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Nitrogen versus sulfur acylation in sugar thioureas: regioselectivity and conformational consequences

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Abstract

The influence of steric and electronic effects in the regioselectivity of base-catalysed acetylation reactions of sugar thioureas and the structural and conformational properties of the resulting products have been investigated. Bulky alkyl substituents favoured *S*-acetylation, whereas aryl substituents directed acylation at nitrogen. The conformational properties of both the *S*- and *N*-acetyl compounds are governed by the existence of a strong six-membered NH···O=C intramolecular hydrogen bond that locks the pseudoamide bonds in a rigid configurational arrangement.

1. Introduction

Sugar thioureas[1,2] figure prominently in neoglycoconjugate synthetic strategies,[3] including neoglycoproteins,[4] glycodendrimers,[5–11] glycoclusters[12–17] and pseudooligosaccharides.[18–20] Most of the NMR studies of this class of compounds are concerned with the partial double-bond character of the pseudoamide N–C(=S) bonds, arising from the contribution of zwitterionic resonance structures (N^+=C–S^-) to the ground state of thioureas.[21] This electronic property results in an approximately planar thiourea framework and rotational kinetic parameters in the range of the chemical shift time scale. In the particular case of deoxythioureido sugars, the coexistence of several hydrogen bond acceptor centres together with the thiourea NH proton donors exerts a dramatic influence on the relative rotameric populations and on the corresponding rotational barrier heights.[22,23] Broad NMR signals are obtained even at temperatures well above room temperature, which seriously hamper NMR structural analysis.

An immediate improvement of the NMR spectral resolution should result if the thiourea segment could be anchored in a precise configurational arrangement. Moreover, we have recently

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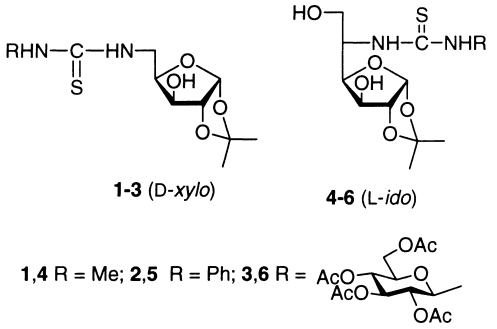
reported that the imposition of conformational constraints at the thiourea grouping may have crucial consequences on the secondary structure and molecular recognition properties of carbohydrate derived thioureas.[24,25] In this context, we became interested in studying the regioselectivity of base-catalysed acetylation reactions of deoxythioureido sugars, taking into account that introduction of an acyl group either at nitrogen or at sulfur must strongly favour six-membered intramolecular hydrogen-bonded patterns, possibly providing configurational integrity at the pseudoamide bonds. The structure of the acetylation products as a function of the primary or secondary carbon atom location of the thioureido group and the nature of the substituents is reported.

2. Results and discussion

The 5-deoxy-5-thioureido-D-xylofuranose and 5-deoxy-5-thioureido-L-idofuranose acetonide derivatives **1**–**3** and **4**–**6**, respectively, were chosen as model compounds for our study. They represent particularly challenging problems due to the exocyclic location of the thiourea group, which complicates the corresponding conformational equilibria. Furthermore, compounds **1**–**6** have been used as synthetic precursors of azasugar-type glycosidase inhibitors.[26,27] They were prepared in virtually quantitative yield by the coupling reaction of 5-amino-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose[28] or 5-amino-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose,[29] respectively, with methyl, phenyl and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate.[30]



In both series, the ^{1}H and ^{13}C NMR spectra exhibited a pronounced line broadening even at 323 K in chloroform-*d* or methanol-d_4 solutions, especially at the H-5 and C-5 region, indicative of relatively slow chemical exchange processes between the (*Z*)- and (*E*)-rotamers about the corresponding N–C(=S) bond. Dynamic NMR data have shown that the contribution of the (*E*)-rotamer to the configurational equilibrium of deoxythioureido sugars is related to the existence of a seven-membered intramolecular hydrogen bond analogous to that characteristic of peptide γ-turns (C_7 conformation).[18,22–25] This folding arrangement, which would engage the furanoid oxygen atom O-5 in the case of **1**–**3** and O-4 or O-6 in the case of **4**–**6** (Fig. 1), brings about a 2 kcal mol^{-1} increase in the activation free energy (ΔG) for rotation, being responsible for the unusually high coalescence temperatures.

Upon treatment with acetic anhydride in pyridine, the D-xylofuranose derivatives **1**–**3** underwent, predominantly, acetylation at nitrogen yet the outcome of the reaction was strongly dependent on the nature of the *N*′-substituent. Thus, the *N*′-methylthioureido sugar **1** yielded a mixture of the *N*- and *N*′-acetyl thioureas **7** and **8** in 1:2 relative proportion, whereas the

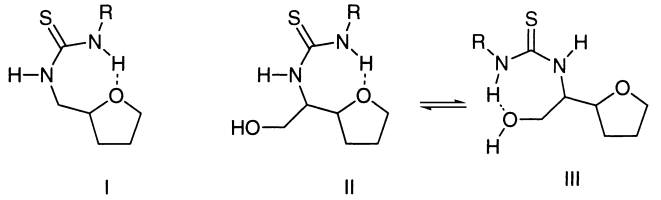
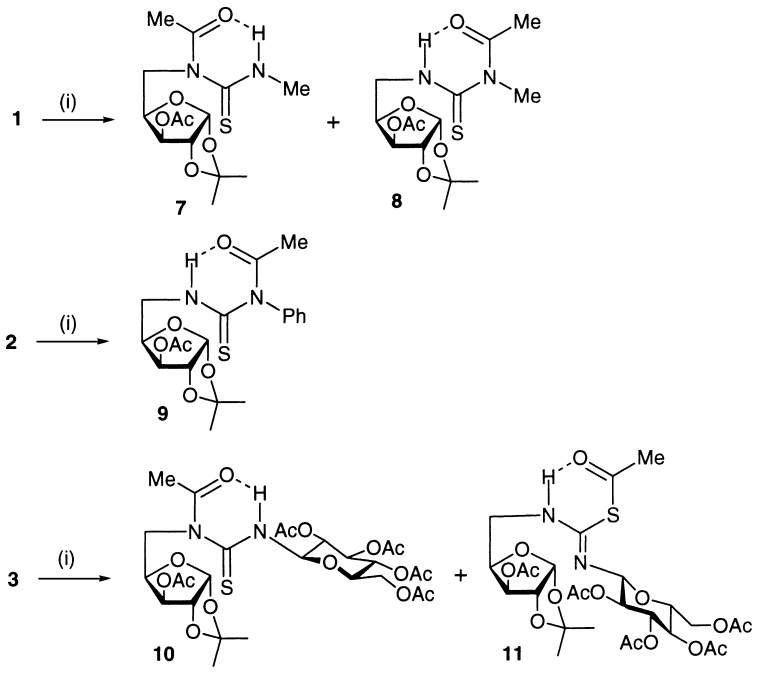


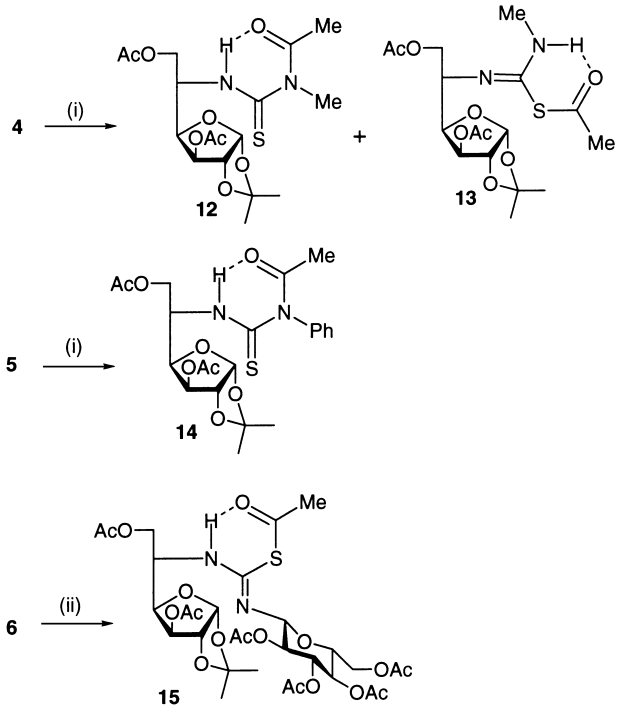
Figure 1. Seven-membered hydrogen-bonded structures of 5-deoxy-5-thioureido sugars; I, NH···O-4 hydrogen bond in pentofuranose derivatives; II and III, NH···O-4 and NH···O-6 hydrogen bonds in hexofuranose derivatives

N′-phenylthioureido sugar **2** led, regiospecifically, to the *N*′-acetyl derivative **9**. Under identical reaction conditions, the (1→5)-thiourea-tethered pseudodisaccharide **3** was acetylated mainly at the non-anomeric nitrogen atom to give **10**. A minor proportion of the isomeric *S*-acetyl isothiourea **11** was also isolated (Scheme 1).



Scheme 1. Regioselectivity of the acetylation reaction of compounds **1**–**3** and structure of the resulting products; (i) 1:1 Ac_2O:pyridine

For the 5-deoxy-5-thioureido-L-idofuranose homologues **4**–**6**, the secondary carbon atom location of the thiourea functionality prevented acetylation at the C-5-linked nitrogen atom, probably due to steric hindrance. In the case of the *N*′-methylthioureido derivative **4** the acetylation reaction proceeded predominantly at the sulfur atom to give **13**, together with a small proportion of the *N*′-acetyl-*N*′-methylthioureido sugar **12**. Acetylation of the *N*′-phenyl and *N*′-glucopyranosyl derivatives **5** and **6** occurred completely regioselectively at the *N*′- and *S*-atoms, respectively, to give **14** and **15** as the sole reaction products (Scheme 2). In the latter case, addition of *N*,*N*-dimethylaminopyridine as base catalyst was advantageous in order to increase the yield of the acetylation product.



Scheme 2. Regioselectivity of the acetylation reaction of compounds **4**–**6** and structure of the resulting products; (i) 1:1 Ac_2O:pyridine; (ii) 1:1 Ac_2O:pyridine, 0.1 equiv. DMAP

In stark contrast to that observed for the deoxythioreido sugar precursors **1**–**6**, all the products of acetylation at nitrogen exhibited well resolved ^1H and ^{13}C NMR spectra at room temperature. The very strong deshielding observed for the remaining NH or N′H proton (11.9–11.6 ppm) is characteristic of strong hydrogen bonding, in agreement with its engagement in a six-membered intramolecular hydrogen bond that anchors the configuration with both carbon substituents in *cis* relationship with respect to the thiocarbonyl sulfur atom. The location of the (*E*)-oriented acyl group was unequivocally induced from the pseudoamide proton $^3J_{H,H}$ relationships.

The isothiourea proton of the *S*-acetyl derivatives **11**, **13** and **15** resonated at 8.6–8.4 ppm in chloroform-*d* solution. Since thiourea protons typically resonate at 7.0–6.0 ppm, these data also suggest the existence of NH···O=C(S) intramolecular hydrogen bonding. Further evidence was obtained from the corresponding chemical shift temperature coefficient values ($\Delta\delta_{NH}/\Delta T < 0.001$ ppm K^{-1}), which were consistent with observed values for the *N*- or *N*′-acetylated derivatives **7**–**10**, **12** and **14** and with previously reported data for intramolecularly hydrogen bonded thiourea protons.[22,25] In the case of compound **13**, the splitting pattern of the methyl signal, a doublet, indicated that the isothiourea group was attached to the carbohydrate moiety through the double-bonded nitrogen atom. The chemical shift difference for the methyl resonances in **13** (3.15 ppm) and its positional isomer **12** (3.68 ppm) is in accordance with that expected for (*E*)- and (*Z*)-dispositions with respect to the sulfur atom,[22,25] respectively, supporting the proposed six-membered hydrogen-bonded structures. Nevertheless, the NMR spectra recorded at 303 K displayed significant line broadening for the resonances of C-4, C-5 and C-6 as well as for the corresponding protons, indicative of relatively slow rotational processes about the N=C bond. Fast exchange was achieved at 313 K.

The ^{1}H NMR spectra of the glucopyranosylisothioureido derivatives **11** and **15** indicated a vicinal relationship for the NH proton and protons at C-5, pointing to a glycosylimino structure. The downfield chemical shift of the anomeric proton (6.10–6.09 ppm) was indicative of close proximity to the sulfur atom, supporting the (*Z*)-configuration at the C=N bond and the *anti* disposition between H-1′ and the N′-lone pair. This scenario is analogous to that encountered at the anomeric region of glycosylthioureas.[1,2] Actually, the alternative (*E*)-configuration would bring the bulky saccharide residues into 1,3-parallel disposition, an unfavourable arrangement. Accordingly, rotation about the C=N bond was prevented for **11** and **15**, resulting in well-resolved ^{1}H and ^{13}C NMR spectra at room temperature.

The ensemble of results can be explained in terms of the steric and electronic effects of the nitrogen substituents at the thiourea functionality. As a general rule, *N*-acylation is strongly disfavoured for thiourea nitrogen atoms attached to bulky alkyl substituents (e.g., the L-idofuranose template in **4**–**6** or the D-glucopyranosyl substituent in **3** and **6**). In contrast, aryl groups direct acylation at nitrogen (e.g., **2** and **5**), probably by increasing the acidity of the corresponding N′H proton due to delocalization of the N′-lone pair into the aromatic ring. Likewise, in *S*-acetyl isothioureas the preferred tautomeric form seems to be determined by the electronic effects of the substituents at the amidine system. Thus, the electron-attracting glucopyranosyl residue in the pseudodisaccharides **11** and **15** is located at the more electronegative imine-type nitrogen, whereas the furanoid residue occupies this position in **13**, with the methyl group (+I effect) at the amine-type terminus.

In any case, acetylation of the thiourea group in deoxythioureido sugars resulted in a remarkable simplification of the conformational equilibria by favouring six-membered intramolecular hydrogen-bonded folding patterns. Further application of this reaction as a tool to control the secondary structures and molecular recognition properties of sugar thiourea-based pseudooligosaccharides and receptors will be reported in due course.

3. Experimental

Optical rotations were measured at room temperature in 1 cm or 1 dm tubes. IR spectra were recorded on an FT-IR instrument. ^{1}H (and ^{13}C) NMR spectra were recorded at 500 (125.7) and 300 (75.5) MHz. In the FABMS spectra, the primary beam consisted on 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 keV. NaI was added as cationizing agent. In the CIMS spectra, isobutane was used as the reactive gas (500 mA, 8 kV). TLC was performed with E. Merck precoated TLC plates, silica gel 30F-245, with visualization by UV light and by charring with 10% sulfuric acid. Microanalyses were performed by the Instituto de Investigaciones Químicas (Sevilla, Spain). Methyl and phenyl isothiocyanates used were commercial grade.

*3.1. General procedure for the preparation of 5-deoxy-1,2-*O*-isopropylidene-5-thioureido-α-D-xylofuranose **1**–**3** and β-L-idofuranose derivatives **4**–**6***

To solutions of 5-amino-1,2-*O*-isopropylidene-5-deoxy-α-D-xylofuranose[28] or 5-amino-1,2-*O*-isopropylidene-5-deoxy-β-L-idofuranose[29] (1.91 mmol) in pyridine (15 mL) were added methyl, phenyl and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate[30] (2.10 mol). The reaction

mixtures were stirred at room temperature until total consumption of the starting amino sugar (TLC), concentrated and purified by column chromatography with the eluent indicated in each case.

3.2. 5-Deoxy-1,2-O-isopropylidene-5-(N′-methylthioureido)-α-D-xylofuranose **1**

Reaction time: 2.5 h. Yield: 0.5 g (99%); $[\alpha]_D = +17.8$ (*c* 0.9, MeOH); R_f 0.26 (20:1 CH_2Cl_2:MeOH); UV (MeOH): 240 nm (ε_{mM} 15.02); IR (KBr) 3376, 3266, 2986, 2917, 1551, 1371, 1217 and 1007 cm^{-1}; δ_H (300 MHz, CD_3OD, 313 K) 1.28, 1.43 (6H, 2s, Me_2C), 2.94 (3H, bs, NMe), 3.56 (1H, dd, $J_{4,5b}$ 6.5, $J_{5a,5b}$ 14.0, H-5b), 3.95 (1H, m, H-5a), 4.07 (1H, d, $J_{2,3}$ 0, $J_{3,4}$ 2.7, H-3), 4.28 (1H, td, $J_{4,5a}$ 6.5, H-4), 4.49 (1H, d, $J_{1,2}$ 3.7, H-2), 5.87 (1H, d, H-1); δ_C (75.5 MHz, CD_3OD, 313 K) 26.3, 26.9 (CMe_2), 30.9 (MeN), 43.9 (C-5), 75.5 (C-3), 80.6 (C-4), 86.7 (C-2), 106.1 (C-1), 112.7 (*C*Me_2), 184.2 (C=S), FABMS: *m*/*z* 285 (100, $[M+Na]^+$), 263 (80, $[M+H]^+$). Anal. calcd for $C_{10}H_{18}O_4N_2S$: C, 45.78; H, 6.90; N, 10.68. Found: C, 45.72; H, 6.96; N, 10.68.

3.3. 5-Deoxy-1,2-O-isopropylidene-5-(N′-phenylthioureido)-α-D-xylofuranose **2**

Reaction time: 2.5 h. Yield: 0.61 g (98%); $[\alpha]_D = +3.9$ (*c* 0.9, CH_2Cl_2); R_f 0.73 (20:1 CH_2Cl_2:MeOH); UV (CH_2Cl_2): 262 nm (ε_{mM} 14.34); IR (KBr) 3306, 2986, 2936, 1543, 1497, 1375, 1215 and 1013 cm^{-1}; δ_H (300 MHz, $CDCl_3$, 313 K) 1.28, 1.44 (6H, 2s, Me_2C), 3.68 (1H, dt, $J_{4,5b} = J_{NH,5b}$ 4.7, $J_{5a,5b}$ 14.9, H-5b), 4.12 (1H, ddd, $J_{3,4}$ 3.1, $J_{4,5a}$ 7.7, H-4), 4.21 (1H, d, $J_{2,3}$ 0, H-3), 4.26 (1H, dd, H-5a), 4.53 (1H, d, $J_{1,2}$ 3.6, H-2), 5.84 (1H, d, H-1), 6.44 (1H, m, NH), 7.49–7.13 (5H, m, Ph), 8.06, (1H, s, NH); δ_C (75.5 MHz, $CDCl_3$, 313 K) 26.4, 26.8 (C*Me*$_2$), 42.9 (C-5), 74.1 (C-3), 79.3 (C-4), 84.9 (C-2), 104.4 (C-1), 111.5 (*C*Me_2), 125.2 (C-2, 6 Ph), 127.8 (C-4 Ph), 131.3 (C-3,5 Ph), 135.5 (C-1 Ph), 182.5 (C=S); FABMS: *m*/*z* 347 (100, $[M+Na]^+$), 325 (80, $[M+H]^+$). Anal. calcd for $C_{15}H_{20}O_4N_2S$: C, 55.54; H, 6.21; N, 8.63. Found: C, 55.68; H, 6.22; N, 8.49.

3.4. 5-Deoxy-1,2-O-isopropylidene-5-[N′-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)thioureido]-α-D-xylofuranose **3**

Reaction time: 4 h. Yield: 0.78 g (71%); $[\alpha]_D = +15.5$ (*c* 0.9, CH_2Cl_2); R_f 0.28 (2:1 EtOAc: petroleum ether); UV (CH_2Cl_2): 250 nm (ε_{mM} 8.16); IR (KBr) 3362, 2949, 1751, 1545, 1375, 1219 and 1036 cm^{-1}; δ_H (500 MHz, $CDCl_3$, 313 K): 1.33, 1.48 (6H, 2s, Me_2C), 2.02, 2.04, 2.07, 2.09 (12H, 4s, 4 Ac), 3.65 (1H, m, H-5b), 3.84 (1H, ddd, $J_{5',6'a}$ 4.8, $J_{4',5'}$ 10.1, $J_{5',6'b}$ 2.0, H-5′), 4.10 (1H, m, H-5a), 4.12 (1H, dd, $J_{6'a,6'b}$ 12.4, H-6′b), 4.18 (1H, d, $J_{2,3}$ 0, $J_{3,4}$ 2.4, H-3), 4.20 (1H, td, $J_{4,5a} = J_{4,5b}$ 7.2, H-4), 4.30 (1H, dd, H-6′a), 4.55 (1H, d, $J_{1,2}$ 3.6, H-2), 4.97 (1H, t, $J_{1',2'} = J_{2',3'}$ 9.5, H-2′), 5.06 (1H, dd, $J_{3',4'}$ 9.5, H-4′), 5.33 (1H, t, H-3′), 5.66 (1H, bt, H-1′), 5.93 (1H, d, H-1), 6.90 (2H, bs, 2 NH); δ_C (125.7 MHz, $CDCl_3$) 20.3–20.5 (*Me*CO), 26.0, 26.5 (C*Me*$_2$), 42.5 (C-5), 61.8 (C-6′), 68.5 (C-4′), 69.8 (C-2′), 72.9 (C-5′), 73.3 (C-3′), 74.4 (C-3), 79.0 (C-4), 82.8 (C-1′), 85.2 (C-2), 104.5 (C-1), 111.9 (*C*Me_2), 171.2–169.0 (CO), 184.2 (C=S); FABMS: *m*/*z* 601 (100, $[M+Na]^+$), 579 (60, $[M+H]^+$). Anal. calcd for $C_{23}H_{34}O_{13}N_2S$: C, 47.74; H, 5.92; N, 4.84. Found: C, 47.66; H, 5.66; N, 4.82.

3.5. 5-Deoxy-1,2-O-isopropylidene-5-(N′-methylthioureido)-β-L-idofuranose **4**

Reaction time: 7 h. Yield: 0.48 g (87%); $[\alpha]_D = -19.5$ (*c* 1.1, MeOH); R_f 0.27 (20:1 CH_2Cl_2:MeOH); UV (MeOH): 240 nm (ε_{mM} 9.1); IR (KBr) 3376, 2926, 1572, 1377, 1215, 1071

and 1007 cm^{-1}; δ_H (300 MHz, CD_3OD, 313 K) 1.30, 1.45 (6H, 2s, Me_2C), 2.97 (3H, s, *Me*NH), 3.73 (2H, d, $J_{5,6}$ 4.4, H-6a, H-6b), 4.13 (1H, d, $J_{2,3}$ 0, $J_{3,4}$ 2.7, H-3), 4.30 (1H, dd, $J_{4,5}$ 8.0, H-4), 4.49 (1H, d, $J_{1,2}$ 3.8, H-2), 4.58 (1H, m, H-5), 5.89 (1H, d, H-1); δ_C (75.5 MHz, CD_3OD, 313 K) 26.3, 26.9 (C*Me*$_2$), 33.0 (MeN), 56.5 (C-5), 62.5 (C-6), 75.6 (C-3), 81.0 (C-4), 86.8 (C-2), 105.8 (C-1), 112.6 (*C*Me$_2$), 182.5 (C=S); FABMS: *m*/*z* 315 (100, $[M+Na]^+$). Anal. calcd for $C_{10}H_{20}O_5N_2S$: C, 47.19; H, 6.90; N, 9.58; S, 10.79. Found: C, 45.20; H, 6.72; N, 9.53; S, 11.07.

3.6. 5-Deoxy-5-(N′-phenylthioureido)-1,2-O-isopropylidene-β-L-idofuranose **5**

Reaction time: 6 h. Yield: 0.61 g (90%); $[\alpha]_D = +14.6$ (*c* 0.69, MeOH); R_f 0.24 (20:1 CH_2Cl_2:MeOH); UV (MeOH): 250 nm (ε_{mM} 14.4); IR (KBr) 3428, 2959, 2848, 1657 and 1021 cm^{-1}; δ_H (300 MHz, CD_3OD, 313 K) 1.29, 1.44 (6H, 2s, *Me*$_2$C), 3.72 (1H, dd, $J_{5,6b}$ 5.2, $J_{6a,6b}$ 11.1, H-6b), 3.79 (1H, dd, $J_{5,6a}$ 3.9, H-6a), 4.15 (1H, d, $J_{2,3}$ 0, $J_{3,4}$ 2.8, H-3), 4.37 (1H, dd, $J_{4,5}$ 7.0, H-4), 4.50 (1H, d, $J_{1,2}$ 3.7, H-2), 4.77 (1H, m, H-5), 5.96 (1H, d, H-1), 7.45–7.15 (5H, m, Ph); δ_C (75.5 MHz, CD_3OD, 313 K) 26.4, 27.0 (C*Me*$_2$), 56.6 (C-5), 62.4 (C-6), 75.8 (C-3), 80.6 (C-4), 86.9 (C-2), 105.9 (C-1), 112.8 (*C*Me$_2$), 125.3, 126.7, 130.2, 139.6, (6C, Ph),182.0 (C=S); FABMS: *m*/*z* 377 (100, $[M+Na]^+$). Anal. calcd for $C_{16}H_{22}O_5N_2S$: C, 54.22; H, 6.26; N, 7.90; S, 9.05. Found: C, 54.24; H, 6.40; N, 7.89; S, 9.05.

3.7. 5-Deoxy-5-[N′-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)thioureido]-1,2-O-isopropylidene-β-L-idofuranose **6**

Reaction time: 24 h. Yield: 1.07 g (93%); $[\alpha]_D = -2.6$ (*c* 0.76, CH_2Cl_2); R_f 0.22 (20:1 CH_2Cl_2:MeOH); UV (MeOH): 248 nm (ε_{mM} 14.5); IR (KBr) 3428, 2951, 1760, 1553, 1236 and 1037 cm^{-1}; δ_H (300 MHz, CD_3OD, 313 K) 1.97, 2.00 (6 H), 2.02 (4 Ac), 1.28, 1.44, (6H, 2 s, C*Me*$_2$), 3.74 (2H, m, H-6a, H-6b), 3.88 (1H, ddd, $J_{5',6'b}$ 2,4, $J_{5',6'a}$ 4.5, $J_{4',5'}$ 9.4, H-5′), 4.09 (1H, dd, $J_{6'a,6'b}$ 12.3, H-6′b), 4.14 (1H, d, $J_{2,3}$ 0, $J_{3,4}$ 2.9, H-3), 4.27 (1H, dd, H-6′a), 4.33 (1H, bd, H-4), 4.48 (1H, d, $J_{1,2}$ 3.8, H-2), 4.65 (1H, m, H-5), 4.98 (1H, dd, $J_{1',2'}$ 7.8, $J_{2',3'}$ 9.4, H-2′), 5.02 (1H, t, $J_{3',4'}$ 9.4 H-4′), 5.31 (1H, t, H-3′), 5.87 (1H, d, H-1), 5.88 (1H, d, H-1′); δ_C (75.5 MHz, CD_3OD, 313 K) 20.5 (*Me*CO), 26.3, 27.0 (C*Me*$_2$), 56.5 (C-5), 61.8 (C-6), 63.1 (C-6′), 69.7 (C-4′), 71.9 (C-2′), 74.4 (C-5′), 74.8 (C-3′), 75.6 (C-3), 80.4 (C-4), 83.5 (C-1′), 86.9 (C-2), 105.9 (C-1), 112.6 (*C*Me$_2$), 171.3, 171.5, 171.6, 172.3 (CO), 185.3 (C=S); FABMS: *m*/*z* 631 (100%, $[M+Na]^+$). Anal. calcd for $C_{24}H_{36}O_{14}N_2S$: C, 47.36; H, 5.97; N, 4.60; S, 5.27. Found: C, 47.01; H, 5.90; N, 4.33; S, 5.00.

3.8. General procedure for acetylation of the 5-deoxy-5-thioureido sugars **1**–**6**

Acetylation of the *N*,*N*′-disubstituted thioureas **1**–**6** (0.5 mmol) was effected conventionally by treatment with 1:1 Ac_2O:pyridine (4 mL) at room temperature for 24 h, followed by purification by column chromatography with the eluent indicated in each case. For compound **6**, addition of a catalylic amount of *N*,*N*-dimethylaminopyridine (0.1 mmol) to the reaction mixture was found advantageous.

3.9. 3-O-Acetyl-5-(N-acetyl-N′-methylthioureido)-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose **7**

Yield: 48 mg (27%); $[\alpha]_D = -38.0$ (*c* 1.0, CH_2Cl_2); R_f 0.49 (20:1 CH_2Cl_2:MeOH); UV (CH_2Cl_2): 271 nm (ε_{mM} 9.31); IR (KBr) 3173, 2988, 2936, 1746, 1672, 1547, 1377, 1225 and 1030 cm^{-1};

δ_H (300 MHz, $CDCl_3$) 1.29, 1.48 (6H, 2s, Me_2C), 2.12 (3H, s, OAc), 2.49 (3H, s, NAc), 3.14 (3H, d, $J_{Me,NH}$ 4.5, MeN), 3.80 (1H, dd, $J_{4,5b}$ 8.3, $J_{5a,5b}$ 15.6, H-5b), 4.51 (1H, d, $J_{2,3}$ 0, $J_{1,2}$ 3.8, H-2), 4.73 (1H, dt, $J_{3,4}=J_{4,5a}$ 3.0, H-4), 5.17 (1H, dd, H-5a), 5.28 (1H, d, H-3), 5.90 (1H, d, H-1), 11.30 (1H, d, NH); δ_C (75.5 MHz, $CDCl_3$) 20.7 (*Me*COO), 26.0, 26.4 (C*Me*$_2$), 26.6 (*Me*CON), 33.2 (MeN), 48.9 (C-5), 77.0 (C-3), 78.4 (C-4), 83.3 (C-2), 104.4 (C-1), 112.2 (*C*Me$_2$), 167.4 (CO ester), 175.5 (CO amide), 184.7 (C=S); CIMS: *m*/*z* 347 (100, $[M+H]^+$). Anal. calcd for $C_{14}H_{22}O_6N_2S$: C, 48.54; H, 6.40; N, 8.08. Found: C, 48.26; H, 6.90; N, 7.76.

*3.10. 3-*O*-Acetyl-5-(*N′*-acetyl-*N′*-methylthioureido)-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose* **8**

Yield: 88 mg (50%); $[\alpha]_D=+8.0$ (*c* 1.0, CH_2Cl_2); R_f 0.64 (20:1 CH_2Cl_2:MeOH); UV (CH_2Cl_2): 273 nm (ε_{mM} 20.32); IR (KBr) 3154, 2988, 2930, 1748, 1674, 1539, 1373, 1221 and 1026 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.30, 1.50 (6H, 2s, Me_2C), 2.10 (3H, s, OAc), 2.37 (3H, s, NAc), 3.34 (1H, ddd, $J_{NH,5b}$ 5.0, $J_{4,5b}$ 7.0, $J_{5a,5b}$ 14.1, H-5b), 3.69 (3H, s, MeN), 4.05 (1H, dt, $J_{4,5a}=J_{NH,5a}$ 5.5, H-5a), 4.52 (1H, d, $J_{2,3}$ 0, $J_{1,2}$ 3.8, H-2), 4.62 (1H, ddd, $J_{3,4}$ 3.1, H-4), 5.20 (1H, d, H-3), 5.92 (1H, d, H-1), 11.60 (1H, s, NH); δ_C (75.5 MHz, $CDCl_3$) 20.6 (*Me*COO), 26.1, 26.6 (C*Me*$_2$), 29.6 (*Me*CON), 38.5 (MeN), 44.9 (C-5), 75.9 (C-3), 76.6 (C-4), 83.6 (C-2), 104.7 (C-1), 112.1 (*C*Me$_2$), 169.6 (CO ester), 174.8 (CO amide), 184.7 (C=S); CIMS: *m*/*z* 347 (100, $[M+H]^+$). Anal. calcd for $C_{14}H_{22}O_6N_2S$: C, 48.54; H, 6.40; N, 8.08. Found: C, 48.42; H, 6.40; N, 7.81.

*3.11. 3-*O*-Acetyl-5-(*N′*-acetyl-*N′*-phenylthioureido)-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose* **9**

Yield: 0.19 g (91%); $[\alpha]_D=-3.3$ (*c* 1.0, CH_2Cl_2); R_f 0.60 (1:1 EtOAc:petroleum ether); UV (CH_2Cl_2): 229 nm (ε_{mM} 11.45); IR (KBr) 3165, 2988, 2938, 1748, 1674, 1537, 1373, 1260, 1051 and 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.30, 1.51 (6H, 2s, Me_2C), 2.11 (3H, s, OAc), 2.33 (3H, s, NAc), 3.88 (1H, ddd, $J_{NH,5b}$ 1.8, $J_{4,5b}$ 6.9, $J_{5a,5b}$ 13.9, H-5b), 4.06 (1H, dt, $J_{4,5a}=J_{NH,5a}$ 5.5, H-5a), 4.54 (1H, d, $J_{2,3}$ 0, $J_{1,2}$ 3.8, H-2), 4.64 (1H, ddd, $J_{3,4}$ 3.0, H-4), 5.22 (1H, d, H-3), 5.95 (1H, d, H-1), 7.43–7.16 (5H, m, Ph), 11.77 (1H, dd, NH); δ_C (75.5 MHz, $CDCl_3$) 20.4 (*Me*COO), 25.8, 26.3 (C*Me*$_2$), 27.5 (*Me*CON), 44.3 (C-5), 75.6 (C-3), 76.2 (C-4), 83.2 (C-2), 104.3 (C-1), 111.7 (*C*Me$_2$), 127.8–129.2 (C-2 to C-6 Ph), 141.8 (C-1 Ph), 169.4 (CO ester), 174.4 (CO amide), 184.1 (C=S); CIMS: *m*/*z* 409 (40%, $[M+H]^+$). Anal. calcd for $C_{19}H_{24}O_6N_2S$: C, 55.87; H, 5.92; N, 6.86. Found: C, 55.71; H, 5.60; N, 6.52.

*3.12. 3-*O*-Acetyl-5-[*N*-acetyl-*N′*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thioureido]-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose* **10**

Yield: 0.14 mg (50%); $[\alpha]_D=-18.8$ (*c* 1.0, CH_2Cl_2); R_f 0.65 (30:1 CH_2Cl_2:MeOH); UV (CH_2Cl_2): 278 nm (ε_{mM} 10.67); IR (KBr) 2988, 2924, 1757, 1686, 1534, 1375, 1221 and 1045 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.27, 1.46 (6H, 2s, Me_2C), 1.99–2.11 (OAc), 2.50 (3H, s, NAc), 3.74 (1H, dd, $J_{4,5b}$ 7.9, $J_{5a,5b}$ 14.9, H-5b), 3.81 (1H, ddd, $J_{5',6'b}$ 2.2, $J_{5,6a}$ 4.5, $J_{4,5}$ 9.5, H-5′), 4.08 (1H, dd, $J_{6'a,6'b}$ 12.5, H-6b′), 4.27 (1H, dd, H-6a′), 4.49 (1H, d, $J_{2,3}$ 0, $J_{1,2}$ 3.8, H-2), 4.70 (1H, ddd, $J_{4,5a}$ 1.8, $J_{3,4}$ 3.1, H-4), 5.03 (1H, dd, H-5a), 5.08 (1H, t, $J_{1',2'}=J_{2',3'}$ 9.5, H-2′), 5.13 (1H, dd, $J_{3',4'}$ 9.5, H-4′), 5.26 (1H, d, H-3), 5.30 (1H, t, H-3′), 5.78 (1H, t, $J_{1',N'H}$ 8.1, H-1′), 5.89 (1H, d, H-1), 11.71 (1H, d, N′H); δ_C (125.7 MHz, $CDCl_3$) 20.5–20.7 (*Me*COO), 26.0, 26.4 (C*Me*$_2$), 26.7 (*Me*CON), 49.5 (C-5),

61.5 (C-6′), 68.1 (C-4′), 70.2 (C-2′), 73.0 (C-5′), 73.5 (C-3′), 77.1 (C-3), 78.1 (C-4), 83.1 (C-1′), 83.2 (C-2), 104.5 (C-1), 112.3 (*C*Me$_2$), 169.3–170.6 (CO ester), 175.5 (CO amide), 186.5 (C=S); FABMS: *m*/*z* 685 (90, [M+Na]$^+$). Anal. calcd for $C_{27}H_{38}O_{15}N_2S$: C, 48.94; H, 5.78; N, 4.23. Found: C, 49.03; H, 6.19; N, 4.41.

3.13. 3-O-*Acetyl-5-[*S*-acetyl-3-(2,3,4,6-tetra*-O*-acetyl-β-D-glucopyranosyl)-1-isothioureido]-5-deoxy-1,2*-O*-isopropylidene-α-D-xylofuranose*[31] **11**

Yield: 44 mg (13%); $[\alpha]_D$ = +78.0 (*c* 1.0, CH_2Cl_2); R_f 0.60 (30:1 CH_2Cl_2:MeOH); UV (CH_2Cl_2): 275 nm (ε_{mM} 8.31); IR (KBr) 3320, 2980, 2938, 1751, 1526, 1373, 1227 and 1038 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.31, 1.50 (6H, 2s, Me_2C), 1.98–2.17 (15H, 5s, OAc), 2.40 (3H, s, SAc), 3.73 (1H, ddd, $J_{NH,5b}$ 4.6, $J_{4,5b}$ 9.1, $J_{5a,5b}$ 14.0, H-5b), 3.85 (1H, ddd, $J_{5',6'b}$ 2.2, $J_{5',6'a}$ 6.2, $J_{4',5'}$ 9.6, H-5′), 3.92 (1H, ddd, $J_{4,5a}$ 3.6, $J_{NH,5a}$ 6.1, H-5a), 4.07 (1H, dd, $J_{6'a,6'b}$ 12.5, H-6′b), 4.35 (1H, dd, H-6′a), 4.58 (1H, d, $J_{2,3}$ 0, $J_{1,2}$ 3.8, H-2), 4.62 (1H, ddd, $J_{3,4}$ 3.0, H-4), 5.08 (1H, t, $J_{1',2'} = J_{2',3'}$ 9.6, H-2′), 5.10 (1H, dd, $J_{3',4'}$ 9.5, H-4′), 5.23 (1H, d, H-3), 5.25 (1H, t, H-3′), 5.97 (1H, d, H-1), 6.10 (1H, d, H-1′), 8.40 (1H, dd, NH); δ_C (125.7 MHz, $CDCl_3$) 20.5–20.7 (*Me*COO), 24.1 (*Me*COS), 26.1, 26.5 (C*Me*$_2$), 45.3 (C-5), 62.2 (C-6′), 67.7 (C-4′), 67.8 (C-2′), 73.8 (C-5′), 74.6 (C-3′), 75.8 (C-3), 76.3 (C-4), 80.2 (C-1′), 83.6 (C-2), 104.6 (C-1), 112.3 (*C*Me$_2$), 170.0–169.3 (CO ester), 170.6 (C=N), 182.5 (CO thioester). Anal. calcd for $C_{27}H_{38}O_{15}N_2S$: C, 48.94; H, 5.78; N, 4.23. Found: C, 49.02; H, 6.11; N, 4.19.

3.14. 3,6-*Di*-O-*acetyl-5-(*N′-*acetyl-*N′-*methylthioureido)-5-deoxy-1,2*-O-*isopropylidene-β-L-idouranose* **12**

Yield: 51 mg (24%); $[\alpha]_D$ = –20.6 (*c* 1.0, CH_2Cl_2); R_f 0.42 (1:1 EtOAc:petroleum ether); UV (CH_2Cl_2): 274 nm (ε_{mM} 11.5); IR (KBr) 3133, 1748, 1674, 1522, 1373, 1225 and 1026 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.29, 1.50 (6H, 2s, Me_2C), 2.05, 2.12 (6H, 2s, OAc), 2.37 (3H, s, NAc), 3.68 (3H, s, MeN), 4.23 (1H, dd, $J_{5,6b}$ 5.6, $J_{6a,6b}$ 12.3, H-6b), 4.27 (1H, dd, $J_{5,6a}$ 5.8, H-6a), 4.47 (1H, d, $J_{2,3}$ 0, $J_{1,2}$ 3.8, H-2), 4.52 (1H, t, $J_{3,4} = J_{4,5}$ 3.4, H-4), 5.07 (1H, m, H-5), 5.26 (1H, d, H-3), 5.96 (1H, d, H-1), 11.80 (1H, d, $J_{5,NH}$ 7.6, NH); δ_C (75.5 MHz, $CDCl_3$) 20.7 (*Me*CO), 26.1, 26.6 (C*Me*$_2$), 38.6 (MeN), 53.9 (C-5), 62.5 (C-6), 76.5 (C-4), 76.7 (C-3), 83.4 (C-2), 104.6 (C-1), 112.2 (*C*Me$_2$), 169.4, 170.5 (CO ester), 174.8 (CO amide), 183.9 (C=S); FABMS: *m*/*z* 441 (100, [M+Na]$^+$). Anal. calcd for $C_{17}H_{26}O_8N_2S$: C, 48.79; H, 6.26; N, 6.69. Found: C, 49.01; H, 6.14; N, 6.68.

3.15. 3,6-*Di*-O-*acetyl-5-(*S*-acetyl-1-methyl-3-isothioureido)-5-deoxy-1,2*-O-*isopropylidene-β-L-idofuranose*[31] **13**

Yield: 136 mg (65%); $[\alpha]_D$ = –53.0 (*c* 1.0, CH_2Cl_2); R_f 0.30 (1:1 EtOAc:petroleum ether); UV (CH_2Cl_2): 272 nm (ε_{mM} 7.8); δ_H (300 MHz, $CDCl_3$) 1.31, 1.48 (6H, 2s, Me_2C), 2.02–2.20 (9H, 3s, Ac), 3.15 (3H, d, $J_{Me,NH}$ 4.8, MeN), 4.30 (1H, dd, $J_{5,6b}$ 5.8, $J_{6a,6b}$ 11.3, H-6b), 4.62 (2H, m, H-5, H-6a), 4.50 (1H, m, H-4), 4.56 (1H, d, $J_{2,3}$ 0, $J_{1,2}$ 3.7, H-2), 5.22 (1H, d, $J_{3,4}$ 2.4, H-3), 5.89 (1H, d, H-1), 8.60 (1H, m, NH); δ_C (75.5 MHz, $CDCl_3$) 20.7 (*Me*CO), 26.3, 26.5 (C*Me*$_2$), 33.2 (MeN), 54.0 (C-5), 61.0 (C-6), 74.8 (C-3), 76.6 (C-4), 83.7 (C-2), 103.6 (C-1), 112.6 (*C*Me$_2$), 169.1–170.5 (CO ester), 183.9 (CO thioester); FABMS: *m*/*z* 441 (100, [M+Na]$^+$). Anal. calcd for $C_{17}H_{26}O_8N_2S$: C, 48.79; H, 6.26; N, 6.69. Found: C, 48.49; H, 6.33; N, 6.69.

3.16. 3,6-Di-O-acetyl-5-(N′-acetyl-N′-phenylthioureido)-5-deoxy-1,2-O-isopropylidene-β-L-idofuranose **14**

Yield: 193 mg (80%); $[\alpha]_D = -4.0$ (*c* 0.6, CH_2Cl_2); R_f 0.42 (1:2 EtOAc:petroleum ether); UV (CH_2Cl_2): 277 nm (ε_{mM} 10.3); IR (KBr) 3476, 2990, 1748, 1682, 1530, 1406, 1232 and 1029, 731 and 694 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.32, 1.53 (6H, 2s, Me_2C), 1.93, 2.07 (6H, 2s, OAc), 2.11 (3H, s, NAc), 4.30 (2H, d, $J_{5,6}$ 5.4, H-6a, H-6b), 4.52 (1H, d, $J_{2,3}$ 0, $J_{1,2}$ 3.7, H-2), 4.59 (1H, t, $J_{3,4} = J_{4,5}$ 3.7, H-4), 5.03 (1H, dtd, $J_{5,NH}$ 7.6, H-5), 5.30 (1H, d, H-3), 6.03 (1H, d, H-1), 7.10–7.50 (5H, m, Ph), 11.90 (1H, d, NH); δ_C (75.5 MHz, $CDCl_3$) 20.7, 20.9 (MeCO), 26.2, 26.7 (CMe_2), 38.6 (MeN), 53.5 (C-5), 62.5 (C-6), 76.8 (C-4), 77.3 (C-3), 83.5 (C-2), 104.6 (C-1), 112.3 (CMe_2), 128.8, 129.3, 129.4, 142.1 (Ph), 169.6, 170.5 (CO ester), 174.6 (CO amide), 183.6 (C=S); FABMS: *m*/*z* 503 (100, $[M+Na]^+$). Anal. calcd for $C_{22}H_{28}O_8N_2S$: C, 54.99; H, 5.87; N, 5.83; S, 6.67. Found: C, 54.76; H, 5.81; N, 5.63; S, 6.58.

3.17. 3,6-Di-O-acetyl-5-[S-acetyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1-isothioureido]-5-deoxy-1,2-O-isopropylidene-β-L-idofuranose[31] **15**

Yield: 172 mg (47%); $[\alpha]_D = +64.5$ (*c* 1.1, CH_2Cl_2); R_f 0.35 (1:2 EtOAc:petroleum ether); UV (CH_2Cl_2): 277 nm (ε_{mM} 13.5); IR (KBr) 3293, 2999, 1760, 1428, 1371, 1236 and 1053 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.32, 1.49 (6H, 2s, Me_2C), 1.97–2.08 (OAc), 2.39 (3H, s, SAc), 3.78 (1H, dd, $J_{5',6'b}$ 2.2, $J_{6'a,6'b}$ 12.4, H-6′b), 3.82 (1H, ddd, $J_{5',6'a}$ 3.6, $J_{4',5'}$ 9.5, H-5′), 4.02 (1H, dd, $J_{5,6b}$ 4.3, $J_{6a,6b}$ 11.8, H-6b), 4.12 (1H, t, $J_{3',4'}$ 9.5, H-4′), 4.58 (1H, d, $J_{2,3}$ 0, $J_{1,2}$ 3.8, H-2), 4.61 (1H, dd, $J_{5,6a}$ 4.3, H-6a), 4.64 (1H, dd, $J_{3,4}$ 3.0, $J_{4,5}$ 9.1, H-4), 4.81 (2H, m, H-5, H-6a′), 5.24 (2H, m, H-2′, H-3′), 5.28 (1H, d, H-3), 6.03 (1H, m, H-1′), 6.09 (1H, d, H-1), 8.51 (1H, m, NH); δ_C (125.7 MHz, $CDCl_3$) 20.5–21.0 (*Me*COO), 23.9 (*Me*COS), 26.0, 26.2 (CMe_2), 54.6 (C-5), 61.4 (C-6), 62.7 (C-6′), 68.4 (C-4′), 74.4 (C-2′), 74.9 (C-3′), 75.6 (C-5′), 77.6 (C-3), 76.8 (C-4), 79.8 (C-1′), 83.5 (C-2), 104.3 (C-1), 112.1 (CMe_2), 169.0–171.1 (CO ester), 171.2 (C=N), 182.3 (CO thioester). Anal. calcd for $C_{30}H_{42}O_{17}N_2S$: C, 49.04; H, 5.76; N, 3.81; S, 4.36. Found: C, 49.00; H, 5.74; N, 3.81; S, 4.14.

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