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Note

Novel 4-thiogalactofuranosyl-containing disaccharides with nitrogen in the interglycosidic linkage

Karla D. Randell, Blair D. Johnston, B. Mario Pinto *

Department of Chemistry, Simon Fraser University, Burnaby BC, Canada V5A 1S6

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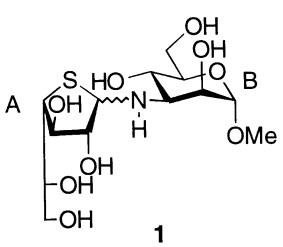
Abstract

The syntheses of three novel disaccharides containing a 4-thiogalactofuranosyl residue as the non-reducing unit and a nitrogen in the interglycosidic linkage are described. Acid-catalyzed condensation reactions of 4-thio-α/β-D-galactofuranose with either methyl 3-amino-3-deoxy-α-D-mannopyranoside, methyl 2-amino-2-deoxy-α-D-mannopyranoside, or methyl 2-acetamido-6-amino-2,6-dideoxy-β-D-glucopyranoside gave methyl 3-amino-3-deoxy-3-*N*-(4-thio-α/β-D-galactofuranosyl)-α-D-mannopyranoside, methyl 2-amino-2-deoxy-2-*N*-(4-thio-α/β-D-galactofuranosyl)-α-D-mannopyranoside, or methyl 2-acetamido-6-amino-2,6-dideoxy-6-*N*-(4-thio-α/β-D-galactofuranosyl)-β-D-glucopyranoside.

Keywords: Disaccharide; Heteroanalogues; 4-Thiogalactofuranose; *S*, *N*-Acetals

1. Introduction

The synthesis, conformational analysis, and enzyme inhibitory activity of disaccharide analogues containing sulfur in the ring and nitrogen in the interglycosidic linkage have been of recent interest in our laboratory [1–4]. Thus far, our efforts have targeted disaccharides containing 5-thiohexopyranosides as the non-reducing sugar. We now report the synthesis of the first examples of a new class of disaccharide (**1**, **2**, and **3**) containing 4-thiogalactofuranose (4-thio-Gal*f*) as the nonreducing sugar and nitrogen in the interglycosidic linkage.



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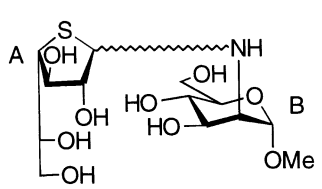

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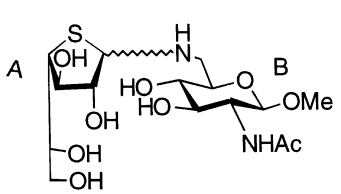

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The synthesis of oligosaccharides containing galactofuranose (Gal*f*) is of interest because Gal*f* is present as a constituent of the external cellular structures of protozoa [5], bacteria

* Corresponding author. Tel.: +1-604-2914327; fax: +1-604-2913765.

E-mail address: bpinto@sfu.ca (B.M. Pinto)

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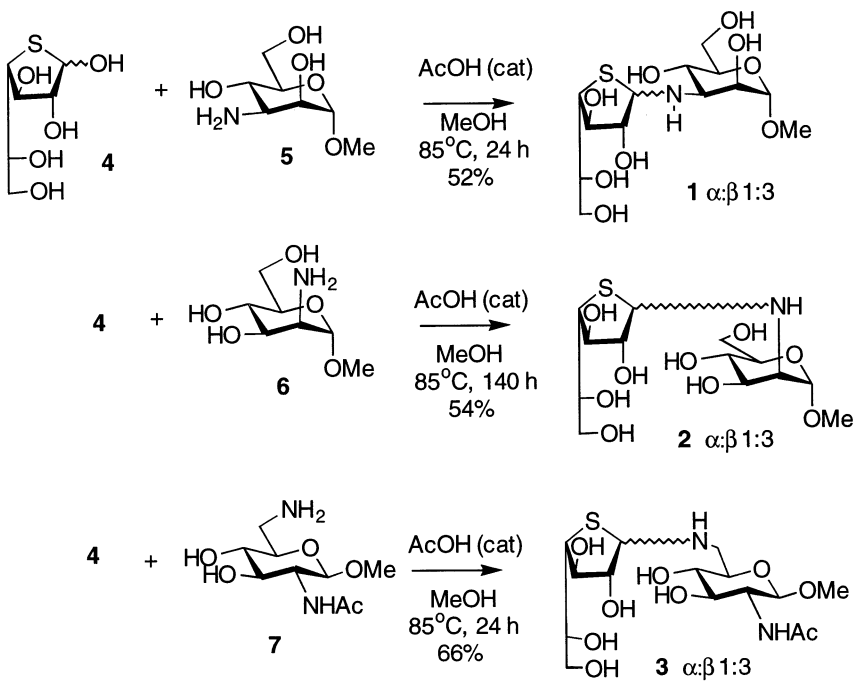
[6,7], and fungi [8]. For example, Gal*f* forms part of the oligosaccharide core of the glycosylinositolphospholipid (GIPL) from the protozoan *Trypanosoma cruzi*, the infectious agent of Chagas disease [9]. Gal*f* is found β-(1→3)-linked to an α-mannopyranosyl unit at the terminal end of the GIPL structure, and as a branched unit, also β-(1→3)-linked to an internal α-mannopyranosyl residue [10]. Previous reports from our laboratory have described the synthesis of oligosaccharides containing β-D-Gal*f* and 4-thio-β-D-Gal*f*, with oxygen atoms in the interglycosidic linkages [11–13]. It is also of interest to synthesize heteroanalogues that might function as substrate mimics to inhibit the processing of native substrates by the enzymes, and we now report the synthesis of **1**–**3** as representatives of a potential new class of inhibitor.

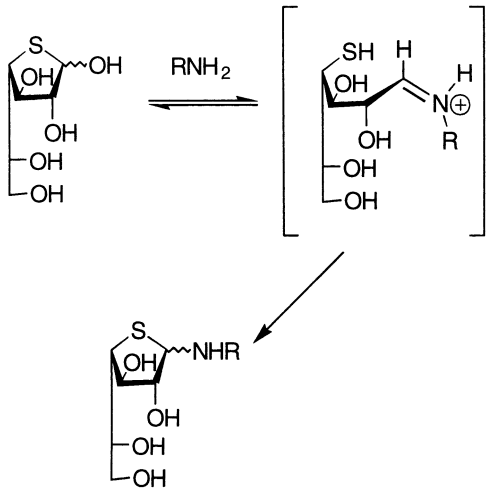
The required monosaccharide derivatives 4-thio-D-Gal*f* (**4**) [14], methyl 3-amino-3-deoxy-α-D-mannopyranoside (**5**) [15], methyl 2-amino-2-deoxy-α-D-mannopyranoside (**6**) [16], and methyl 2-acetamido-6-amino-2,6-dideoxy-β-D-glucopyranoside (**7**) [17] were synthesized by literature methods. Syntheses of the glycosylamines were performed using acetic acid as a catalyst in refluxing methanol, without the use of protecting groups on the monosaccharide units. Reactions of **4** with **5**, **6**, or **7** gave α:β mixtures of products **1**, **2**, and **3**, respectively (see Scheme 1). The isomers were not separable by column chromatography. The α:β mixtures were characterized by NMR spectroscopy using a COSY spectrum, together with a C–H correlation spectrum, to fully assign the ^{1}H and ^{13}C NMR signals of the 4-thio-Gal*f* ring (A) and the mannopyranosyl ring (B).

In an attempt to assign the anomeric configuration of the major and minor isomers in **1**–**3**, 2D NOESY spectra were obtained in D_2O. There was substantial overlapping of the ^{1}H NMR signals of the 4-thio-Gal*f* (A) rings in the spectra of **1**–**3** obtained in D_2O at 400 MHz, including two multiplets containing H-2A and H-3A of the major and minor isomers, respectively. The cross-peak between H-1A and H-3A, which is indicative of a β-linkage, was overlapped with the cross-peak between H-1A and H-2A. This latter cross-peak would be present in both the α and β isomers.

In the case of **1**, the 1D and 2D NOESY spectra were obtained in D_2O at 600 MHz in order to increase spectral dispersion. The ^{1}H NMR spectrum of **1** showed less overlap of the signals in the minor isomer, but unfortunately, the signals attributable to the major



Scheme 1.

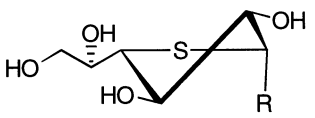


Scheme 2.

isomer were still not fully resolved. There did not appear to be a cross-peak between H-1A and H-3A in the spectrum of the minor isomer, but to be certain, another set of spectra for **1** was obtained using methanol-d_4 as a solvent. In this case, the multiplet containing H-2A and H-3A of the major isomer separated. The 2D NOESY spectra of **1** in methanol-d_4 showed the presence of only one H-1A and H-3A cross-peak, which corresponded to the signals of the major isomer. This enabled definitive assignment of the major isomer as the β isomer. The absence of the H-1A–H-3A cross-peak in the spectra of the minor isomer in both D_2O and methanol-d_4 was consistent with the presence of an α linkage between the 4-thio-Gal*f* ring (A) and the mannopyranosyl ring (B).

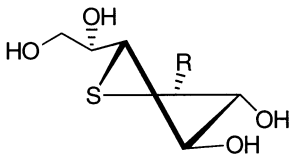
The coupling constants observed in the ^{1}H NMR spectra for the 4-thio-Gal*f* residues are of interest. The *J* values in D_2O [$J_{1,2}$ (5.3 Hz), $J_{2,3}$ (8.7 Hz) and $J_{3,4}$ (8.7 Hz)] for the 4-thio-Gal*f* residue in **1α** suggest that the ring is in a $^2T_3$ (D) conformation [18]. In this conformation, the anomeric linkage from 4-thio-Gal*f* (A) to Man*p* (B) is quasi-axially oriented, and the other substituents are quasi-equatorial. The large *J* values indicate that H-2 and H-3 and also H-3 and H-4 must have dihedral angles near 180°. This was also observed by Varela et al. [14] for the case of 1,2,3,5,6-penta-*O*-acetyl-4-thio-α-D-galactofuranose.

The *J* values in methanol-d_4 [$J_{1,2}$ (7.2 Hz), $J_{2,3}$ (8.1 Hz) and $J_{3,4}$ (7.2 Hz)] for the 4-thio-Gal*f* residue in **1β** suggest that it exists as a mixture of conformations, including $^4T_3$ (D) [12,18–20].



α-S-series $^2T_3$ (D)

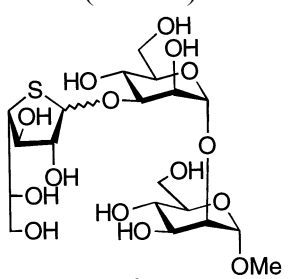
1α



β-S-series $^4T_3$ (D)

1β, 8

In the case of methyl (4-thio-α/β-D-galacto-furanosyl)-(1→3)-α-D-mannopyranosyl-(1→2)-α-D-mannopyranoside (**8**) [12], the 4-thio-Gal*f* ring adopts a twist conformation causing $J_{1,2}$ for the β isomer (5.8 Hz) to be larger than $J_{1,2}$ for the α isomer (4.2 Hz).



8

In furanosides, the $J_{1,2}$ values are usually indicative of α or β configuration [21], where a syn orientation between H-1 and H-2 leads to a larger *J* value than an anti orientation between H-1 and H-2, but this was not found to be true for the 4-thio-Gal*f* compounds. The conformation of the 4-thio-Gal*f* ring in **1** of the minor isomer was judged to be very similar in methanol-d_4 to that observed in D_2O, so it was assumed that the conformation of the major isomer would be similar in D_2O or methanol-d_4. In support of this contention, the NOE contacts were similar in both solvents.

The α:β ratios (1:3) of **1**–**3** were found to be the same, so the major isomer was tentatively assigned as the β isomer in **2** and **3**. This assignment was confirmed by several methods. (1) The $J_{1,2}$ values were consistently larger for

the major isomer in **2** and **3**, as was the case with **1** and **8**. (2) ^{1}H NMR resonances observed for the 4-thio-Gal*f* H-4 protons in the minor isomers consistently showed an upfield chemical shift as compared with those of the major isomers. In the case of **1** and **8** [12], we have shown that an α linked 4-thio-Gal*f* moiety has a similar upfield chemical shift for H-4 compared with a β linked 4-thio-Gal*f* moiety. Therefore, the major and minor isomers of **2** and **3** were assigned as β and α, respectively. The 2D NOESY spectra of **1**, **2**, and **3** also showed the presence of cross-peaks between H-1A and H-3B, H-1A and H-2B, and H-1A and H-6B, respectively, across the interglycosidic linkages.

The occurrence of compounds **1**–**3** as anomeric mixtures is not a serious concern since we expect that processing enzymes will bind one of the anomers preferentially, as was the case with glucoamylase binding of the α anomer in an α:β equilibrium mixture of a disaccharide analogue containing a 5-thiohexopyranosylamine [1,4].

Since compounds **1**–**3** do not hydrolyze appreciably in aqueous solution, we propose that anomerization proceeds by endocyclic C–S bond cleavage of the sulfur-containing ring to give the intermediate iminium ions. Subsequent ring closure by nucleophilic attack of the thiol/thiolate on the opposite face of the iminium ion then occurs in preference to nucleophilic attack by water (see Scheme 2). This mechanism is in agreement with results from a study of the lifetime of an acyclic aliphatic iminium ion, $CF_3CH_2N^+$–(CH_3)=CH_2, in aqueous solution, formed during the solvolysis of the corresponding thiol, $CF_3CH_2N(CH_3)$-$CH_2SC_6H_4$-2-COO– [22]. The lifetime of the iminium ion was determined to be $\sim 5.5 \times 10^{-8}$ s, and the relative rates of the diffusion-controlled reaction of the nucleophilic leaving group RS^- versus the reaction with solvent (H_2O) were determined to be $k_{RS^-}/k_{H_2O} = 280$ [22]. An attempt to increase the efficiency of the synthesis of **1** using mercuric chloride ($HgCl_2$) catalysis, as was described in our earlier work with 5-thiohexopyranosylamines [2,3], was not successful in this case.

In summary, the synthesis of a new class of disaccharides (**1**, **2**, and **3**) containing sulfur in the nonreducing galactofuranose ring and nitrogen in the interglycosidic linkage has been achieved.

2. Experimental

General methods.—Optical rotations were measured at 21 °C with a Rudolph Research Autopol II automatic polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-400 NMR spectrometer at 400.13 and 100.6 MHz, for proton and carbon, respectively. The ^{1}H NMR spectra of **1** were also recorded on a Bruker AMX-600 NMR spectrometer at 600.13 MHz. Chemical shifts are given in ppm downfield from 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) for those spectra measured in D_2O. Chemical shifts and coupling constants were obtained from a first-order analysis of the spectra. All assignments were confirmed with the aid of two-dimensional ^{1}H/^{1}H (COSYDFTP), ^{1}H/^{13}C (INVBTP), and ^{1}H (NOESYTP) experiments using standard Bruker pulse programs and an inverse detection, ^{1}H/X double-resonance probe. High-resolution liquid secondary ion mass spectra (FAB) were recorded on a Kratos Concept H instrument using *m*-nitrobenzyl alcohol as the matrix. Analytical thin-layer chromatography (TLC) was performed on aluminum plates precoated with Merck Silica Gel 60F-254 as the adsorbent. The developed plates were air-dried, exposed to UV light and/or sprayed with a solution containing 1% $Ce(SO_4)_2$ and 1.5% molybdic acid in 10% aq H_2SO_4, and heated. Compounds were purified by flash column chromatography on Kieselgel 60 (230–400 mesh). Solvents were distilled before use and were dried, as necessary, by literature procedures. Solvents were evaporated under reduced pressure and below 40 °C.

General procedure for glycosylation reactions.—A mixture of 4-thio-D-galactofuranose (**4**), the deoxyamino sugar **5**, **6** or **7** (1.5 equiv), and AcOH (0.05 equiv relative to the amine) was heated to 85 °C in dry MeOH (15–20 mL/mmol of **4**) in a sealed tube for 24–140 h. The reaction mixture was cooled to room temperature (rt) and the solvent removed in vacuo. The residue was purified by

column chromatography using 6:2:1 EtOAc–MeOH–water (for **1** and **2**) or 4:2:1 EtOAc–MeOH–water (for **3**) as the eluant.

*Methyl 3-amino-3-deoxy-3-*N*-(4-thio-α/β-*D*-galactofuranosyl)-α-*D*-mannopyranoside* (**1**). —R_f 0.68; 4:2:1 EtOAc–MeOH–water; (α:β 1:3, 52%).

1β. ^{1}H NMR (D_2O): δ 4.72 (d, 1 H, H-1B), 4.40 (m, 1 H, H-1A), 3.95–3.89 (m, 4 H, H-2B, H-2A, H-3A, H-5A), 3.86 (dd, 1 H, $J_{5,6}$ 2.1, $J_{6,6'}$ 12.1 Hz, H-6B), 3.71 (dd, 1 H, $J_{5,6'}$ 6.2 Hz, H-6′B), 3.62 (ddd, 1 H, $J_{4,5}$ 9.9 Hz, H-5B), 3.55–3.50 (m, 2 H, H-4B, H-6A), 3.47 (dd, 1H, $J_{5,6'}$ 7.0, $J_{6,6'}$ 11.8 Hz, H-6′A), 3.42 (m, 1 H, $J_{3,4}$ 8.8, $J_{4,5}$ 3.5 Hz, H-4A), 3.39 (s, 3 H, OCH_3), 2.87 (dd, 1 H, $J_{2,3}$ 3.0, $J_{3,4}$ 9.9 Hz, H-3B). ^{13}C NMR (D_2O): δ 102.78 (C-1B), 83.08, 77.85 (C-2A, C-3A), 75.31 (C-5B), 72.69 (C-5A), 68.86 (C-2B), 67.77, 67.05 (C-4B, C-6A), 66.80 (C-1A), 63.71 (C-6B), 60.32 (C-3B), 57.42 (OCH_3), 51.36 (C-4A). ^{1}H NMR (methanol-d_4): δ 4.64 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1B), 4.35 (d, 1 H, $J_{1,2}$ 7.2 Hz, H-1A), 3.92 (dd, 1 H, $J_{3,4}$ 7.9 Hz, H-3A), 3.90–3.81 (m, 1 H, H-5A), 3.82 (dd, 1 H, $J_{2,3}$ 8.1 Hz, H-2A), 3.79 (dd, 1 H, $J_{2,3}$ 2.8 Hz, H-2B), 3.76–3.64 (m, 2 H, H-6B, H-6′B), 3.58–3.36 (m, 5 H, H-5B, H-4B, H-6A, H-6′A, H-4A), 3.38 (s, 3 H, OCH_3), 2.89 (dd, 1 H, $J_{3,4}$ 9.2 Hz, H-3B).

1α. ^{1}H NMR (D_2O): δ 4.72 (d, 1 H, H-1B), 4.47 (d, 1 H, $J_{1,2}$ 4.6 Hz, H-1A), 4.12 (dd, 1 H, $J_{1,2}$ 1.7, $J_{2,3}$ 2.9 Hz, H-2B), 4.08–4.05 (m, 2 H, H-2A, H-3A), 3.95–3.89 (m, 1 H, H-5A), 3.85 (dd, 1 H, $J_{5,6}$ 2.1, $J_{6,6'}$ 11.9 Hz, H-6B), 3.70 (dd, 1 H, $J_{5,6'}$ 6.0 Hz, H-6′B), 3.62 (ddd, 1 H, $J_{4,5}$ 9.9 Hz, H-5B), 3.55–3.50 (m, 2 H, H-4B, H-6A), 3.47 (dd, 1 H, $J_{5,6'}$ 7.2, $J_{6,6'}$ 11.4 Hz, H-6′A), 3.39 (s, 3 H, OCH_3), 3.24 (dd, 1 H, $J_{4,5}$ 3.7, $J_{3,4}$ 6.7 Hz, H-4A), 2.86 (dd, 1 H, $J_{3,4}$ 9.3 Hz, H-3B). ^{13}C NMR (D_2O): δ 103.04 (C-1B), 80.22, 79.21 (C-2A, C-3A), 75.44 (C-5B), 73.35 (C-5A), 70.74 (C-2B), 68.64 (C-1A), 67.77, 67.05 (C-4B, C-6A), 63.71 (C-6B), 62.76 (C-3B), 57.42 (OCH_3), 52.56 (C-4A). ^{1}H NMR (methanol-d_4): δ 4.65 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1B), 4.31 (d, 1 H, $J_{1,2}$ 5.3 Hz, H-1A), 4.13 (dd, 1 H, $J_{2,3}$ 3.0 Hz, H-2B), 4.06 (dd, 1 H, $J_{3,4}$ 6.4 Hz, H-3A), 3.97 (dd, 1 H, $J_{2,3}$ 8.5 Hz, H-2A), 3.90–3.81 (m, 1 H, H-5A), 3.76–3.64 (m, 2 H, H-6B, H-6′B), 3.58–3.36 (m, 4 H, H-5B, H-4B, H-6A, H-6′A), 3.38 (s, 3 H, OCH_3), 3.19 (dd, 1 H, $J_{4,5}$ 2.6 Hz, H-4A), 2.74 (dd, 1 H, $J_{3,4}$ 9.7 Hz, H-3B). HRFABMS Calcd for $C_{13}H_{25}NO_9S$ + H: 372.1328. Found: M + H: 372.1337.

*Methyl 2-amino-2-deoxy-2-*N*-(4-thio-α/β-*D*-galactofuranosyl)-α-*D*-mannopyranoside* (**2**). —R_f 0.66; 4:2:1 EtOAc–MeOH–water; (α:β 1:3, 54%).

2β. ^{1}H NMR (D_2O): δ 4.74 (d, 1 H, H-1B), 4.38 (d, 1 H, $J_{1,2}$ 7.5 Hz, H-1A), 3.91 (ddd, 1 H, H-5A), 3.89–3.80 (m, 4 H, H-3B, H-2A, H-3A, H-6B), 3.72 (dd, 1 H, $J_{5,6}$ 5.2, $J_{6,6'}$ 12.2 Hz, H-6′B), 3.58 (m, 1 H, H-5B), 3.56–3.48 (m, 2 H, H-4B, H-6A), 3.46 (dd, 1 H, $J_{5,6'}$ 7.1, $J_{6,6'}$ 11.7 Hz, H-6′A), 3.39 (dd, 1 H, dd, $J_{3,4}$ 8.5, $J_{4,5}$ 3.5 Hz, H-4A), 3.36 (s, 3 H, OCH_3), 3.04 (dd, 1 H, $J_{1,2}$ 1.2, $J_{2,3}$ 4.6 Hz, H-2B). ^{13}C NMR (D_2O): δ 101.89 (C-1B), 82.70, 77.79 (C-2A, C-3A), 74.89 (C-5B), 72.71 (C-5A), 71.99 (C-3B), 69.37 (C-4B), 68.97 (C-1A), 67.09 (C-6A), 63.39 (C-6B), 61.31 (C-2B), 57.50 (OCH_3), 51.40 (C-4A).

2α. ^{1}H NMR (D_2O): δ 5.06 (d, 1 H, $J_{1,2}$ 1.3 Hz, H-1B), 4.38 (d, 1 H, H-1A), 4.04–4.00 (m, 2 H, H-2A, H-3A), 3.91 (ddd, 1 H, H-5A), 3.89–3.80 (m, 1 H, H-6B), 3.78 (dd, 1 H, $J_{2,3}$ 4.6, $J_{3,4}$ 9.1 Hz, H-3B), 3.73 (dd, 1 H, $J_{5,6}$ 5.0, $J_{6,6'}$ 12.4 Hz, H-6′B), 3.58 (m, 1 H, H-5B), 3.56–3.48 (m, 2 H, H-4B, H-6A), 3.46 (dd, 1 H, $J_{5,6'}$ 7.0, $J_{6,6'}$ 11.5 Hz, H-6′A), 3.37 (s, 3 H, OCH_3), 3.22 (dd, 1 H, $J_{3,4}$ 6.7, $J_{4,5}$ 3.7 Hz, H-4A), 3.04 (dd, 1 H, $J_{2,3}$ 4.6 Hz, H-2B). ^{13}C NMR (D_2O): δ 102.34 (C-1B), 80.34, 79.01 (C-2A, C-3A), 74.89 (C-5B), 73.48 (C-5A), 72.71 (C-3B), 69.93 (C-4B), 69.22 (C-1A), 66.98 (C-6A), 64.15 (C-2B), 63.39 (C-6B), 57.50 (OCH_3), 52.52 (C-4A). HRFABMS Calcd for $C_{13}H_{25}NO_9S$ + H: 372.1328. Found: M + H: 372.1325.

*Methyl 2-acetamido-6-amino-2,6-dideoxy-6-*N*-(4-thio-α/β-*D*-galactofuranosyl)-β-*D*-glucopyranoside* (**3**).—R_f 0.49; 4:2:1 EtOAc–MeOH–water; (α:β 1:3, 66%).

3β. H NMR (D_2O): δ 4.39 (d, 1 H, $J_{1,2}$ 8.5 Hz, H-1B), 4.32 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1A), 3.94–3.87 (m, 1 H, H-5A), 3.87–3.78 (m, 2 H, H-2A, H-3A), 3.65 (dd, 1 H, $J_{1,2}$ 8.5, $J_{2,3}$ 10.3 Hz, H-2B), 3.52–3.42 (m, 4 H, H-6A, H-6′A, H-3B, H-5B), 3.47 (s, 3 H, OCH_3), 3.37 (dd, 1 H, $J_{3,4}$ 8.6, $J_{4,5}$ 3.5 Hz, H-4A), 3.31 (dd, 1 H,

$J_{3,4}$ $J_{4,5}$ 9.9 Hz, H-4B), 3.08 (dd, 1 H, $J_{5,6}$ 2.4, $J_{6,6'}$ 13.5 Hz, H-6B), 2.82 (dd, 1 H, $J_{5,6'}$ 8.5 Hz, H-6′B), 1.99 (s, 3 H, NHCOCH_3). ^{13}C NMR (D_2O): δ 177.31 (NH*C*OCH$_3$), 104.49 (C-1B), 82.81, 77.65 (C-2A, C-3A), 77.19, 76.51 (C-3B, C-5B), 74.55 (C-4B), 72.66 (C-5A), 69.58 (C-1A), 67.02 (C-6A), 60.07 (O*C*H$_3$), 58.13 (C-2B), 51.21 (C-4A), 50.47 (C-6B), 24.81 (NHCO*C*H$_3$).

3α. ^{1}H NMR (D_2O): δ 4.42 (d, 1 H, $J_{1,2}$ 5.9 Hz, H-1A), 4.40 (d, 1 H, $J_{1,2}$ 8.5 Hz, H-1B), 4.12–4.07 (m, 2 H, H-2A, H-3A), 3.94–3.87 (m, 1 H, H-5A), 3.65 (d, 1 H, d, $J_{2,3}$ 10.2 Hz, H-2B), 3.52–3.42 (m, 4 H, H-6A, H-6′A, H-3B, H-5B), 3.45 (s, 3 H, OCH_3), 3.31 (dd, 1 H, $J_{3,4}$, $J_{4,5}$ 9.1 Hz, H-4B), 3.29 (dd, 1 H, $J_{3,4}$ 6.3, $J_{4,5}$ 4.0 Hz, H-4A), 2.99 (dd, 1 H, $J_{5,6}$ 2.9, $J_{6,6'}$ 12.7 Hz, H-6B), 2.92 (dd, 1 H, $J_{5,6'}$ 8.6 Hz, H-6′B), 1.99 (s, 3 H, NHCOCH_3), ^{13}C NMR (D_2O): δ 177.31 (NH*C*OCH$_3$), 104.49 (C-1B), 79.80, 79.29 (C-2A, C-3A), 76.72, 76.44 (C-3B, C-5B), 74.71 (C-4B), 73.22 (C-5A), 69.00 (C-1A), 66.86 (C-6A), 59.91 (O*C*H$_3$), 57.86 (C-2B), 52.96 (C-4A), 51.21 (C-6B), 24.81 (NHCO*C*H$_3$). HRFABMS Calcd for $C_{15}H_{28}N_2O_9S$ + H: 413.1593. Found: M + H: 413.1591.

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