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Synthesis of (1→3) Thiodisaccharides of GlcNAc and the Serendipitous Formation of 2,3-Dideoxy-(1→2)-thiodisaccharides through a Vinyl Azide Intermediate

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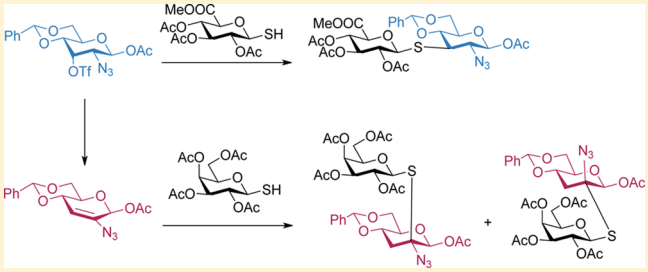
Supporting Information

ABSTRACT: The syntheses of β-*S*-GlcA(1→3)GlcNAc and β-*S*-Gal(1→3)GlcNAc thiodisaccharides, which can be considered mimetics of the repeating units of hyaluronan and keratan respectively, were achieved by S_N2 displacement of a triflate group allocated at the 3-position of a convenient 2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranose precursor by the corresponding nucleophilic suitable protected thioaldoses derived from glucuronic acid (GlcA) and galactose (Gal). The study of the reaction led to the finding that the vinyl azide formed by competitive E2 reaction of the mentioned triflate was an interesting precursor of a new kind of 2,3-dideoxy-2-azido-(1→2) thiodisaccharides through an addition reaction. Determination of the stereochemistry of the new stereocenter at C-2 was achieved by NOESY experiments. Final protecting group manipulation of the (1→3) thiodisaccharides led to a family of derivatives that could be used as building blocks for the synthesis of complex glycomimetics.



INTRODUCTION

The synthesis of thiodisaccharides, that is, disaccharides in which the interglycosidic oxygen is replaced by a sulfur atom, has been largely addressed over the past 30 years or more.[1,2] Still, thiodisaccharides represent a synthetic challenge for carbohydrate chemists for their increasing importance in the glycobiology field. It is well known that these are considered carbohydrate mimetics with great potential as enzyme inhibitors or new ligands for lectins with increased resistance in biological media.[3−6]

Different synthetic approaches have been explored to access these compounds. Nucleophilic replacement of a good leaving group present in one sugar residue by an activated thioaldose in basic medium (through a classic S_N2 mechanism) accounted for the synthesis of a variety of structures.[7−10]

The incorporation of *S*-D-GlcNAc and *S*-D-GalNAc residues, components of a range of relevant bioactive glycans (as those found in glycosaminoglycans) poses extra challenges. It should be noted that the presence of the −NHAc group in the 2-position favors the formation of 1,2-oxazoline derivatives when an oxocarbenium ion is involved, thus hampering glycosylation reactions.[11] Additionally, it is well known that −NHAc participates through H-bonding, which may lead to unexpected and inconvenient secondary products.[12] Also, when a good leaving group, such as mesylate or triflate, is attached to the OH-3, both 2,3-oxazolines and 2,3-aziridines can be obtained.[13] The formation of stable 2,3-oxazoline rings is a major disadvantage as this group needs a strong acid medium to be hydrolyzed, which is incompatible with the required further protecting group manipulation.[14,15]

Figure 1 summarizes the different approaches reported on the synthesis of thiodisaccharides bearing *N*-acetylhexosamine residues. The ring-opening reaction of 2,3-aziridines with α-L-FucSH in strong basic conditions led to a (1→3) thiodisaccharide, together with its (1→2) isomer, having the nitrogenated function in the 3-position (Figure 1, path a).[16] In another report, the thiodisaccharide β-GalNAc(1→4)GlcA, which is mimetic of the chondroitin sulfate repetitive unit, was synthesized through an S_N2 reaction, and its binding to chondroitin AC lyase was studied.[17] The same approach gave rise to β-GlcNAc(1→4)GlcNAc thiodisaccharide, from a 2-acetamido-4-*O*-triflate-D-galactopyranosyl substrate and GlcNAcSH as a nucleophile (Figure 1, path b). As the E2-type elimination reaction usually competes with S_N2 displacements, the 4,5-elimination product was also obtained.[18] The

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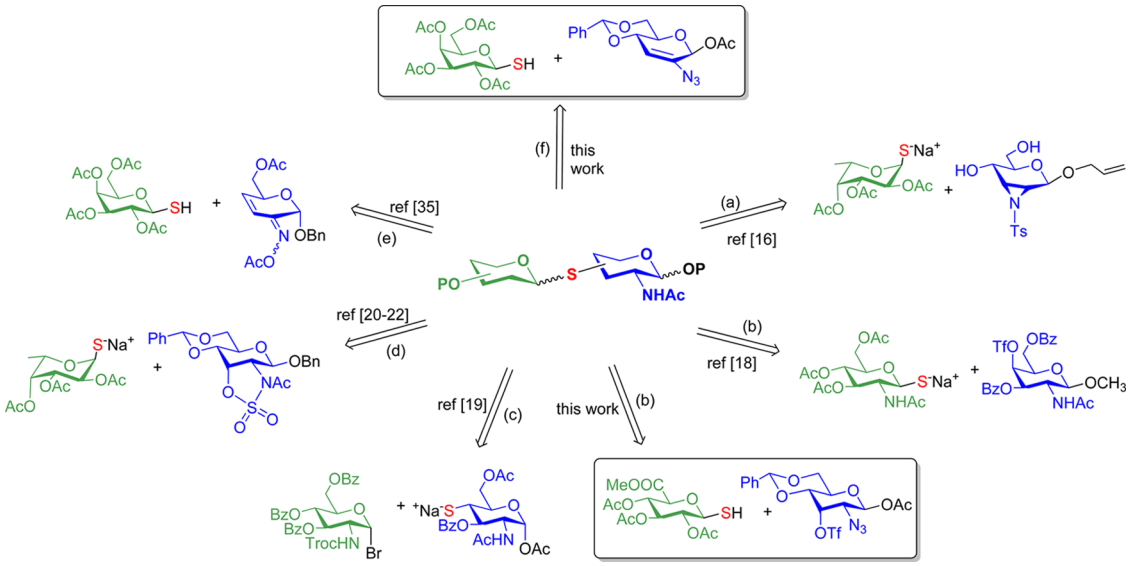

Figure 1. Synthetic approaches reported on the synthesis of thiodisaccharides from *N*-acetylhexosamine precursors: (a) ring-opening reaction of aziridines, (b) S_N2 reaction, (c) thioglycosylation reaction, (d) ring-opening reaction of a 2,3-sulfamidate, (e) Michael addition of a thioaldose to acetyl oximes, and (f) addition reaction of thioaldoses to vinyl azides.

same thiodisaccharide was synthesized through a thioglycosylation reaction from a 4-thio-GlcNAc derivative and GlcNAc bromide by treatment with NaH in THF (Figure 1, path c).[19] Alternatively, thioglycosylation could be accomplished by a reaction of other glycosyl donors, such as an imidate donor, with a thiol, avoiding strong basic conditions. However, as far as we know, there are no reports on the synthesis of thiodisaccharides by this methodology involving hexosamine precursors.

Besides the S_N2 mechanism to construct the thioglycosidic bond, alternative approaches were explored. The nucleophilic opening of a cyclic 2,3-sulfamidate was the key step to obtain the α-*S*-Fuc(1→3)GlcNAc thiodisaccharide (Figure 1, path d). This 2,3-sulfamidate intermediate was generated from an *allo*-configured precursor and 1,1′-sulfonyl diimidazole followed by treatment with acetyl chloride.[20−22] This ring-opening reaction was later used to obtain the nitrophenyl glycosides of 3-thio-β-GlcNAc and 3-thio-β-GalNAc,[23] which could be also envisioned as precursors in the synthesis of glycomimetics.

In another approach, the Michael addition of thioaldoses to the α,β-unsaturated systems of sugar enones successfully produced 3- and 4-deoxythiodisaccharides and other structurally related compounds.[24−30] Some of the thiodisaccharides obtained proved to be good inhibitors of glycosidases such as the *Escherichia coli* β-galactosidase[27,30] and others.[31]

The ring-opening reaction of epoxides also yielded (1→3) and (1→4) thiodisaccharides under stereoselective processes.[16,32] Similarly, when starting with episulfides as precursors, branched thiotrisaccharides were also obtained through an S_N2-like mechanism, in some cases with variable amounts of sugar disulfides.[33,34]

In a very recent approach, a complete study on the Michael addition of β-D-GalSH to *E* and *Z* acetyl oximes derived from sugar enones was reported. This strategy broadened the perspectives for the access to thiodisaccharides having a GlcNAc or GalNAc residue in the reducing end (Figure 1, path e).[35]

Additionally, it is worth stating that vinyl azides have been proven to be valuable precursors in the organic synthesis field, mainly for the synthesis of heterocyclic compounds.[36,37] For example, a number of methodologies involving vinyl azides and 1,3-dicarbonyl compounds under transition metal catalysis proved to be unique to obtain a wide range of heterocyclic structures. Thermal- or photoinduced reactions of these precursors also led to heterocycles through vinyl nitrenes and 2*H*-azirines as intermediates.[38]

Vinyl azides can also behave as enamine-like nucleophiles to give iminodiazonium ions. The mostly explored transformation of the latter is the 1,2-substituent migration (Schmidt reaction), which finally leads to amides by nitrogen elimination.[39] Moreover, iminodiazonium ions can also react with nucleophiles to give addition products. In this respect, the fluoro- and bromo-alkoxylation of vinyl azides was developed, providing α-alkoxy-β-haloalkyl azides in good yields.[40]

Vinyl azides deriving from carbohydrates were first described by Hanessian in 1968.[41] These have been obtained as undesired collateral E2 products in a number of S_N2 reactions of triflyl derivatives having a vicinal azide group, as above-mentioned.[42−44] Yet, as far as we know, carbohydrate-derived vinyl azides have not been explored as synthetic precursors of modified carbohydrates, even though this functional group has proved to have a great potential in an extensive variety of applications.

Thus, we present herein the results obtained in our way to the thiodisaccharide β-*S*-GlcA(1→3)GlcNAc, mimetic of the hyaluronan repetitive unit, through a 2-azido-3-*O*-triflate having an *allo* configuration as a key intermediate. The reaction was studied also by using GalSH as a nucleophile, and thus, β-*S*-Gal(1→3)GlcNAc thiodisaccharide, related to the keratan repetitive unit, was also synthesized (Figure 1, path b, this work). Unexpectedly, the reaction also led to a particular class of derivatives, namely, 2,3-dideoxy-2-azido-(1→2)-thiodisaccharides. We have demonstrated that the latter were obtained by addition of the thioaldose to a vinyl azide intermediate formed by E2 reaction of the mentioned *allo*-configured triflate (Figure 1, path f, this work). The determination of the configuration of these compounds was

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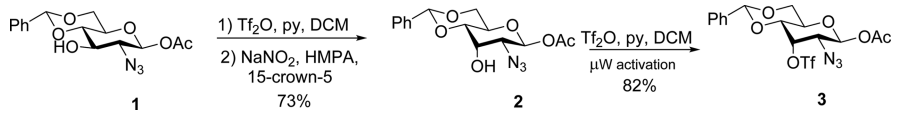
Scheme 1. Synthesis of 1-*O*-Acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-trifluoromethanesulfonyl-*β*-D-allopyranoside 3



Scheme 2. Synthesis of (1→3) Thiodisaccharides 6 and 10 and Formation of Byproducts 7, 8, 9, and 11

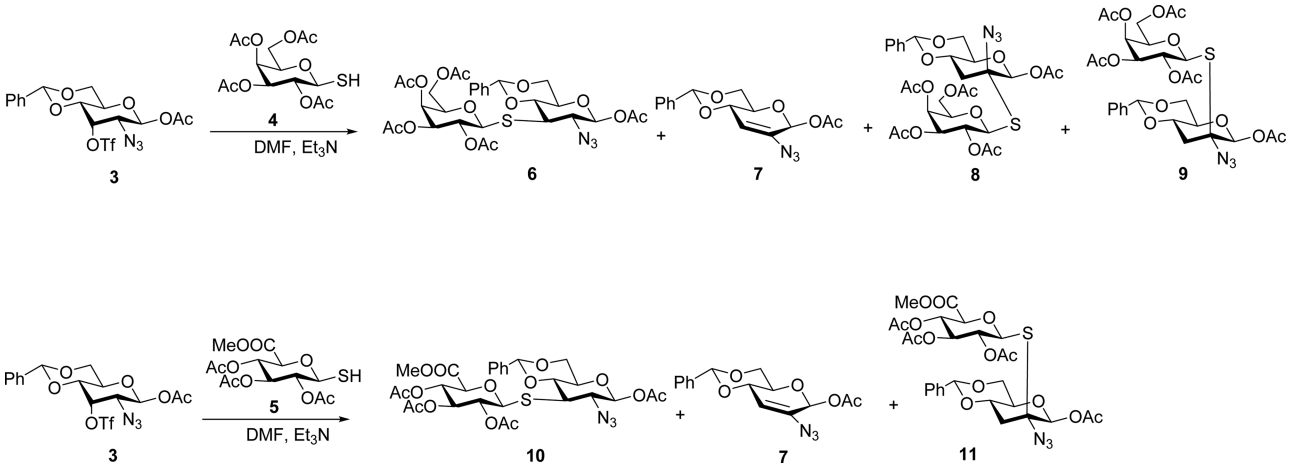
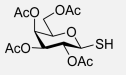
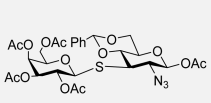
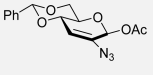
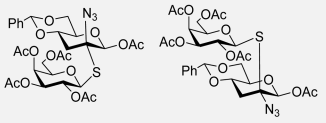
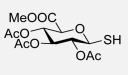
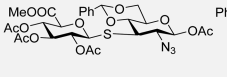
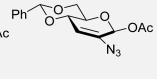
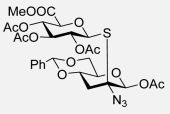


Table 1. Reaction Conditions for (1→3) Thiodisaccharides 6 and 10

Entry	**3**:**4**	Equiv Et_3N	Temperature	Solvent	Thioaldose	Yield **6** (%)	Yield **7** (%)	Yield **8** + **9** (%)
								
					4	**6**	**7**	**8** + **9**
1	1:1.1	0.0	-10	DMF		-	-	-
2	1:1.5	4.5	-30	DMF/HMPA 1:1		19	79	<2
3	1:1.1	1.2	-10	DMF		40	<1	55
4	1:1.2	2.4	-10	DMF/HMPA 9:1		27	14	35
Entry	**3**:**5**	Equiv Et_3N	Temperature	Solvent	Thioaldose	Yield **10** (%)	Yield **7** (%)	Yield **11** (%)
								
					5	**10**	**7**	**11**
5	1:1.2	2.4	-10	DMF/HMPA 9:1		45	51	n.d.
6	1:1.3	1.6	-30	DMF/HMPA 9:1		36	42	<1
7	1:1.7	5.1	-30	DMF		30	39	8

achieved by a combination of NMR experiments (2D-NOESY) and molecular modeling.

RESULTS AND DISCUSSION

Inspired by the structure of hyaluronan, constituted by the repetitive disaccharide [→4)*β*GlcA(1→3)*β*GlcNAc(1→], we envisioned the synthesis of (1→3) thiodisaccharides of GlcNAc through a C-3 double inversion strategy from a *gluco*-configured precursor, conveniently protected in 4,6-positions. The presence of an −NHAc group in the 2-position should be avoided because of its participation in S_N2 displacements to give a 2,3-oxazoline.[21] Thus, we synthesized **1**, as a suitable precursor, in a three-step sequence from D-GlcNH$_2$ hydrochloride (see Scheme S1).[45] It should be mentioned that the installation of the 2-azide group was performed using imidazole-1-sulfonyl azide hydrogen sulfate, as an azido transfer reagent, in a more convenient procedure than that involving TfN_3.[46]

Thus, **1** was treated with Tf_2O and pyridine in anhydrous DCM and was subsequently displaced with sodium nitrite in HMPA in the presence of 15-crown-5[45] to obtain **2** (Scheme 1). The signal corresponding to H-3 in the ^{1}H NMR spectrum

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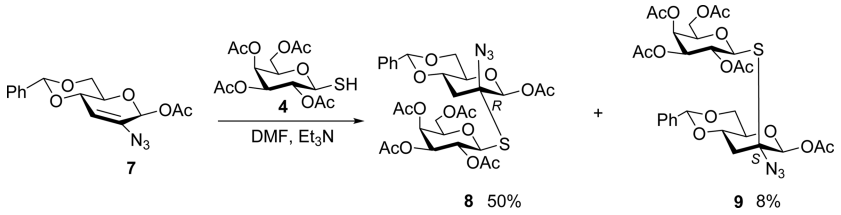
Scheme 3. Synthesis of (1→2) Thiodisaccharides 8 and 9 from Vinylazide 7



appeared at 4.45 ppm, showing a $J_{2,3} = J_{3,4} = 2.7$ Hz, confirming the *allo* configuration. These values agree with those reported by Hung and co-workers for their 2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranosyl benzoate.[45]

Then, we faced the synthesis of **3**, the 3-*O*-triflate of **2**. Treatment of **2** with Tf_2O and pyridine in anhydrous DCM under standard conditions was not effective. The reaction required low-power microwave irradiation probably because the axial disposition of HO-3 lessens its reactivity as described for *gulo*-configured derivatives[47] (Scheme 1). Surprisingly, compound **2** and its triflate **3** had the same chromatographic mobility in a number of solvents, a fact that complicated the analysis. The ^{1}H NMR spectrum of **3** showed that H-3 appeared strongly deshielded at 5.39 ppm. This signal was again characteristic of the *allo* configuration, appearing as a triplet with $J_{2,3} = J_{3,4} = 2.7$ Hz.

Compound **3** was stable enough to be isolated and purified by column chromatography for characterization. However, in the following reactions, it was used without purification. The complete transformation of **2** into **3** was verified by ^{1}H NMR by observing the signals of the H-3 described. Thus, nucleophilic displacement of the triflate group with the 1-thioaldoses **4** and **5** in the presence of Et_3N led to the desired thiodisaccharides β-Gal(1→3)GlcN$_3$ (**6**) and β-GlcA(1→3)GlcN$_3$ (**10**), respectively (Scheme 2). As in our initial experiments these products were obtained in low yields together with a number of byproducts, the reaction was studied under different conditions. The effects of temperature, concentration of reactants and base, and the solvent used were explored to optimize the yield of the thiodisaccharides (Table 1), which were isolated from the other products by column chromatography.

First, it was determined that, in the absence of base, the reaction did not proceed (Table 1, entry 1). In contrast, in the presence of an excess of base, the vinyl azide **7** was the main product (Table 1, entry 2). Using GalSH (**4**) as a nucleophile, **6** was obtained in 40% yield (Table 1, entry 3) when the reaction was carried out in the presence of 1.2 equiv of Et_3N at −10 °C. The ^{1}H NMR spectrum of **6** showed a triplet at 2.97 ppm, with $J_{2,3} \cong J_{3,4} = 10.8$ Hz, diagnostic for the H-3, which correlated with a signal at 50.0 ppm in the ^{1}H-^{13}C-HSQC NMR spectrum. Conversely, when using GlcASH (**5**), the reaction required 2.4 equiv of base and HMPA as a co-solvent, giving 45% yield of **10** (Table 1, entry 5). Similarly, H-3 appeared as a triplet at 3.02 ppm ($J_{2,3} \cong J_{3,4} = 10.7$ Hz) in the ^{1}H NMR spectrum, while C-3 was observed at 49.5 ppm in the ^{13}C NMR spectrum. It is noteworthy that, despite any attempt to the contrary, compound **7** was obtained in all cases, as a result of the E2 elimination of the 3-*O*-triflate group and the H-2, which are in antiperiplanar disposition.

Compound **7** was characterized on the basis of its ^{1}H and ^{13}C NMR spectra, together with the corresponding 2D-HSQC, COSY, and HMBC experiments. The H-1 appeared at 6.34 ppm as a double-doublet with a $J_{1,3} = 0.7$ Hz and $J_{1,4} = 2.1$ Hz. The signal for H-3 at 5.87 ppm appeared as a broad singlet. In the ^{13}C NMR spectrum, a signal at 115.7 ppm was assigned to C-3, as it correlated with the H-3 signal in the ^{1}H-^{13}C HSQC spectrum. The 2D-HMBC experiment was important for the assignment as the system H-1/H-3/H-4 was coupled. The coupling between the carbonylic carbon of the anomeric acetate and the proton at 6.34 ppm confirmed the assignment of the latter to H-1.

Furthermore, unexpected additional compounds (indicated as compounds **8**, **9**, and **11**) were obtained, as shown in Table 1 (entries 3 and 7, and Scheme 2). NMR spectra of these products presented the signals of both the thioaldose and the benzylidene-protected precursor. Interestingly, in all cases, the H-1 appeared as deshielded singlets, consistent with the presence of the 1-*O*-acetyl group, and two protected signals appeared in the range of 2.70−2.00 ppm, suggesting the presence of a methylene, which meant an unfunctionalized carbon. Shielding of the C-3 signal to ∼40 ppm was also diagnostic for the presence of a methylene. Further studies to confirm the structures of **8**, **9**, and **11** were carried out as described below.

Synthesis and Structural Elucidation of (1→2) Thiodisaccharides 8, 9, and 11. As mentioned in the Introduction section, vinyl azides have been reported as versatile intermediates for the synthesis of organic compounds. It was recently reported that, by reacting with an electrophilic halonium, an iminodiazonium cation is formed, which suffer from the attack of an alcohol as a nucleophile, to give addition products, namely α-alkoxy-β-haloalkyl azides.[40] This report was encouraging to consider that **8**, **9**, and **11** were the addition products of thioaldoses **4** or **5** to the olefin present in **7** formed through a similar mechanism. If that were the case, vinyl azide **7** could be an unexpected useful precursor for the synthesis of (1→2) thiodisaccharides of unreported structures. To confirm this hypothesis, it was necessary to carry out the reaction starting from vinyl azide **7**.

Thus, **7** was prepared in 83% yield by treatment of **3** with Et_3N in DMF for 18 h at room temperature. Then, compound **7** was treated with **4** and Et_3N in DMF at −10 °C for 2 h. Then, we were pleased to verify that the same mixture of products **8** and **9** were obtained in 50 and 8% yield, respectively (Scheme 3). Compounds **8** and **9** could be successfully isolated by careful column chromatography using silica gel (particle size of <45 μm, for thin layer chromatography) as a stationary phase and mixtures of EtOAc/hexane.

Spectroscopic analysis by NMR confirmed the proposed structures of **8** and **9**, as stereoisomers differing in the stereochemistry of C-2. As stated above, the signals in the ^{1}H NMR corresponding to the anomeric protons appeared as singlets, and the protons corresponding to H-3ax and H-3eq, as multiplets at 2.70−2.00 ppm. Chemical shifts of H-3ax and

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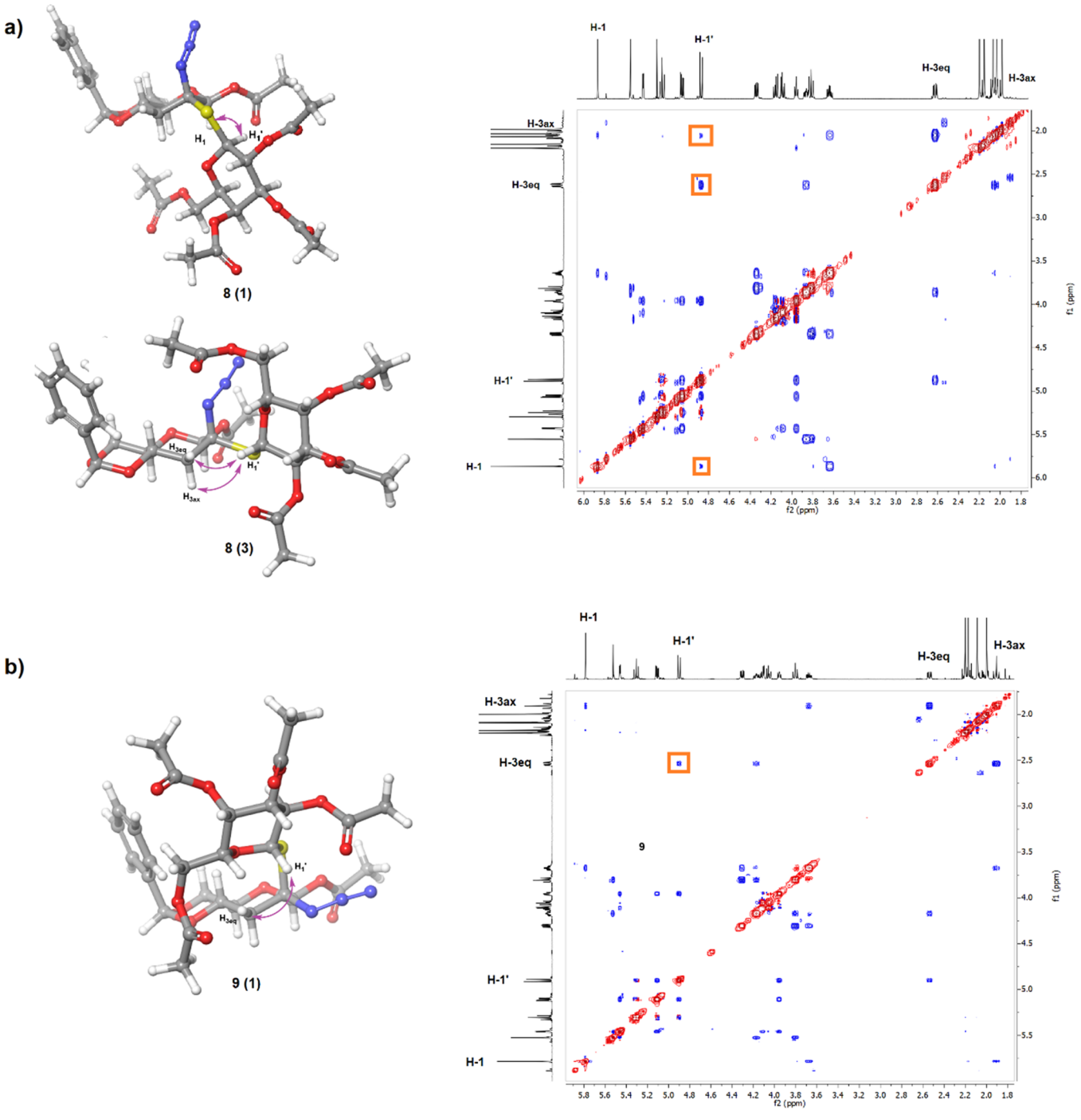

Figure 2. Three-dimensional models of (a) **8** and (b) **9** representing low-energy conformers obtained by MCMM/LMOD (MacroModel) and NOESY experiments (mixing time: 0.9 s, T = 298.2 K). Diagnostic NOE contacts are labeled.

H-4 were the main differences between the ^{1}H NMR spectra of **8** and **9**. Also, the low-intensity carbon signal appearing at 72–74 ppm in the ^{13}C spectrum was assigned to C-2, a quaternary carbon, as it did not correlate with any proton in the 2D ^{1}H-^{13}C-HSQC spectrum. The challenging step was to determine the stereochemistry at C-2. This was unambiguously achieved by 2D ^{1}H-NOESY NMR experiments as follows.

In the case of **8**, the 2D ^{1}H-NOESY spectrum revealed the following inter-residue NOE contacts: H-3ax/H-1′, H-3eq/H-1′, and H-1/H-1′. For **9**, in turn, only H-3eq/H-1′ inter-residue NOE contact was observed. This confirmed the equatorial disposition of the thiogalactosyl residue in **8**, which allows the proximity of H-1 and H-1′, in contrast to **9**, where the thiogalactosyl residue is axially disposed (Figure 2). Thus, the absolute configuration of C-2 was *R* in the case of **8** and *S* in the case of **9**.

Molecular modeling of both structures confirmed this fact. Conformational analysis of compounds **8** and **9** was performed with MacroModel (Schrödinger Suites) applying a procedure that includes a final step of mixed Monte Carlo Multiple Minimum/Low-mode sampling (MCMM/LMOD). Conformers **8(1)**, **8(3)**, and **9(1)** are shown in Figure 2 (see also Figure S1 and Table S1). H-1/H-1′ interprotonic distance measured in conformer **8(1)** was 2.3 Å, while H-3ax/H-1′ and H-3eq/H-

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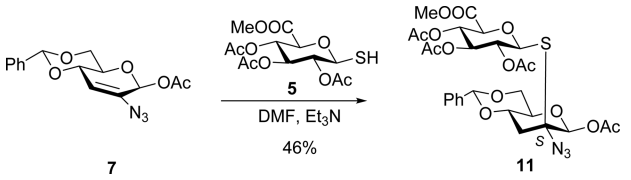
1′ distances determined in conformer **8**(**3**) were 3.1 and 2.2 Å, respectively. Conversely, the only NOE contact observed for **9** (H-3eq/H-1′) was consistent with the distance determined in conformer **9**(**1**) of 2.6 Å.

The addition product of **5** to the vinyl azide **7** under the same conditions described for **8** and **9** was thiodisaccharide **11** (Scheme 4), which was obtained in 46% yield. The axial

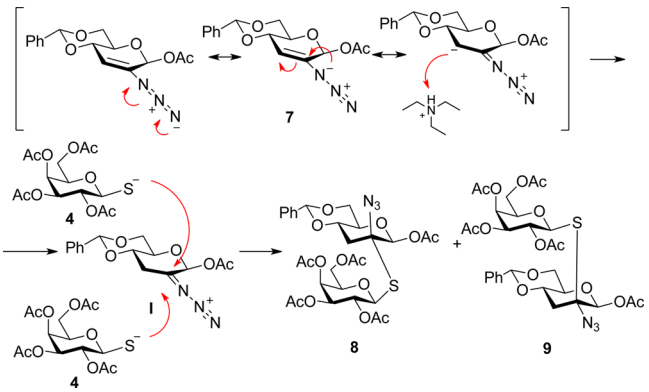
Scheme 4. Synthesis of (1→2) Thiodisaccharide 11 from Vinylazide 7



disposition of the *S*-GlcA residue, and thus, the *S* configuration for C-2 was determined by 2D ^{1}H-NOESY as described for **9**, given that the only inter-residue NOE contact observed was that corresponding to H-3eq/H-1′ (Figure S1 and Table S1). Conformational analysis of compound **11** confirmed this: for the most stable conformer **11**(**1**), the H-3eq/H-1′ distance was 2.7 Å.

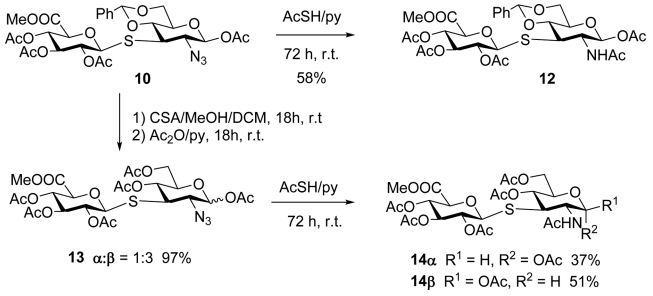
To explain the formation of **8**, **9**, and **11**, a mechanism involving an initial reaction of the vinyl azide **7** with the electrophile H^+ to give the iminodiazonium cation **I** is proposed. The second step is the nucleophilic attack of the thioaldose (Scheme 5).[40] The selectivity observed in each case probably results from electronic and steric factors and has not been thoroughly investigated yet.

Scheme 5. Proposed Mechanism for the Synthesis of (1→2) Thiodisaccharides 8 and 9



Modification of the (1→3) Thiodisaccharides 6 and 10. At this moment, it became interesting to have alternative derivatives that could be used as building blocks for the synthesis of more complex glycomimetics, given that thiodisaccharides **6** and **10** might be considered as starting materials in glycosylation reactions. Thus, our particular interest in glycosaminoglycan mimetics led us to first modify compound **10** by two different approaches. On the one hand, the installation of the −NHAc group in the 2-position was evaluated by treatment of **10** with AcSH in pyridine[48,49] at room temperature for 72 h, giving compound **12** in 58% yield (Scheme 6).

Scheme 6. Transformation of 10 in the Thiodisaccharides 12, 13α,β, and 14α,β



On the other hand, treatment of **10** with CSA in DCM/MeOH at room temperature required 18 h to be completed. Further acetylation under standard conditions led to compound **13** in almost quantitatively yield (97%), though as a mixture of anomers, probably due to the extended treatment in acidic conditions (Scheme 6). Finally, successful reductive acylation of the azide group was achieved by treatment of **13α,β** with AcSH/py for 72 h at room temperature, and thus, **14** was obtained as an α/β (0.7:1.0) mixture of anomers in 88% global yield. The anomers were successfully resolved by column chromatography, as described in the Experimental Section.

Similarly, compound **15α,β** was obtained in 72% yield by treatment of **6** with CSA in DCM/MeOH at room temperature for 18 h followed by acetylation (Scheme 7). Further reduction of the azide group with AcSH/py led to **16α,β** in a 68% combined yield as an α/β (1:2) mixture of anomers. Again, resolution of the anomers was successfully achieved by column chromatography.

CONCLUSIONS

It is well known that *N*-acetyl-D-glucosamine is a relevant sugar because of its presence in numerous glycoconjugates, such as *N*- and *O*-linked glycans in glycoproteins, and also as a main component of glycosaminoglycans.[50] Thus, its incorporation in glycomimetic oligosaccharides may lead to useful derivatives for the study of biological processes associated to such glycoconjugates.

As a common procedure in carbohydrate synthetic chemistry, the challenges posed by the presence of the −NHAc group can be overcome by incorporating an azide group at C-2 of the selected sugar precursor,[51,52] given that this azide substituent can be efficiently reduced at the final stages of a glycan synthesis. That is why, this approach was adopted.

Thus, in this report, we successfully obtained (1→3) thiodisaccharides having a GlcNAc residue. The key precursor was a 3-*O*-triflate prepared from a 2-azido derivative having the *allo* configuration. It should be noted that an alternative method to construct the thioglycosidic bond involving a 3-thioGlcN$_3$ precursor and a suitable glycosyl donor (Figure 1, path c) would unnecessarily lengthen the synthetic sequence. Moreover, the low reactivity of GlcA-derived glycosyl donors due to the presence of the carboxylic group at C-5 would have posed extra difficulties.[53]

The azido-thiodisaccharides obtained (**6** and **10**) can be considered useful glycosyl donors for the synthesis of more complex glycomimetics by classic glycosylation methods as they still have the azide group at C-2. Hydrolysis of the 4,6-*O*-benzylidene protecting group present in **6** and **10** caused

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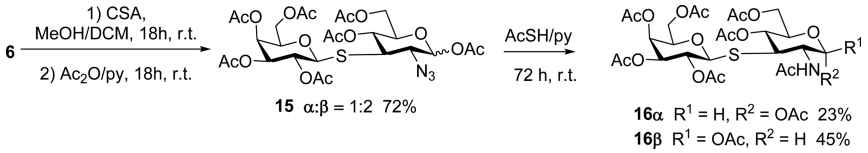
Scheme 7. Transformation of 6 in the Thiodisaccharides 15α,β and 16α,β



anomerization. In situ, further peracetylation led efficiently to **15α,β** and **13α,β**, respectively. These anomeric mixtures constitute alternative building blocks for further conjugation, taking into account that the absence of the benzylidene group makes them also compatible with thioglycosylation methods involving strong Lewis acids, such as $BF_3{\cdot}OEt_2$.[54] Moreover, reduction of the azide present in the thiodisaccharides obtained could be effectively achieved by the classical reported procedure using AcSH/pyridine.[48,49]

A relevant finding associated to the S_N2 reaction explored in this work was that vinyl azide **7** was formed by an elimination reaction of triflate **3**. The addition reaction of thioaldoses **4** and **5** to **7** serendipitously gave rise to a new class of 2,3-dideoxy-2-azido-(1→2) thiodisaccharides, having a thioaminal-type linkage at C-2. Compounds **8**, **9**, and **11** were fully characterized, and the stereochemistry of the newly tetrasubstituted stereogenic centers at C-2 was unambiguously determined by a combination of 2D-NOESY methods and molecular modeling calculations.

To the best of our knowledge, the addition reaction of nucleophiles to sugar-derived vinyl azides has not been reported previously. Taking into account that vinyl azides have been extensively used as precursors for the synthesis of heterocycles and, in most cases, the elimination of nitrogen is concomitant with cyclization, the reactivity observed here is remarkable as the azide group remains at C-2. Besides the potentiality of compounds **8**, **9**, and **11** as synthetic building blocks, as stated above for **6** and **10**, the 2-azide group also makes them interesting substrates for a variety of reactions as, for example, the CuAAC reaction. Due to the features of these unexplored structures, further studies on its reactivity, as well as binding experiments with proteins, would be relevant.

Additional studies on both the use of **6**, **10**, **13α,β**, **14α,β**, **15α,β**, and **16α,β** as glycosyl donors in glycosylation and/or thioglycosylation reactions and the use of **8**, **9**, and **11** as recognition elements in the construction of multivalent ligands by click chemistry are on the way. Moreover, given the extraordinary reactivity shown by sugar-derived vinyl azide **7**, its use as a precursor for the construction of modified carbohydrates and glycomimetics is under study.

EXPERIMENTAL SECTION

General Methods. Solvents were distilled before use. Thin layer chromatography (TLC) was performed on silica gel 60 F254 plates (Merck). The compounds were detected with 5% (v/v) sulfuric acid in EtOH containing 0.5% *p*-anisaldehyde. Column chromatography was performed on silica gel 60, particle sizes of 40−63 μm or <45 μm (for thin layer chromatography) from Merck by elution with the solvents indicated in each case. Thioaldoses **4** and **5** were prepared by reported methods.[32,34,55,56] Reactions under microwave irradiation were carried out in an Anton-Paar Monowave 300 instrument with a System Internal IR probe type under low power activation (T = 35 °C, t = 1.5 h). ^{1}H and ^{13}C{^{1}H} nuclear magnetic resonance (NMR) spectra were recorded at 25 °C at 500 and 125.7 MHz, respectively, in a Bruker Avance Neo 500 spectrometer. ^{1}H and ^{13}C chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane or the residual solvent peak ($CHCl_3$: ^{1}H: δ 7.26 ppm, ^{13}C: δ 77.2 ppm). Assignments of ^{1}H, ^{13}C, and stereochemistry were determined by analysis of coupling constants and assisted by 2D ^{1}H COSY, 2D ^{1}H-^{13}C HSQC, 2D ^{1}H-^{13}C HMBC, and 2D ^{1}H NOESY (mixing time: 0.9 s) experiments. High-resolution mass spectra (HRMS) were obtained by electrospray ionization (ESI) and Q-TOF in a Bruker micrOTOF-Q II spectrometer. Optical rotations were determined in a Perkin-Elmer 343 polarimeter at 20 °C in a 1 dm cell. Melting points were measured in a Fisher-Jones apparatus.

1-*O*-Acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (1). The sequence indicated in Scheme S1 was performed as follows. In a round-bottom flask, glucosamine hydrochloride (3 g, 13.9 mmol), imidazole-1-sulfonyl azide hydrogen sulfate (3.96 g, 14.6 mmol), $CuSO_4{\cdot}5H_2O$ (35 mg, 0.139 mmol), and K_2CO_3 (4.8 g, 34.75 mmol) were suspended in MeOH (60 mL) at room temperature. The reaction mixture was stirred for 4 h. Completion of the reaction was determined by TLC using EtOAc/MeOH 9:1 with 1% H_2O as a solvent (R_f = 0.48). The reaction mixture was filtered through a pad of silica gel and concentrated under vacuum.

The crude residue containing the $GlcN_3$ derivative was dissolved in anhydrous DMF (50 mL), and α,α-dimethoxytoluene (4 mL, 27.8 mmol) and CSA (0.71 g, 3.06 mmol) were added. The reaction mixture was stirred for 3 h in a rotary evaporator (50 °C, 100 mbar). After this, the reaction was quenched with Et_3N until pH = 7, and the solvent was evaporated. Column chromatography (9:1 → 3:2 hexane/EtOAc) of the residue gave compound **4,6-*O*-Benzylidene-GlcN$_3$** (3.8 g, 93%), whose spectroscopic properties were in accordance with those reported previously.[45]

To a stirred solution of compound **4,6-*O*-Benzylidene-GlcN$_3$** (1.2 g, 4.1 mmol) in DCM (12.4 mL) and Et_3N (5.1 mL, 36.9 mmol) under a nitrogen atmosphere at 0 °C, acetic anhydride (0.44 mL, 4.51 mmol) was added dropwise. The reaction was gradually warmed to room temperature and stirred for 18 h. After this, MeOH (2.6 mL) was added, and solvents were evaporated under vacuum. The residue was dissolved in EtOAc (25 mL), washed with $NaHCO_3$ (3 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. Column chromatography (9:1 → 4:1 hexane/EtOAc) of the residue gave compound **1** (0.87 g, 63%) as a white solid: R_f = 0.75 (1:1 hexane/EtOAc). The spectroscopic properties were in accordance with those previously reported.[45]

1-*O*-Acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranose (2). To a stirred solution of **1** (400 mg, 1.2 mmol) in anhydrous DCM (4.0 mL) and pyridine (1.6 mL) at 0 °C, Tf_2O (240 μL, 1.4 mmol) was added dropwise. After 2 h, MeOH was added, and the mixture concentrated under vacuum. The residue was dissolved in EtOAc (40 mL) and extracted with HCl (1 × 10 mL), $NaHCO_3$ s.s. (1 × 15 mL), and brine (1 × 15 mL) and then dried over $MgSO_4$ and concentrated under vacuum.

The crude *gluco*-configured triflate was redissolved in HMPA (6.4 mL), and sodium nitrite (890 mg, 12.9 mmol) and 15-crown-5 (265 μL, 1.3 mmol) were added. The reaction mixture was stirred for 3 h and then diluted with EtOAc (40 mL), washed with water (4 × 20 mL), dried ($MgSO_4$), and concentrated under vacuum. Column chromatography (9:1 → 4:1 hexane/EtOAc) of the residue gave compound **2** (294 mg, 73%) as a white solid, mp 94−95 °C (from H_2O): R_f = 0.48 (7:3 hexane/EtOAc); $[\alpha]_D^{20}$ − 18.3 (c 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.47 (m, 2 H, H-aromatic), 7.39−7.37 (m, 3 H, H-aromatic), 6.08 (d, 1 H, $J_{1,2}$ = 8.6 Hz, H-1), 5.58 (s, 1 H, PhC*H*O), 4.45 (dd, 1H, $J_{2,3}$ = 2.8, $J_{3,4}$ = 2.4 Hz, H-3), 4.41 (dd, 1 H, $J_{5,6eq}$ = 5.1, $J_{6eq,6ax}$ = 10.5 Hz, H-6eq), 4.19 (ddd, 1 H,

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$J_{5,6eq}$ = 5.1, $J_{4,5}$ = 9.5, $J_{5,6ax}$ = 10.5, H-5), 3.74 (t, 1 H, $J_{6eq,6ax} \cong J_{5,6ax}$ = 10.5 Hz, H-6ax), 3.62 (dd, 1 H, $J_{3,4}$ = 2.4, $J_{4,5}$ = 9.5 Hz, H-4), 3.53 (dd, 1 H, $J_{2,3}$ = 2.8, $J_{1,2}$ = 8.6 Hz, H-2), 2.19, (s, 3 H, CH_3CO); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 168.9 (CO), 136.8, 129.6, 128.5, 126.3 (C-aromatic), 102.2 (PhCHO), 91.7 (C-1), 78.2 (C-4), 68.8, 68.6 (C-6, C-3), 64.1 (C-5), 61.9 (C-2), 21.1 (CH_3CO). ESI-HRMS: $[M + Na]^+$ calcd for $C_{15}H_{17}N_3NaO_6$: 358.1010, found: 358.1002.

1-*O*-Acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-trifluoromethansulfonyl-β-D-allopyranose (3). To a solution of compound **2** (200 mg, 0.6 mmol) in anhydrous DCM (6 mL) and pyridine (170 μL, 2.2 mmol) in an Anton-Paar microwave capped vessel was added dropwise trifluoromethansulfonic anhydride (160 μL, 1.0 mmol) at 0 °C. The ice bath was removed, and the reaction flask was gradually warmed up to room temperature. Low-power activation was performed under microwave irradiation for 1.5 h at 35 °C. Column chromatography (9:1 → 4:1 hexane/EtOAc) of the residue gave compound **3** (228 mg, 82%) as a white solid, mp 112 °C (d) (from EtOH/H_2O): R_f = 0.50 (7:3 hexane/EtOAc); $[\alpha]_D^{20}$ − 18.5 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.36 (m, 5 H, H-aromatic), 5.92 (d, 1 H, $J_{1,2}$ = 8.4 Hz, H-1), 5.57 (s, 1 H, PhC*H*O), 5.40 (t, 1 H, $J_{2,3} \cong J_{3,4}$ = 2.6 Hz, H-3), 4.42 (dd, 1 H, $J_{5,6eq}$ = 5.1, $J_{6ax,6eq}$ = 10.6 Hz, H-6eq), 4.07 (ddd, 1 H, $J_{5,6eq}$ = 5.1, $J_{4,5}$ = 9.5, $J_{5,6ax}$ = 10.3 Hz, H-5), 3.85 (dd, 1 H, $J_{2,3}$ = 2.6, $J_{1,2}$ = 8.4 Hz, H-2), 3.77 (dd, 1 H, $J_{3,4}$ = 2.6, $J_{4,5}$ = 9.5 Hz, H-4), 3.75 (dd, 1 H, $J_{5,6ax}$ = 10.3, $J_{6ax,6eq}$ = 10.6 Hz, H-6ax), 2.20 (s, 3 H, CH_3CO); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 168.4 (CO), 136.1, 129.7, 128.6, 126.4 (C-aromatic), 118.5 (q, 1 C, J_{C-F} = 319 Hz, CF_3), 102.7 (PhCHO), 91.8 (C-1), 81.9 (C-3), 75.5 (C-4), 68.6 (C-6), 64.7 (C-5), 60.1 (C-2), 21.0 (CH_3CO). ESI-HRMS: $[M + H]^+$ calcd for $C_{16}H_{17}F_3N_3O_8S$: 468.0683, found: 468.0698.

General Conditions for the Synthesis of the (1→3) Thiodisaccharides. The synthesis of triflate **3** was performed as described above starting from **2**. As compounds **2** and **3** showed the same mobility by TLC (R_f = 0.50, 7:3 hexane/EtOAc), consumption of the starting material **2** was checked by NMR by observing the total disappearance of the signal corresponding to H-3 (4.45 ppm) and the presence of the one corresponding to **3** (5.39 ppm). The solution was then transferred to a round-bottom flask, and solvents were evaporated under vacuum. This led to the *allo*-configured crude triflate **3**, which was used subsequently without any purification. To a solution of the latter in dry DMF and HMPA (in the proportion indicated in each case, see below and Table 1) were added sequentially the thioaldose (**4** or **5**) and Et_3N, and the reaction was stirred for 2 h. The mixture was diluted with EtOAc (10 mL), washed with 5% LiCl (3 × 2 mL), dried ($MgSO_4$), and concentrated. The residues were purified by column chromatography as described in each case. Variable amounts of the other products indicated in Table 1 were recovered. Characterization of **7** is described below, when obtained by elimination reaction of **3**. Characterizations of **8**, **9**, and **11** are described below, when obtained from **7**.

*1-O-Acetyl-2-azido-3-S-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-4,6-O-benzylidene-2,3-dideoxy-3-thio-β-D-glucopyranose (**6**).* Compound **6** was prepared from crude triflate **3** obtained from **2** (100 mg, 0.30 mmol) and **4** (120 mg, 0.33 mmol) in anh. DMF (1.5 mL) at −10 °C using Et_3N (0.36 mmol, 50 μL) as described above. Column chromatography (9:1 → 7:3 hexane/EtOAc) first gave the mixture of compounds **8** and **9** (112 mg, 55%), which were characterized afterward, when obtained by the reaction between **7** and **4** (see below). Further elution of the column gave compound **6** (82 mg, 40%) as a white solid, mp 198−199 °C (from hexane/EtOAc): R_f = 0.37 (3:2 hexane/EtOAc); $[\alpha]_D^{20}$ − 17.9 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.46 (m, 2 H, H-aromatic), 7.36−7.35 (m, 3 H, H-aromatic), 5.56 (d, 1 H, $J_{1,2}$ = 8.3 Hz, H-1), 5.55 (s, 1 H, PhC*H*O), 5.39 (d, 1 H, $J_{3',4'}$ = 2.9 Hz, H-4′), 5.20 (t, 1 H, $J_{1',2'} \cong J_{2',3'}$ = 10.0 Hz, H-2′), 5.05 (dd, 1 H, $J_{2',3'}$ = 10.0, $J_{3',4'}$ = 3.4 Hz, H-3′), 4.83 (d, 1 H, $J_{1',2'}$ = 10.0 Hz, H-1′), 4.36 (dd, 1 H, $J_{6ax,6eq}$ = 10.5, $J_{5,6eq}$ = 4.6 Hz, H-6eq), 4.09 (dd, 1 H, $J_{6'a,6'b}$ = 11.3, $J_{5',6'a}$ = 6.2 Hz, H-6′a), 3.94 (dd, 1 H, $J_{6'a,6'b}$ = 11.3, $J_{5',6'b}$ = 6.9 Hz, H-6′b), 3.82 (dd, 1 H, $J_{5',6'a}$ = 6.2, $J_{5',6'b}$ = 6.9 Hz, H-5′), 3.74 (t, 1 H, $J_{6ax,6eq} \cong J_{5,6ax}$ = 10.5 Hz, H-6ax), 3.62−3.55 (m, 3 H, H-2, H-4, H-5), 2.97 (t, 1 H, $J_{2,3} \cong J_{3,4}$ = 10.8 Hz, H-3), 2.18, 2.14, 2.04, 1.97, 1.93 (5 s, 15 H, 5 × CH_3CO); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 170.4 (× 2), 170.2, 169.7, 168.7 (CO), 136.7, 129.5, 128.5, 126.2 (C-aromatic), 102.2 (PhCHO), 94.7 (C-1), 83.4 (C-1′), 77.5 (C-4), 74.6 (C-5′), 71.8 (C-3′), 70.3 (C-5), 68.4 (C-6), 67.9 (C-2′), 67.2 (C-4′), 65.2 (C-2), 61.8 (C-6′), 50.0 (C-3), 21.0, 20.8 (× 2), 20.7 (× 2) (CH_3CO). ESI-HRMS: $[M + Na]^+$ calcd for $C_{29}H_{35}N_3NaO_{14}S$: 704.1732, found: 704.1723, $[M + K]^+$ calcd for $C_{29}H_{35}KN_3O_{14}S$: 720.1471, found: 720.1485.

*1-O-Acetyl-2-azido-4,6-O-benzylidene-2,3-dideoxy-3-S-(methyl 2,3,4-tri-O-acetyl-β-D-glucopyranosyluronate)-3-thio-β-D-glucopyranose (**10**).* Compound **10** was obtained from crude triflate **3** obtained from **2** (250 mg, 0.75 mmol) and **5** (315 mg, 0.90 mmol) in a mixture of anh. DMF (4 mL) and HMPA (0.6 mL) using Et_3N (1.8 mmol, 250 μL) as described above. Column chromatography (9:1 → 3:2 hexane/EtOAc) first gave compound **7** (122 mg) and then thiodisaccharide **10** (226 mg, 45%) as a white solid, mp 175−176 °C (from hexane/EtOAc): R_f = 0.45 (1:1 hexane/EtOAc); $[\alpha]_D^{20}$ − 31.1 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.45 (m, 2 H, H-aromatic), 7.37−7.35 (m, 3 H, H-aromatic), 5.75 (d, 1 H, $J_{1,2}$ = 8.2 Hz, H-1), 5.54 (s, 1 H, PhC*H*O), 5.24 (t, 1 H, $J_{3',4'} \cong J_{4',5'}$ = 9.5 Hz, H-4′), 5.17 (dd, 1 H, $J_{2',3'}$ = 8.9, $J_{3',4'}$ = 9.5 Hz, H-3′), 5.00 (dd, 1 H, $J_{2',3'}$ = 8.9, $J_{1',2'}$ = 10.2, Hz, H-2′), 4.91 (d, 1 H, $J_{1',2'}$ = 10.2 Hz, H-1′), 4.35 (dd, 1 H, $J_{5,6eq}$ = 4.5, $J_{6ax,6eq}$ = 10.6 Hz, H-6eq), 3.88 (d, 1 H, $J_{4',5'}$ = 9.5 Hz, H-5′), 3.74 (dd, $J_{5,6ax}$ = 9.0, $J_{6ax,6eq}$ = 10.5 Hz, H-6ax), 3.70 (s, 3 H, CH_3O), 3.63−3.53 (m, 3 H, H-2, H-4, H-5), 3.02 (t, $J_{2,3} \cong J_{3,4}$ = 10.7 Hz, H-3), 2.19, 2.01, 2.00, 1.95 (4 s, 12 H, 4 × CH_3CO); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 170.2, 169.5, 169.4, 168.7, 166.7 (CO), 136.7, 129.4, 128.5, 126.2 (C-aromatic), 102.1 (PhCHO), 94.6 (C-1), 83.1 (C-1′), 78.2 (C-4), 76.1 (C-5′), 73.0 (C-4′), 70.8 (C-2′), 70.3 (C-5), 69.1 (C-3′), 68.4 (C-6), 65.0 (C-2), 53.0 (OCH_3), 49.5 (C-3), 21.0, 20.7 (× 2), 20.6 (CH_3CO). ESI-HRMS: $[M + Na]^+$ calcd for $C_{28}H_{33}N_3NaO_{14}S$: 690.1575, found: 690.1582, $[M + H]^+$ calcd for $C_{28}H_{34}N_3O_{14}S$: 668.1756, found: 668.1757.

1-*O*-Acetyl-2-azido-4,6-*O*-benzylidene-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranose (7). To a solution of compound **3** (80 mg, 0.17 mmol) in anh. DMF (2 mL) at room temperature, Et_3N was added (0.36 mmol, 50 μL), and the reaction mixture was stirred for 18 h. After this, solvents were evaporated under vacuum. Column chromatography of the residue (hexane → 4:1 hexane/EtOAc) gave compound **7** (45 mg, 83%) as an amorphous solid, R_f = 0.40 (4:1 hexane/EtOAc); $[\alpha]_D^{20}$ − 51.8 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.37 (m, 5 H, H-aromatic), 6.34 (dd, 1 H, $J_{1,3}$ = 0.7, $J_{1,4}$ = 2.1 Hz, H-1), 5.87 (brs, 1 H, H-3), 5.62 (s, 1 H, PhC*H*O), 4.45 (dt, 1 H, $J_{1,4} \cong J_{3,4}$ = 2.1, $J_{4,5}$ = 8.3 Hz, H-4), 4.34 (dd, 1 H, $J_{5,6eq}$ = 4.2, $J_{6eq,6ax}$ = 10.2 Hz, H-6eq), 3.89 (t, $J_{5,6ax} \cong J_{ax,eq}$ = 10.2 Hz, H-6ax), 3.80 (ddd, 1 H, $J_{5,6eq}$ = 4.2, $J_{4,5}$ = 8.3, $J_{5,6ax}$ = 10.2 Hz, H-5), 2.17 (s, 3 H, CH_3CO); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 169.3 (CO), 136.9 (C-aromatic), 135.6 (C-2), 129.5, 128.5, 126.3 (C-aromatic), 115.7 (C-3), 102.1 (PhCHO), 89.4 (C-1), 74.1 (C-4), 71.2 (C-5), 68.7 (C-6), 21.0 (CH_3CO). ESI-HRMS: $[M + Na]^+$ calcd for $C_{15}H_{15}N_3NaO_5$: 340.0904, found: 340.0907.

General Procedure for the Synthesis of the 2-*C*-Azido-(1→2) Thiodisaccharides. Compound **7** was dissolved in anh. DMF, the solution was cooled to −10 °C, and the thioaldose (**4** or **5**) and Et_3N were added. The reaction mixture was stirred for 2 h and then diluted with EtOAc and washed twice with 5% LiCl. Column chromatography of the residue in silica gel (particle size of <45 μm, for thin layer chromatography) gave the desired products as described below.

*1-O-Acetyl-2-C-azido-2-S-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-4,6-O-benzylidene-2,3-dideoxy-2-thio-β-D-ribohexopyranose (**8**) and 1-O-Acetyl-2-C-azido-2-S-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-4,6-O-benzylidene-2,3-dideoxy-2-thio-β-D-arabinohexopyranose (**9**).* Compounds **8** and **9** were obtained by reaction of **7** (62 mg, 0.19 mmol) and **4** (90 mg, 0.24 mmol) in the presence of Et_3N (100 μL) in anh. DMF (1.30 mL). Column chromatography of the residue using silica gel (particle size of <45 μm, for thin layer chromatography) and hexane/EtOAc mixtures (9:1

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→ 3:1) first gave **9** (11 mg, 8%) and then **8** (67 mg, 50%) as white solids.

8: mp 105−106 °C (from hexane/EtOAc), R_f = 0.44 (3:2 hexane/EtOAc); $[\alpha]_D^{20}$ + 33.7 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.44 (m, 2 H, H-aromatic), 7.38−7.36 (m, 3 H, H-aromatic), 5.87 (s, 1 H, H-1), 5.55 (s, 1 H, PhC*H*O), 5.43 (dd, 1 H, $J_{4',5'}$ = 1.2, $J_{3',4'}$ = 3.4 Hz, H-4′), 5.25 (t, 1 H, $J_{1',2'} \cong J_{2',3'}$ = 10.1 Hz, H-2′), 5.06 (dd, 1 H, $J_{3',4'}$ = 3.4, $J_{2',3'}$ = 10.1 Hz, H-3′), 4.87 (d, 1 H, $J_{1',2'}$ = 10.1 Hz, H-1′), 4.35 (dd, 1 H, $J_{5,6eq}$ = 4.9, $J_{6ax,6eq}$ = 10.5 Hz, H-6eq), 4.16 (dd, 1 H, $J_{5',6'a}$ = 7.0, $J_{6'a,6'b}$ = 11.5 Hz, H-6′a), 4.09 (dd, 1 H, $J_{5',6'b}$ = 6.0, $J_{6'a,6'b}$ = 11.5 Hz, H-6′b), 3.96 (ddd, 1 H, $J_{4',5'}$ = 1.2, $J_{5',6'b}$ = 6.0, $J_{5',6'a}$ = 7.0 Hz, H-5′), 3.86 (ddd, 1 H, $J_{3eq,4}$ = 4.2, $J_{4,5}$ = 9.2, $J_{3ax,4}$ = 11.3 Hz, H-4), 3.82 (t, 1 H, $J_{5,6ax} \cong J_{6ax,6eq}$ = 10.5 Hz, H-6ax), 3.64 (ddd, 1 H, $J_{5,6eq}$ = 4.9, $J_{4,5}$ = 9.2, $J_{4,6ax}$ = 10.5 Hz, H-5), 2.62 (dd, 1 H, $J_{3eq,4}$ = 4.2, $J_{3ax,3eq}$ = 13.0 Hz, H-3eq), 2.20, 2.15, (2 s, 6 H, 2 × CH_3CO), 2.09−1.98 (m, 10 H, H-3ax + 3 × CH_3CO); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 170.6, 170.3, 170.1, 169.5, 168.2 (*C*O), 136.9, 129.5, 128.5, 126.2 (C-aromatic), 102.2 (PhCHO), 95.9 (C-1), 81.2 (C-1′), 74.8 (C-5′), 73.6 (C-4), 72.1 (C-2), 72.0 (C-3′), 71.9 (C-5), 68.5 (C-6), 67.2 (C-4′), 67.0 (C-3′), 61.7 (C-6′), 40.0 (C-3), 21.0, 20.8 (× 2), 20.7 (× 2) (*C*H_3CO). ESI-HRMS: $[M + Na]^+$ calcd for $C_{29}H_{35}N_3NaO_{14}S$: 704.1732, found: 704.1715, $[M + NH_4]^+$ calcd for $C_{29}H_{36}N_4O_{14}S$: 699.2178, found: 699.2151.

9: mp 184−185 °C (from hexane/EtOAc), R_f = 0.49 (3:2 hexane-EtOAc); $[\alpha]_D^{20}$ − 39.4 (*c* 0.9, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.40 (m, 2 H, H-aromatic), 7.38−7.32 (m, 3 H, H-aromatic), 5.78 (s, 1 H, H-1), 5.52 (s, 1 H, PhC*H*O), 5.46 (dd, 1 H, $J_{4',5'}$ = 1.1, $J_{3',4'}$ = 3.5 Hz, H-4′), 5.31 (t, 1 H, $J_{1',2'} \cong J_{2',3'}$ = 10.1 Hz, H-2′), 5.11 (dd, 1 H, $J_{3',4'}$ = 3.4, $J_{2',3'}$ = 10.1 Hz, H-3′), 4.90 (d, 1 H, $J_{1',2'}$ = 10.1 Hz, H-1′), 4.31 (dd, 1 H, $J_{5,6eq}$ = 4.8, $J_{6ax,6eq}$ = 10.3 Hz, H-6eq), 4.16 (ddd, 1 H, $J_{3eq,4}$ = 4.1, $J_{4,5}$ = 9.3, $J_{3ax,4}$ = 11.4 Hz, H-4), 4.11 (dd, 1 H, $J_{5',6'b}$ = 5.1, $J_{6'a,6'b}$ = 11.5 Hz, H-6′b), 4.05 (dd, 1 H, $J_{5',6'b}$ = 7.3, $J_{6'a,6'b}$ = 11.5 Hz, H-6′a), 3.95 (ddd, 1 H, $J_{4',5'}$ = 1.1, $J_{5',6'b}$ = 5.1, $J_{5',6'a}$ = 7.3 Hz, H-5′), 3.81 (t, 1 H, $J_{6ax,6eq} \cong J_{5,6ax}$ = 10.3 Hz, H-6ax), 3.68 (ddd, 1 H, $J_{5,6eq}$ = 4.8, $J_{5,6ax}$ = 9.8, $J_{4,5}$ = 9.3, Hz, H-5), 2.54 (dd, 1 H, $J_{3eq,4}$ = 4.1, $J_{3ax,3eq}$ = 13.2 Hz, H-3eq), 2.20, 2.17, 2.09, 2.00 (4 s, 12 H, 4 × CH_3CO), 1.91 (dd, 1 H, $J_{3ax,4}$ = 11.4, $J_{3ax,3eq}$ = 13.2 Hz, H-3ax), 1.69 (s, 3 H, CH_3CO); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 170.7, 170.3, 170.1, 169.8, 168.4 (*C*O), 137.1, 129.5, 128.5, 126.3 (C-aromatic), 102.5 (PhCHO), 96.6 (C-1), 82.1 (C-1′), 75.2 (C-5′), 74.1 (C-4), 74.0 (C-2), 72.7 (C-5), 72.0 (C-3′), 68.5 (C-6), 67.5 (C-4′), 66.8 (C-3′), 62.2 (C-6′), 39.8 (C-3), 21.1, 20.9 (× 2), 20.7, 20.4 (*C*H_3CO). ESI-HRMS: $[M + H]^+$ calcd for $C_{29}H_{36}N_3O_{14}S$: 682.1913, found: 682.1905.

*1-O-Acetyl-2-C-azido-2-S-(methyl 2,3,4-tri-O-acetyl-β-D-glucopyranosyluronate)-4,6-O-benzylidene-2,3-dideoxy-2-thio-β-D-arabinohexopyranose (**11**).* Compound **11** was obtained by reaction of **7** (100 mg, 0.32 mmol) and **5** (130 mg, 0.37 mmol) in the presence of Et_3N (130 μL) in anh. DMF (2 mL). Column chromatography of the residue using silica gel (particle size of <45 μm, for thin layer chromatography) and hexane/EtOAc mixtures (9:1 → 7:3) gave **11** (96 mg, 46%) as a white solid, mp 197−198 °C (from hexane/EtOAc), R_f = 0.55 (1:1 hexane/EtOAc); $[\alpha]_D^{20}$ − 9.8 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.43 (m, 2 H, H-aromatic), 7.39−7.35 (m, 3 H, H-aromatic), 5.85 (s, 1 H, H-1), 5.55 (s, 1 H, PhC*H*O), 5.27 (dd, 1 H, $J_{2',3'}$ = 8.6, $J_{3',4'}$ = 9.5 Hz, H-3′), 5.22 (t, 1 H, $J_{3',4'} \cong J_{4',5'}$ = 9.5 Hz, H-4′), 5.04 (dd, 1 H, $J_{2',3'}$ = 8.6, $J_{1',2'}$ = 10.3 Hz, H-2′), 4.96 (d, 1 H, $J_{1',2'}$ = 10.3 Hz, H-1′), 4.33 (dd, 1 H, $J_{5,6eq}$ = 4.9, $J_{6ax,6eq}$ = 10.5 Hz, H-6eq), 4.02 (d, $J_{4',5'}$ = 9.5 Hz, H-5′), 3.86 (ddd, 1 H, $J_{3eq,4}$ = 4.2, $J_{4,5}$ = 9.2, $J_{3ax,4}$ = 11.4 Hz, H-4), 3.80 (t, 1 H, $J_{5,6ax} \cong J_{6ax,6eq}$ = 10.5 Hz, H-6ax), 3.75 (s, 3 H, OCH_3), 3.62 (ddd, 1 H, $J_{5,6aq}$ = 4.9, $J_{4,5}$ = 9.2, $J_{5,6ax}$ = 10.5 Hz, H-5), 2.59 (dd, 1 H, $J_{3eq,4}$ = 4.2, $J_{3ax,3eq}$ = 13.1 Hz, H-3eq), 2.16 (s, 3 H, CH_3CO), 2.07−2.01 (m, 13 H, H-3ax + 3 × CH_3CO); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 170.1, 169.4, 169.3, 168.1, 166.5 (*C*O), 136.9, 129.5, 128.5, 126.2 (C-aromatic), 102.2 (PhCHO), 96.1 (C-1), 80.9 (C-1′), 76.3 (C-5′), 73.5 (C-4), 73.1 (C-3′), 72.0 (C-2), 71.9 (C-5), 69.6 (C-2′), 69.1 (C-4′), 68.5 (C-6), 53.2 (OCH_3), 39.6 (C-3), 20.9, 20.8, 20.7, 20.6 (*C*H_3CO). ESI-HRMS: $[M + Na]^+$ calcd for $C_{28}H_{33}N_3NaO_{14}S$: 690.1575, found: 690.1567.

1-*O*-Acetyl-2-acetamido-4,6-*O*-benzylidene-2,3-dideoxy-3-*S*-(methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)-3-thio-β-D-glucopyranose (12). To a stirred solution of compound **10** (100 mg, 0.15 mmol) in pyridine (3.2 mL), thioacetic acid was added (215 μL, 3 mmol) under an argon atmosphere. The mixture was stirred at room temperature for 72 h. After this, the mixture was concentrated under vacuum. Then, it was redissolved in EtOAc (20 mL), extracted with 1 M HCl (1 × 5 mL), sat. $NaHCO_3$ (1 × 10 mL), and brine (1 × 10 mL), dried ($MgSO_4$), and concentrated. Column chromatography (3:1 → 1:3 hexane/EtOAc) of the residue gave compound **12** as a white solid (60 mg, 58%), mp 188−189 °C (from EtOH): R_f = 0.46 (EtOAc); $[\alpha]_D^{20}$ − 50.5 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.45 (m, 2 H, H-aromatic), 7.35−7.34 (m, 3 H, H-aromatic), 6.28 (d, 1 H, $J_{NH,2}$ = 7.4 Hz, N*H*), 6.05 (d, 1 H, $J_{1,2}$ = 7.9 Hz, H-1), 5.52 (s, 1 H, PhC*H*O), 5.30 (t, 1 H, $J_{2',3'} \cong J_{3',4'}$ = 9.3 Hz, H-3′), 5.12 (dd, 1 H, $J_{3',4'}$ = 9.3, $J_{4',5'}$ = 10.0 Hz, H-4′), 4.90 (d, 1 H, $J_{1',2'}$ = 10.1 Hz, H-1′), 4.77 (dd, 1 H, $J_{2',3'}$ = 9.3, $J_{1',2'}$ = 10.1 Hz, H-2′), 4.36 (dd, 1 H, $J_{5,6eq}$ = 3.5, $J_{6eq,6ax}$ = 9.1, Hz, H-6eq), 3.97 (d, 1 H, $J_{4',5'}$ = 10.0 Hz, H-5′), 3.76−3.59 (m, 7 H, H-2 + H-3 + H-5 + H-6ax, OCH_3), 3.49 (t, $J_{3,4} \cong J_{4,5}$ = 9.3 Hz, H-4), 2.10, 2.02, 1.97, 1.96, 1.74 (5 s, 15 H, 5 × CH_3CO); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 171.0, 170.1, 169.6, 169.4, 169.2, 167.5 (*C*O), 136.9, 129.3, 128.4, 126.4 (C-aromatic), 102.3 (PhCHO), 93.6 (C-1), 80.2 (C-1′), 78.6 (C-4), 75.2 (C-5′), 72.7 (C-3′), 71.2 (C-2′), 70.4 (C-5), 68.9 (C-4′), 68.7 (C-6), 55.0 (C-3), 53.2 (OCH_3), 46.1 (C-2), 23.3, 21.0, 20.7, 20.6 (× 2) (*C*H_3CO). ESI-HRMS: $[M + Na]^+$ calcd for $C_{30}H_{37}NNaO_{15}S$: 706.1776, found: 706.1786, $[M + H]^+$ calcd for $C_{30}H_{38}NO_{15}S$: 684.1957, found: 684.1971.

1,4,6-tri-*O*-Acetyl-2-azido-3-*S*-(methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)-2,3-dideoxy-3-thio-α,β-D-glucopyranose (13α,β). Compound **10** (100 mg, 0.15 mmol) was treated with CSA (63 mg, 0.27 mmol) in a solution of MeOH/DCM (1:1, 12.8 mL), and the reaction mixture was stirred for 18 h at room temperature. Then, it was quenched with Et_3N and concentrated under vacuum. The residue was treated with acetic anhydride (3 mL, 32 mmol) in pyridine (3 mL) for 18 h at room temperature. After this, MeOH was added, and solvents were evaporated under vacuum. Column chromatography (8:2 → 1:1 hexane/EtOAc) of the residue gave **13α,β** (96 mg, 97%) as a white solid in a relation α/β (1:3), R_f = 0.39 (1:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.28 (d, 0.35 H, $J_{1,2}$ = 3.6 Hz, H-1α), 5.45 (d, 1 H, $J_{1,2}$ = 8.4 Hz, H-1β), 5.29 (2t superimposed, 1.35 H, $J_{2',3'} \cong J_{3',4'}$ = 9.2 Hz, H-3′α + H-3′β), 5.20 (2t superimposed, 1.35 H, $J_{3',4'} \cong J_{4',5'}$ = 9.7 Hz, H-4′α + H-4′β), 5.00−4.90 (m, 2.7 H, H-2′α + H-2′β + H-4α + H-4β), 4.88 (2 d superimposed, 1.35 H, $J_{1',2'}$ = 10.1 Hz, H-1′α + H-1′β), 4.26−4.23 (2 dd superimposed, 1.35 H, H-6aα + H-6aβ), 4.10−4.00 (m, 3.00 H, H-5′α + H-5′β + H-5α + H-6bα + H-6bβ), 3.90 (dd, 0.35 H, $J_{1,2}$ = 3.6, $J_{2,3}$ = 11.7 Hz, H-2α), 3.77−3.73 (m, 5.00 H, H-5β + OCH_3α + OCH_3β), 3.71 (dd, 1 H, $J_{1,2}$ = 8.4, $J_{2,3}$ = 11.2 Hz, H-2β), 3.10 (t, 0.35 H, $J_{2,3} \cong J_{3,4}$ = 11.7 Hz, H-3α), 2.75 (t, 1 H, $J_{2,3} \cong J_{3,4}$ = 11.2 Hz, H-3β), 2.2−2.0 (m, 24.3 H, 6 × CH_3CO-α + 6 × CH_3CO-β); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 170.7, 170.1, 169.6, 169.5, 169.3, 168.8, 168.7, 166.8, 166.7 (*C*O), 94.3 (C-1β), 89.7 (C-1α), 83.9 (C-1′β), 83.8 (C-1′α), 76.0 (C-5′α), 75.9 (C-5′β), 75.4 (C-5β), 73.1 (C-3′α + C-3′β), 70.8 (C-5α), 70.0 (C-2′α + C-2′β), 69.3 (C-4′α), 69.2 (C-4′β), 65.5 (C-4α), 65.4 (C-4β), 65.3 (C-2β), 63.1 (C-2α), 62.1 (C-6α), 62.0 (C-6β), 53.0 (OCH_3α), 52.9 (OCH_3β), 51.4 (C-3β), 49.2 (C-3α), 21.1, 20.9 (× 2), 20.7 (× 3), 20.6 (× 2) (CH_3CO). ESI-HRMS: $[M + Na]^+$ calcd for $C_{25}H_{33}N_3NaO_{16}S$: 686.1474, found: 686.1487.

1,4,6-tri-*O*-Acetyl-2-acetamido-3-*S*-(methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)-2,3-dideoxy-3-thio-α- and β-D-glucopyranose (14α and 14β). The anomeric mixture **13α,β** (87 mg, 0.13 mmol) was dissolved in pyridine (2.8 mL). Under an argon atmosphere, AcSH (190 μL, 2.6 mmol) was added. The reaction mixture was stirred at room temperature for 72 h. Then, solvents were evaporated under vacuum, and column chromatography of the residue using silica gel (particle size of <45 μm, for thin layer chromatography) and hexane/EtOAc mixtures (3:7 → 1:9) first

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gave **14β** (30 mg, 51%) and then **14α** (22 mg, 37%) as white solids. The combined yield was 88%.

14α: mp 216−217 °C (from hexane/EtOAc), R_f = 0.37 (EtOAc); $[\alpha]_D^{20}$ − 2.8 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (d, 1 H, $J_{NH,2}$ = 8.3 Hz, N*H*), 6.25 (d, 1 H, $J_{1,2}$ = 3.1 Hz, H-1), 5.39−5.36 (m, 1 H, H-3′), 5.11 (t, 1 H, $J_{3',4'} \cong J_{4',5'}$ = 10.0 Hz, H-4′), 5.00 (dd, 1 H, $J_{4,5}$ = 10.3, $J_{3,4}$ = 11.7 Hz, H-4), 4.82−4.77 (m, 2 H, H-1′ + H-2′), 4.27−4.22 (m, 1 H, H-2), 4.23 (dd, 1 H, $J_{6a,5}$ = 3.9, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.12 (d, 1 H, $J_{4',5'}$ = 10.0 Hz, H-5′), 4.04−3.99 (m, 2 H, H-5 + H-6b), 3.75 (s, 3 H, OCH_3), 3.32 (t, 1 H, $J_{2,3} \cong J_{3,4}$ = 11.7 Hz, H-3), 2.17, 2.08 (× 2), 2.05, 2.03, 2.02, 1.88 (7 s, 21 H, 7 × CH_3CO); $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$) δ 170.9, 170.4, 170.0, 169.8, 169.7, 169.5, 169.0, 167.8 (*C*O), 90.7 (C-1), 79.4 (C-1′), 75.4 (C-5′), 72.7 (C-3′), 72.1 (C-2′), 71.7 (C-5), 68.8 (C-4′), 66.8 (C-4), 62.2 (C-6), 53.4 (OCH_3), 52.1 (C-2), 43.7 (C-3), 23.0, 21.0, 20.9 (× 2), 20.8, 20.7, 20.6 (CH_3CO). ESI-HRMS: $[M + Na]^+$ calcd for $C_{27}H_{37}NNaO_{17}S$: 702.1674, found: 702.1669.

14β: mp 102−103 °C (from hexane/EtOAc), R_f = 0.42 (EtOAc); $[\alpha]_D^{20}$ + 12.3 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71 (d, 1 H, $J_{NH,2}$ = 7.0 Hz, N*H*), 6.33 (d, 1 H, $J_{1,2}$ = 8.2 Hz, H-1), 5.33 (t, 1 H, $J_{2',3'} \cong J_{3',4'}$ = 9.2 Hz, H-3′), 5.14 (dd, 1 H, $J_{3',4'}$ = 9.2, $J_{4',5'}$ = 9.8 Hz, H-4′), 4.96 (t, 1 H, $J_{3,4} \cong J_{4,5}$ = 10.2 Hz, H-4), 4.90 (dd, 1 H, $J_{2',3'}$ = 9.2, $J_{1',2'}$ = 10.0 Hz, H-2′), 4.84 (d, 1 H, $J_{1',2'}$ = 10.0 Hz, H-1′), 4.31 (dd, 1 H, $J_{6a,5}$ = 4.6, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.08 (d, 1 H, $J_{4',5'}$ = 9.8 Hz, H-5′), 4.06 (dd, 1 H, $J_{6b,5}$ = 1.8, $J_{6a,6b}$ = 12.5 Hz, H-6b), 3.93−3.85 (m, 2 H, H-3 + H-5), 3.76 (s, 3 H, OCH_3), 3.16 (ddd, 1 H, $J_{NH,2}$ = 7.0, $J_{1,2}$ = 8.2, $J_{2,3}$ = 11.7 Hz, H-2), 2.10, 2.09, 2.05, 2.03, 2.02, 2.01, 1.99 (7 s, 21 H, 7 × CH_3CO); $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$) δ 171.5, 170.9, 169.9, 169.7, 169.4 (× 2), 168.8, 167.8 (*C*O), 92.2 (C-1), 80.6 (C-1′), 75.2 (C-5), 74.2 (C-5′), 72.9 (C-3′), 69.9 (C-2′), 68.6 (C-4′), 66.3 (C-4), 62.3 (C-6), 56.3 (C-2), 53.3 (OCH_3), 47.1 (C-3), 23.5, 21.1, 21.0, 20.8, 20.7, 20.6 (× 2) (*C*H_3CO). ESI-HRMS: $[M + Na]^+$ calcd for $C_{27}H_{37}NNaO_{17}S$: 702.1674, found: 702.1671.

1,4,6-tri-*O*-Acetyl-2-azido-3-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2,3-dideoxy-3-thio-α,β-D-glucopyranose (15α,β). Compound **6** (70 mg, 0.10 mmol) was treated with CSA (43 mg, 0.19 mmol) in a solution of MeOH/DCM (1:1, 8.4 mL), and the reaction mixture was stirred for 18 h at room temperature. Then, it was quenched with Et_3N and concentrated under vacuum. The residue was treated with acetic anhydride (1.4 mL, 14.8 mmol) in pyridine (1.4 mL) for 18 h at room temperature. After this, MeOH was added, and solvents were evaporated under vacuum. Column chromatography (8:2 → 1:1 hexane/EtOAc) of the residue gave **15α,β** (50 mg, 72%) as a white solid in a relation α/β (1:2), R_f = 0.35 (1:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.25 (d, 0.45 H, $J_{1,2}$ = 3.6 Hz, H-1α), 5.45−5.43 (m, 2.45 H, H-1β + H-4′α + H-4′β), 5.22−5.16 (2t superimposed, 1.45 H, $J_{1',2'} \cong J_{2',3'}$ = 9.9 Hz, H-2′α + H-2′β), 5.09−5.05 (m, 1.45 H, H-3′α + H-3′β), 5.04−4.95 (m, 1.45 H, H-4α + H-4β), 4.91−4.88 (2 d superimposed, 1.45 H, $J_{1',2'}$ = 9.9 Hz, H-1′α + H-1′β), 4.29−4.23 (2 dd superimposed, 1.45 H, H-6aα + H-6aβ), 4.17−3.97 (m, 6.25 H, H-5′α, H-5′β, H-5α + H-6bα + H-6bβ + H-6′aα + H-6′aβ + H-6′bα + H-6′bβ), 3.91 (dd, 0.45 H, $J_{1,2}$ = 3.6, $J_{2,3}$ = 11.3 Hz, H-2α), 3.79 (dd, 1 H, $J_{1,2}$ = 8.4, $J_{2,3}$ = 11.5 Hz, H-2β), 3.75 (ddd, 1 H, $J_{4,5}$ = 2.2, $J_{5,6a}$ = 4.9, $J_{5,6b}$ = 9.6 Hz, H-5β), 3.12 (t, 0.45 H, $J_{2,3} \cong J_{3,4}$ = 11.3 Hz, H-3α), 2.74 (t, 1 H, $J_{2,3} \cong J_{3,4}$ = 11.5 Hz, H-3β), 2.20−1.87 (m, 34.80 H, 8 × CH_3CO-α + 8 × CH_3CO-β); $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$) δ 170.7, 170.5, 170.4, 170.3, 170.1 (× 2), 169.6, 169.4, 168.7 (× 2) (*C*O), 94.5 (C-1β), 89.8 (C-1α), 83.0 (C-1′β), 82.9 (C-1′α), 75.5 (C-5β), 74.6 (C-5′α + C-5′β), 71.8 (C-3′α + C-3′β), 70.8 (C-5α), 67.4, 67.3, 67.2 (C-2′β, C-4′α, C-4′β), 65.2 (C-4α + C-4β), 64.6 (C-2β), 62.5, 62.3, 62.2, 62.1 (C-6α, C-6β, C-6′α, C-6′β), 51.4 (C-3β), 48.7 (C-3α), 21.1 (× 2), 20.9 (× 2), 20.8 (× 5), 20.7 ($CH_3COα$). ESI-HRMS: $[M + Na]^+$ calcd for $C_{26}H_{35}N_3NaO_{16}S$: 700.1630, found: 700.1644.

1,4,6-tri-*O*-Acetyl-2-acetamido-3-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2,3-dideoxy-3-thio-α- and β-D-glucopyranose (16α and 16β). The anomeric mixture **15α,β** (50 mg, 0.07 mmol) was dissolved in pyridine (1.6 mL). Under an argon atmosphere, AcSH (110 μL, 1.5 mmol) was added. The reaction mixture was stirred at room temperature for 72 h. Then, solvents were evaporated under vacuum, and column chromatography of the residue using silica gel (particle size of <45 μm, for thin layer chromatography) and hexane/EtOAc mixtures (3:7 → 1:9) first gave **16β** (23 mg, 45%) and then **16α** (11 mg, 23%) as white solids. The combined yield was 68%.

16α: mp 108−109 °C (from hexane/EtOAc), R_f = 0.28 (EtOAc); $[\alpha]_D^{20}$ + 29.7 (*c* 0.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (d, 1 H, $J_{1,2}$ = 3.3 Hz, H-1), 5.62 (d, 1 H, $J_{NH,2}$ = 6.7 Hz, N*H*), 5.41 (dd, 1 H, $J_{4',5'}$ = 1.0, $J_{3',4'}$ = 3.1 Hz, H-4′), 5.12−5.03 (m, 3 H, H-2′ + H-3′ + H-4), 4.79 (d, 1 H, $J_{1',2'}$ = 9.3 Hz, H-1′), 4.27 (ddd, 1 H, $J_{1,2}$ = 3.3, $J_{NH,2}$ = 6.7, $J_{2,3}$ = 11.7 Hz, H-2), 4.23 (dd, 1 H, $J_{5,6a}$ = 4.3, $J_{6a,6b}$ = 12.3 Hz, H-6a), 4.12−4.05 (m, 3 H, H-6b + H-6′a + H-6′b), 4.00−3.95 (m, 2 H, H-5 + H-5′), 3.12 (t, 1 H, $J_{2,3} \cong J_{3,4}$ = 11.7 Hz, H-3), 2.16, 2.14, 2.10, 2.09, 2.06, 2.05, 2.00, 1.97 (8 s, 24 H, 8 × CH_3CO); $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$) δ 170.9, 170.6, 170.2, 170.0 (× 2), 169.7, 169.2, 168.7 (*C*O), 90.2 (C-1), 81.9 (C-1′), 74.6 (C-5′), 71.8 (C-3′), 70.9 (C-5), 67.6 (C-2′), 67.0 (C-4′), 66.2 (C-4), 62.3 (C-6), 61.1 (C-6′), 52.0 (C-2), 46.5 (C-3), 23.2, 21.1, 20.9, 20.8 (× 4), 20.7 (CH_3CO). ESI-HRMS: $[M + Na]^+$ calcd for $C_{28}H_{39}NNaO_{17}S$: 716.1831, found: 716.1832.

16β: mp 105−106 °C (from hexane/EtOAc), R_f = 0.38 (EtOAc); $[\alpha]_D^{20}$ + 38.4 (*c* 0.9, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (d, 1 H, $J_{1,2}$ = 8.3 Hz, H-1), 6.13 (d, 1 H, $J_{NH,2}$ = 6.9 Hz, N*H*), 5.46 (dd, 1 H, $J_{4',5'}$ = 1.2, $J_{3',4'}$ = 3.4 Hz, H-4′), 5.14 (t, 1 H, $J_{1',2'} \cong J_{2',3'}$ = 10.0 Hz H-2′), 5.06 (dd, 1 H, $J_{3',4'}$ = 3.4, $J_{2',3'}$ = 10.0 Hz, H-3′), 4.96 (t, 1 H, $J_{3,4} \cong J_{4,5}$ = 10.0 Hz, H-4), 4.76 (d, 1 H, $J_{1',2'}$ = 10.0 Hz, H-1′), 4.29 (dd, 1 H, $J_{5,6a}$ = 5.1, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.21 (dd, 1 H, $J_{5',6'a}$ = 4.0, $J_{6'a,6'b}$ = 11.7 Hz, H-6′a), 4.12 (dd, 1 H, $J_{5',6'b}$ = 8.0, $J_{6'a,6'b}$ = 11.7 Hz, H-6′b), 4.06 (dd, 1 H, $J_{5,6b}$ = 2.4, $J_{6a,6b}$ = 12.4 Hz, H-6b), 3.97 (ddd, 1 H, $J_{4',5'}$ = 1.2, $J_{5',6'a}$ = 4.0, $J_{5',6'b}$ = 8.0 Hz, H-5′), 3.90−3.84 (m, 2 H, H-3 + H-5), 3.19 (ddd, 1 H, $J_{NH,2}$ = 6.9, $J_{1,2}$ = 8.3, $J_{2,3}$ = 11.7 Hz, H-2), 2.16, 2.14, 2.09, 2.08, 2.04 (× 2), 1.99, 1.96 (8 s, 24 H, 8 × CH_3CO); $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$) δ 171.2, 170.8, 170.6, 170.2, 170.0, 169.7, 169.3, 168.6 (*C*O), 92.2 (C-1), 81.7 (C-1′), 75.3 (C-5), 74.8 (C-5′), 71.8 (C-3′), 67.6 (C-4′), 66.5 (C-2′), 66.4 (C-4), 62.8 (C-6′), 62.4 (C-6), 56.3 (C-2), 47.4 (C-3), 23.6, 21.1, 21.0, 20.8 (× 3), 20.7, 20.6 (*C*H_3CO). ESI-HRMS: $[M + Na]^+$ calcd for $C_{28}H_{39}NNaO_{17}S$: 716.1831, found: 716.1833.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b01883.

The SI file includes the analysis of the conformers of **8**, **9**, and **11** obtained by molecular modeling and copies of ^{1}H and $^{13}C\{^1H\}$ NMR spectra for all compounds synthesized. 2D ^{1}H-COSY and ^{1}H-^{13}C HSQC experiments of compounds **6**−**11**, and ^{1}H-^{13}C HMBC experiment of compound **7** and ^{1}H-NOESY experiments of compounds **8**, **9**, and **11** are also included (PDF)

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Notes

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