme 2, a),[12] Ritter-like reaction of transient glycosyl isonitriles (Scheme 2, b)[13] and intramolecular nucleophilic displacement in 2-deoxy-2-iodoaldosylamides, respectively (Scheme 2, c).[14] We have chosen the first two methodologies for accessing aldopyranose- (**6**, **13**−**16**) and aldofuranose- (**17**) or ketose-derived oxazolines (**18**, **19**), respectively (see the Supporting Information).

In all cases, the formation of cis-fused heterocycles is thermodynamically favored, therefore placing the key nitrogen and oxygen atoms in the desired cis-orientation. We reasoned that further reaction with thiophosgene would initially occur

SCHEME 3. Possible Routes Involved in the Transformation of Glycooxazolines into Glycosyl Isothiocyanates



with retention of the configuration to give a transient *N*-chlorothioformyl oxazolinium cation (**7**) that, after hydrolysis, would lead to an *N*-glycosylchlorothioformamide (**8**α). Further elimination of hydrogen chloride would provide the target glycosyl isothiocyanate with 1,2-cis relative configuration (**3**α; Scheme 3, route a). Two parallel processes may, however, compete with the above reaction sequence. First, glycooxazolines are relatively moisture sensitive and can undergo hydrolysis to a kinetic axial glycosylamine (**9**α) that experiences fast isomerization to the equatorial anomer (**9**β; Scheme 3, route b).[15] Second, the transient chlorothioformamide is also susceptible of undergoing anomerization (→ **8**β; Scheme 3, route c).[16] In both cases, the final reaction product would be the 1,2-trans glycosyl isothiocyanate (**3**β). In order to assess the relative prevalence of these three possible concomitant pathways and determine the optimum reaction conditions, preliminary studies on the D-glucopyranosyloxazoline derivative **6** were undertaken.

In dry dichloromethane, the reaction of **6** with thiophosgene led to a complex mixture of highly polar compounds arising, probably, from oligomerization reactions of the highly reactive *N*-chlorothioformyloxazolinium intermediate **7** (Table 1, entry 1). When the reaction was carried out in a heterogeneous mixture of dichloromethane−water−calcium carbonate, a fast conversion into the peracetylated β-D-glucopyranosyl isothiocyanate **3**β was achieved (Table 1, entry 2). The transformation is much faster than oxazoline hydrolysis, suggesting that epimerization of the *N*-glucopyranosylthioamide intermediate is the main reaction pathway. To confirm this point, an experiment using thiocarbonyldiimidazole (TCI) instead of thiophosgene as the isothiocyanation reagent was performed. TLC monitoring of the

(10) Alternative approaches for the synthesis of glycosyl isothiocyanates have been reported on the basis of the addition of iodoisothiocyanate to glycals and on the phosphine imide type reaction of glycosyl azides with triphenylphosphine and carbon disulfide, yet none of these approaches allows accessing the target relative stereochemistry either. See: (a) Santoyo-González, F.; García-Calvo-Flores, F.; Isac-García, J.; Hernández-Mateo, F.; García-Mendoza, P.; Robles-Díaz, R. *Tetrahedron* **1994**, *50*, 2877−2894. (b) Menuel, S.; Porwanski, S., Marsura, A. *New J. Chem.* **2006**, *30*, 603−608.

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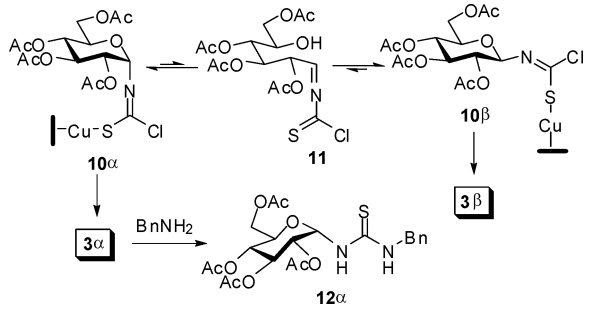
TABLE 1. Synthesis of Glucopyranosyl Isothiocyanates from Glucooxazoline 6

entry	reagent/base	solvent	*T* (°C) reaction time	product[a] (%)	α/β ratio
1	$CSCl_2/Et_3N$	CH_2Cl_2	0−25/1 h	mixture	
2	$CSCl_2/CaCO_3$	$CH_2Cl_2-H_2O$	25/10 min	**3**β (75)	0:100
3	TCI	CH_2Cl_2	0/6 h	**3**β (65)	0:100
4	$CSCl_2/CaCO_3$	acetone	0/2 h	**3**α:**3**β (60)	29:71
5	$CSCl_2-CuCl_2/CaCO_3$	$CH_2Cl_2-H_2O$	25/2 h	**3**α:**3**β (83)	60:40

[a] Isolated yields. When mixtures of anomers are formed, the total yield matches the sum of the individual isolated yields.

SCHEME 4. Copper(II)-Mediated Synthesis of 3α



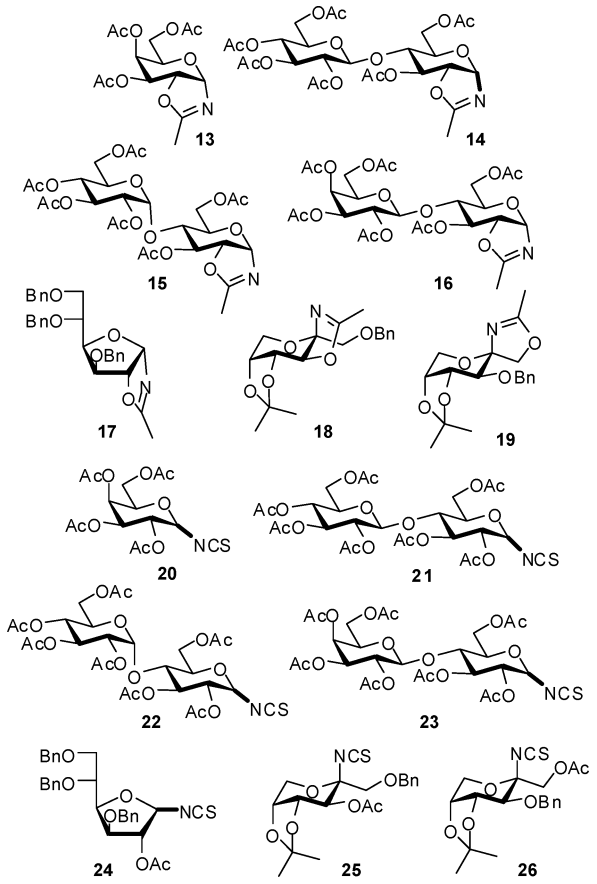
reaction mixture in dry dichloromethane revealed total consumption of the starting compound **6** after 5 h. No formation of glycosyl isothiocyanate **3**β was detected at this stage, however, which discards participation of the reactive glycosylamine **9**β and suggests that the reactions stops at the initial *N*-thiocarbonyl oxazolinium adduct **7**. During the aqueous workup, transformation into **3**β occurred (Table 1, entry 3), which strongly supports an anomerization step at the level of the *N*-glucosylthioamide intermediate **8**α.

From the above results, it was inferred that decreasing the anomerization/elimination ratio was critical in order to shift the reaction toward the target 1,2-cis diastereomer **3**α. Using wet acetone as the solvent, therefore increasing the solvent polarity, afforded a 1:2.5 mixture of **3**α and **3**β, although in lower yield (Table 1, entry 3). Alternatively, the use of copper(II) chloride as an additive was attempted. We hypothesized that the highly thiophilic copper(II) cation would coordinate to the thiocarbonyl sulfur atom in the transient thioformamide (**8**α). Formation of this complex should slow the anomerization process (→ **8**β) through the open-chain form **11** and facilitate chloride anion departure (Scheme 4). Accordingly, under these conditions the **3**α/**3**β ratio rose up to 1.5:1 (83% yield; Table 1, entry 5). The pure 1,2-cis compound **3**α was further transformed into the corresponding *N*-benzyl-*N*′-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)thiourea **12**α with total steroselectivity by reaction with benzylamine, thus confirming its suitability to access α-configured thiourea-linked neoglycoconjugates.

The generality of the methodology was further demonstrated by the transformation of a series of mono- and disaccharide oxazoline derivatives into the corresponding glycosyl isothiocyanates (Chart 1 and Table 2).

The reactivity of the mono- and disaccharide aldopyranosyloxazolines derived from D-galactose, cellobiose, maltose, and lactose **13**−**16**, respectively, was first examined (Table 2, entries 1−8). In all cases, the reaction with thiophosgene in the absence of copper(II) led to corresponding β-glycopyranosyl isothiocyanate (**20**β−**23**β) as the only reaction product, while a binary mixture of the α and β anomers was obtained in the presence

CHART 1. Structures of Glycooxazolines 13−19[a] and Glycosyl Isothiocyanates 20−26[b]



[a] Compound **14** was obtained as an inseparable mixture of the α- and β-anomers that was directly used for its transformation into the corresponding cellobiosyl isothiocyanate **21**. [b]The individual anomers for the aldosyl derivatives **20**−**24** could separated in all cases. They are referred to in the text by the corresponding number followed by the stereochemical notation α or β.

TABLE 2. Synthesis of Glycosyl Isothiocyanates from Glycooxazoline Precursors

entry	oxazoline precursor	reagent/base	solvent	*T* (°C) reactn time	product[a] (%)	α/β ratio
1	**13**	$CSCl_2/CaCO_3$	$CH_2Cl_2-H_2O$	25/1	**20**β (83)	0:100
2	**13**	$CSCl_2-CuCl_2/CaCO_3$	$CH_2Cl_2-H_2O$	25/2	**20**α/**20**β (86)	77:23
3	**14**	$CSCl_2/CaCO_3$	$CH_2Cl_2-H_2O$	25/1	**21**β (78)	0:100
4	**14**	$CSCl_2-CuCl_2/CaCO_3$	$CH_2Cl_2-H_2O$	25/2	**21**α/**21**β (74)	71:29
5	**15**	$CSCl_2/CaCO_3$	$CH_2Cl_2-H_2O$	25/1	**22**β (80)	0:100
6	**15**	$CSCl_2-CuCl_2/CaCO_3$	$CH_2Cl_2-H_2O$	25/2	**22**α/**22**β (86)	91:9
7	**16**	$CSCl_2/CaCO_3$	$CH_2Cl_2-H_2O$	25/1	**23**β (65)	0:100
8	**16**	$CSCl_2-CuCl_2/CaCO$	$CH_2Cl_2-H_2O$	25/2	**23**α/**23**β (63)	37:63
9	**17**	$CSCl_2/CaCO_3$	$CH_2Cl_2-H_2O$	25/3	**24**α/**24**β (71)	57:43
10	**17**	$CSCl_2-CuCl_2/CaCO$	$CH_2Cl_2-H_2O$	25/3	**24**α/**24**β (71)	67:33
11	**18**	$CSCl_2/CaCO_3$	$CH_2Cl_2-H_2O$	25/1[b]	**25** (97)	0:100
12	**19**	$CSCl_2/CaCO_3$	$CH_2Cl_2-H_2O$	25/16	**26** (22)	0:100

[a] Isolated yields. When mixtures of anomers are formed, the total yield matches the sum of the individual isolated yields. [b] Longer reaction times resulted in lower yields due to concomitant hydrolysis of the isopropylidene group under the reaction conditions.

of copper(II) chloride. The relative proportion of the anomers was strongly sensitive upon the orientation and the nature of the substituent at C-4, going from 1:1.7 in the case of lactose

up to 10.3:1 for maltose, which probably reflects differences in anomerization rates of the transient chlorothioformamides.

The above copper(II)-mediated reversion of the anomeric stereoselectivity is remarkable. For the D-galactopyranosyl isothiocyanate **20**, a α/β ratio ranging from 1:9 to 1:8 has been previously reported from the reaction of the corresponding peracetylated glycosyl bromide with potassium thiocyanate or trimethylsilyl isothiocyanate.[7a,b] The 3.3:1 ratio obtained from galactooxazoline **13** implies a 25−30-fold increase in the α-selectivity. In the case of the D-gluco derivative **3** and the disaccharide isothiocyanates **21**−**23**, the α-anomers had not been detected before. Interestingly, the isothiocyanation step can be effected on the crude oxazoline precursor (see the Supporting Information), thereby avoiding yield losses due to hydrolysis during column chromatography purification. Globally, this methodology allows the one-pot transformation of a per-*O*-acetyl-β-glycopyranosyl azide into the corresponding β- or α-glycopyranosyl isothiocyanate.

In order to expand the repertoire of the approach, the transformations of the D-glucofuranose (**17**) and D-fructopyranose oxazolines (**18** and **19**) into glycosyl isothiocyanates were next examined (Table 2, entries 9−12). Compound **17** afforded a mixture of the α- and β-D-glucofuranosyl isothiocyanates **24**α and **24**β upon reaction with thiophosgene, the α/β relative proportion increasing from 1.3:1 to 2:1 in the presence of copper(II) chloride. For the fructose derivatives **18** and **19** the isothiocyanation reaction proceeded with retention of the anomeric configuration, independently of the presence or absence of the copper(II) additive, to give the corresponding β-fructopyranosyl isothiocyanates **25** or **26**. In both cases, the vicinal coupling constants around the pyranoid ring were consistent with the $^2C_5$ conformation, which is consistent with that reported in the literature for β-D-fructopyronsyl derivatives bearing nitrogen substituents.[17] The absence of NOE contacts between the H-1 and H-6_{axial} protons further supports the axial orientation of the NCS group.

The relatively high proportion of **24**α in the reaction mixture of **17** with thiophosgene is consistent with the expected weaker contribution of the reverse anomeric effect in the transient furanoid chlorothioformamide as compared with pyranoid derivatives. On the other hand, anomerization processes are faster for five-membered rings, which is probably responsible for the lower increase in the **24**α/**24**β ratio in he presence of copper(II). In the fructose series, the α-configuration would imply either the axial orientation of the bulky carbon substituent (C-1) or the inversion of the chair conformation, both being unfavorable arrangements.

In conclusion, a robust and flexible methodology for the preparation of acylated glycosyl isothiocyanates from *N*-glycooxazoline precursors is reported. The preference for the α- or β-configuration in the final compounds can be tuned, to some extent, by using copper(II) chloride as an additive. Noteworthy, the strategy allows the global transformation of β-glycopyranosyl azides into a-glycopyranosyl isothiocyanates with axial−equatorial 1,2-cis dispositions. Further endeavors will include reactivity experiments and neoglycoconjugate synthesis.

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Experimental Section

General Procedure for the Preparation of Glycosyl Isothiocyanates 3 and 20−26 from Glycooxazolines. To a heterogeneous mixture of the corresponding oxazoline derivative **6** and **13**−**19** (see refs 12 and 13 and the Supporting Information) in CH_2Cl_2−H_2O (1:1, 5 mL per 100 mg of reacting oxazoline) were added $CaCO_3$ (3 equiv), $CuCl_2 \cdot 2H_2O$ (1.5 equiv), and $CSCl_2$ (1.5 equiv). The mixture was vigorously stirred for the indicated time (Tables 1 and 2) in a round-bottomed flask provided with a system for evacuation of gases and then filtered (**CAUTION: use a well-ventilated hood**). The organic layer was separated, washed with water, dried ($MgSO_4$), and concentrated to dryness. The resulting residue was purified by column chromatography using the eluent indicated in each case.

In the absence of $CuCl_2$, the above procedure afforded exclusively the β-anomer, except for the glucofuranosyl oxazoline derivative **17**, which led to a 57:43 **24**α/**24**β mixture (Table 2).

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl Isothiocyanate (3α). Compound **3**α (92 mg, 49%) was obtained, together with **3**β (61 mg, 34%), by isothiocyanation of **6** (160 mg, 0.49 mmol) in the presence of $CuCl_2$ after column chromatography using 1:2 EtOAc−petroleum ether: R_f (**3**α) = 0.55 (1:1 EtOAc−petroleum ether); R_f (**3**β) = 0.46 (1:1 EtOAc−petroleum ether). The spectroscopic and physicochemical data of **3**β were identical to those reported in the literature.[1] The α-anomer **3**α, isolated as an amorphous solid, had $[\alpha]_D$ = +125 (*c* 1.0, CH_2Cl_2). IR (KBr): ν_{max} 2956, 2014, 1755, 1433, 911 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.81 (d, 1 H, $J_{1,2}$ = 4.5 Hz, H-1), 5.39 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz, H-3), 5.10 (t, 1 H, $J_{4,5}$ = 9.6 Hz, H-4), 5.01 (dd, 1 H, H-2), 4.24 (dd, 1 H, $J_{6a,6b}$ = 12.9 Hz, $J_{5,6a}$ = 4.8 Hz, H-6a), 4.10 (dd, 1 H, $J_{5,6b}$ = 2.4 Hz, H-6b), 4.09 (ddd, 1 H, H-5), 2.09, 2.07, 2.06, 2.05 (4 s, 12 H, 4 MeCO). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 169.8−170.5 (4 CO), 144.7 (NCS), 81.9 (C-1), 70.5 (C-3, C-5), 69.8 (C-2), 67.5 (C-4), 61.2 (C-6), 20.6 (*Me*CO). ESIMS: *m*/*z* = 428 ($[M + K]^+$), 412 ($[M + Na]^+$). Anal. Calcd for $C_{15}H_{19}NO_9S$: C, 46.27; H, 4.92; N, 3.60. Found: C, 46.08; H, 4.87; N, 3.65.

***N*-Benzyl-*N*′-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)thiourea (12α).** A solution of **3**α (115 mg, 0.295 mmol), benzylamine hydrochloride (47.2 mg, 1.1 equiv), and DIPEA (37 μL, 1.1 equiv) in CH_2Cl_2 (3.5 mL) was stirred at room temperature for 3 h. Solvent was removed, and the resulting residue was purified by column chromatography (1:2 EtOAc−petroleum ether) to give **12**α (93 mg, 72%) as an amorphous solid. R_f = 0.27 (1:1 EtOAc−petroleum ether). $[\alpha]_D$: +135 (*c* 1.0, CH_2Cl_2). UV (CH_2Cl_2): λ_{max} 256 nm, (ϵ_{mm} = 8.5). IR (KBr): ν_{max} 3367, 1749, 1536, 1223, 1036 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 313 K): δ (ppm) 7.34−7.26 (m, 5 H, Ph), 7.05 (bt, 1 H, $J_{NH,H}$ = 5.5 Hz, N′H), 6.43 (bs, 1 H, NH), 5.45 (bt, 1 H, H-1), 5.29 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 10.0 Hz, H-3), 5.01 (dd, 1 H, $J_{1,2}$ = 5.0 Hz, H-2), 4.97 (t, 1H, $J_{4,5}$ = 11.5 Hz, H-4), 4.81 (dd, 1 H, $^2J_{H,H}$ = 15.0 Hz, *CH*Ph), 4.73 (dd, 1 H, *CH*Ph), 4.07 (dd, 1 H, $J_{5,6a}$ = 5.5, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.03 (ddd, 1 H, H-5), 3.89 (dd, 1 H, $J_{5,6b}$ = 2.0 Hz, H-6b), 2.11, 2.02, 1.97, 1.96 (4 s, 12 H, 4 MeCO). ^{13}C NMR (125.7 MHz, $CDCl_3$, 323 K): δ (ppm) 184.8 (CS), 170.1−169.0 (4 *C*O), 137.0−127.6 (Ph), 78.8 (C-1), 69.8 (C-2), 68.6 (C-3), 68.1 (C-4,5), 61.7 (C-6), 49.8 (CH_2), 20.4−20.2 (*Me*CO). ESIMS: *m*/*z* = 535 ($[M + Na]^+$), 497 ($[M + H]^+$). Anal. Calcd for $C_{22}H_{28}N_2O_9S$: C, 53.22; H, 5.68; N, 5.64. Found: C, 53.21; H, 5.55; N, 5.52.

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Supporting Information Available: Experimental procedures, compound characterization data, and copies of the ^1H and ^{13}C NMR spectra for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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