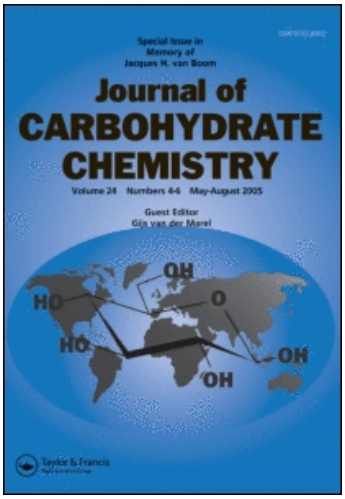

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Synthesis, Glycosidation, and Hydrolytic Stability of Novel Glycosyl Thioimidates

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Synthesis, Glycosidation, and Hydrolytic Stability of Novel Glycosyl Thioimidates

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INTRODUCTION

Despite significant progress in the area of synthetic carbohydrate chemistry, the necessity to form a glycosidic bond with *complete* stereoselectivity remains to be the main reason chemical *O*-glycosylation is still ranked among the most challenging problems of modern synthetic chemistry. The development of new glycosylation techniques persists to be of paramount importance for the rapidly developing area of glycosciences. Factors affecting the stereoselectivity of glycosylation include temperature, pressure, structure, conformation, solvent, promoter, steric hindrance, or leaving group.[1] While some of these factors influence the stereoselectivity dramatically, the leaving group is undoubtedly one of the major players in this respect. As a result, a number of glycosyl donors have been developed,[2] among which glycosyl halides,[3] trichloroacetimidates,[4] and alkyl/aryl thioglycosides,[5] though most commonly used, still have significant drawbacks. For example, thioglycosides are inert under other glycosyl donor activation conditions, and therefore can fit into various orthogonal and (chemo)selective strategies for complex oligosaccharide assembly.[6] Unfortunately, only modest stereoselectivity is

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typically achieved with these stable compounds.[1] Conversely, being rather unstable glycosyl donors, trichloroacetimidates or halides (especially iodides)[7] often demonstrate complete stereoselectively in glycosylations.[1] Unfortunately, these compounds are not sufficiently stable to be used in block oligosaccharide synthesis via convergent pathways.[6]

Our work on the development of glycosylation methods has resulted in the discovery of novel glycosyl donors with a generic thioimidoyl leaving group ($SCR_1 = NR_2$, **1**, Fig. 1). We have already reported that S-benzoxazolyl (**2**, SBox)[8,9] and, especially, S-thiazolinyl (**3**, STaz)[10] moieties are sufficiently stable to be used at the anomeric center; also, they can be mildly activated under a variety of reaction conditions for glycosylation. The high stability along with accessibility and excellent stereoselectivity make these derivatives attractive and very promising targets for future studies. Conversely, a fairly low stability was reported for a number of previously studied thioimidates, which was the major reason benzothiazolyl,[11] pyridin-2-yl,[12,13] pyrimidin-2-yl,[12,14] imidazolin-2-yl,[12] and 1′-phenyl-1*H*-tetrazolyl[15] glycosides could not be applied as building blocks in convergent oligosaccharide syntheses. We wanted to clarify this disagreement and here we report our studies on the synthesis, glycosidation, and stability evaluation of a range of cyclic glycosyl thioimidates structurally related to thioimidates **2** and **3**.

RESULTS AND DISCUSSION

The major motivation for these systematic studies was the discovery and appreciation of the unique properties of the thioimidoyl glycosides. The SBox and STaz glycosyl donors have several useful features. First, these compounds can be efficiently synthesized from inexpensive odorless aglycones.[9,10] While this is a convenient feature for laboratory preparation, it becomes increasingly important for industrial applications. Second, glycosidation of **2** and **3** allowed very high stereoselectivity and excellent yields (often over 90%) of glycosidations.[9,10] Third, high stability of the SBox and STaz glycosides toward major protecting group manipulations and other glycosyl donor activation conditions makes it possible to use these moieties as a temporary protection of the anomeric center.[10,16] Lastly, it has been demonstrated that glycosyl thio

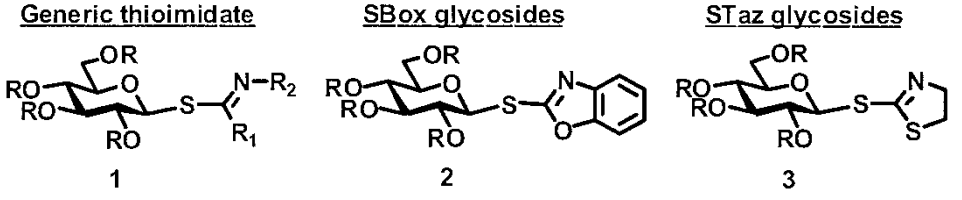


Figure 1

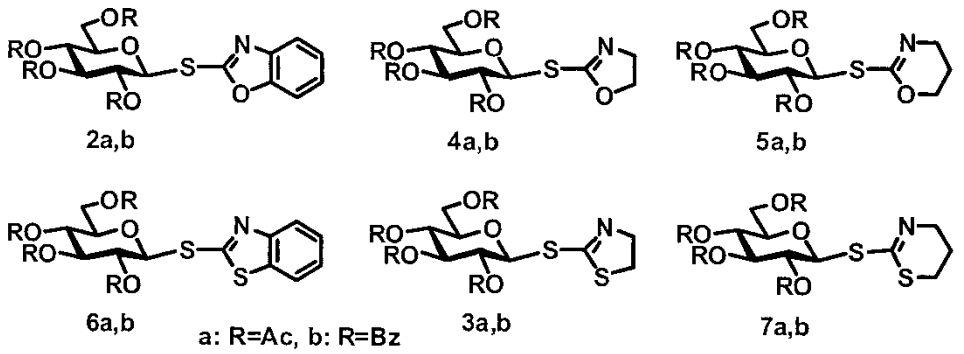


Figure 2

imidates not only easily fit into existing glycosylation strategies for complex oligosaccharide synthesis, but also permit conceptually new strategies, such as temporary deactivation approach.[17]

However, our knowledge of this promising methodology is not yet complete. In this respect it seemed essential to extend these studies to a range of five- and six-membered heterocyclic moieties, structurally related to our first targets, SBox and STaz glycosides. For this purpose we obtained novel per-acylated S-oxazolinyl (**4**), S-oxazinyl (**5**), S-benzothiazolyl (**6**), and S-thiazinyl (**7**) derivatives. It should be noted that per-benzylated S-benzothiazolyl glucosides and peracetylated S-benzothiazolyl furanosides have been previously synthesized (Fig. 2).[11,18]

Synthesis of Aglycones

A general procedure to introduce the anomeric moiety (aglycone) involved the use of anomeric acetates or bromides as suitable starting compounds for these syntheses. In this context, aglycones **8–11** for the synthesis of **2, 6, 4**, and **3**, respectively, are readily available from commercial sources, while tetrahydro-1,3-oxazine-2-thione (**12**)[19] and tetrahydro-1,3-thiazine-2-thione (**13**)[20] needed to be synthesized (Fig. 3). For this purpose, a common precursor 3-aminopropanol was used as a starting material. The synthesis of **12** was achieved by the reaction of 3-aminopropanol with CS_2 in the presence of triethylamine in methanol at 0°C followed by the treatment with 30% H_2O_2.[19] Compound **13**

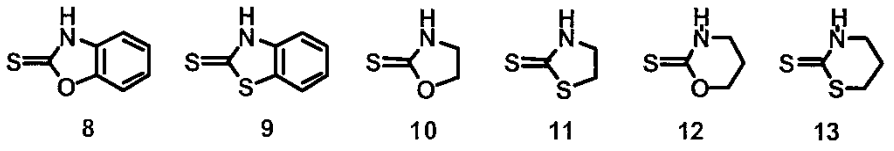


Figure 3

was obtained by refluxing a mixture of 3-aminopropanol and CS_2 in 1M aqueous KOH.[20] Therefore, obtained derivatives **12** and **13** were then purified by crystallization.

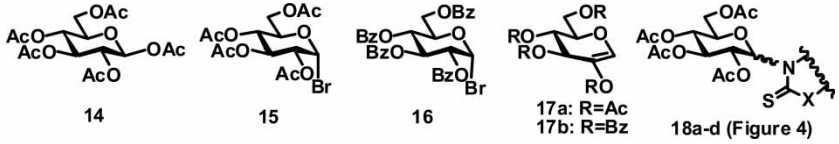
Synthesis of Glycosyl Thioimidates

Having acquired the aglycone derivatives suitable for introduction at the anomeric center, we turned our attention to the synthesis of acylated glycosyl thioimidates. These syntheses were accomplished by slightly modified experimental procedures in comparison to those previously developed for the synthesis of SBox and STaz glycosides.[8–10] Thus, per-acetylated thioimidoyl derivatives **4**–**7** were obtained from glucose pentaacetate **14** in the presence of TMSOTf at room temperature; in this context, SBox and STaz glycosides were obtained in the presence of BF_3-Et_2O at low temperature. The synthesis of acetylated thioimidates was also accomplished from acetobromoglucose **15**[21] by the reaction of a potassium salt of **10**–**13** in acetone or MeCN at room temperature. Similarly, benzobromoglucose **16**[21] was employed in the syntheses of perbenzoylated thioimidates. It should be noted that while the sodium salt was previously found to be advantageous in the synthesis of STaz glycosides **3**,[10] better results were obtained with the use of potassium salts in this case. The synthesis of benzoylated thioimidates were accomplished in the presence of 18-crown-6. The use of the crown ether was not only found to be essential for the efficient conversion, but also very influential for the synthesis of the desired S- linked derivatives.

While the results obtained for the synthesis of structurally similar benzoxazolyl (**2**) and benzothiazolyl (**3**) derivatives were very comparable (entries 1–3 vs. 4–6, Table 1), other pairs of the structurally similar derivatives provided very different results. Overall, the introduction of the sulfur-containing heterocyclic moieties at the anomeric center was significantly more simple and high yielding than that of their oxygen-containing counterparts. Thus, the syntheses of thiazolinyl **3a** and thiazinyl **7a** from pentaacetate **14** were achieved in high yields of 91% and 84% (entries 10 and 16), respectively, whereas the syntheses of oxazolinyl **4a** and oxazinyl **5a** under similar reaction conditions failed (entries 7 and 13). Along with these observations, notably higher yields were obtained in the syntheses of sulfur-containing heterocyclic anomeric moieties from halides **15** or **16**.

Thus, for the synthesis of the sulfur-containing five-membered heterocyclic anomeric moieties: **3a** and **3b** was obtained in 53% and 50% yield, respectively (entries 11 and 12), whereas the synthesis of structurally similar oxygen-containing **4a** and **4b** was achieved in only 34% and 23%, respectively. Similar correlation, but lower yields, was obtained in the syntheses of the sixmembered heterocyclic leaving groups (**5** and **7**, entries 13–19).

Table 1: Synthesis of glycosyl thioimidates **2**–**7**.



Entry	SM	Aglycone	Conditions	Product	Yield	Side products	Ref.
1	**14**	**8**	BF_3-Et_2O, CH_2Cl_2, 0°C → rt	**2a**	79%		(9)
2	**15**	**8**	K_2CO_3, acetone, 50°C	**2a**	96%		(9)
3	**16**	**8**, K salt	18-c-6, acetone, rt	**2b**	99%		(9)
4	**14**	**9**	TMSOTf, CH_2Cl_2, rt	**6a**	85%		
5	**15**	**9**, K salt	acetone, rt	**6a**	99%		
6	**16**	**9**, K salt	18-c-6, acetone, rt	**6b**	88%		
7	**14**	**10**	TMSOTf, CH_2Cl_2, rt	**4a**	0%	**18a** (80%)	
8	**15**	**10**, K salt	MeCN, rt	**4a**	34%	**17a** (36%), **18a** (24%)	
9	**16**	**10**, K salt	18-c-6, MeCN, rt	**4b**	23%	**17b** (49%)	
10	**14**	**11**	BF_3-Et_2O, CH_2Cl_2, 0°C → rt	**3a**	91%		(10)
11	**15**	**11**, Na salt	MeCN, rt	**3a**	53%	**17a** (13%), **18b** (11%)	(10)
12	**16**	**11**, Na salt	15-c-5, MeCN, rt	**3b**	50%	**17b** (41%)	(10)
13	**14**	**12**	TMSOTf, CH_2Cl_2, rt	**5a**	0%	Complex mixture	
14	**15**	**12**, K salt	MeCN, rt	**5a**	0%	**17a** (58%), **18c** (27%)	
15	**16**	**12**, K salt	18-c-6, MeCN, rt	**5b**	12%	**17b** (70%)	
16	**14**	**13**	TMSOTf, CH_2Cl_2, rt	**7a**	84%		
17	**15**	**13**, K salt	MeCN, rt	**7a**	22%	**17a** (54%), **18d** (18%)	
18	**16**	**13**, K salt	18-c-6, MeCN, rt	**7b**	18%	**17b** (55%)	
19	**7a**	—	1. MeONa, 2. $BzCl/C_5H_5N$	**7b**	72 %		

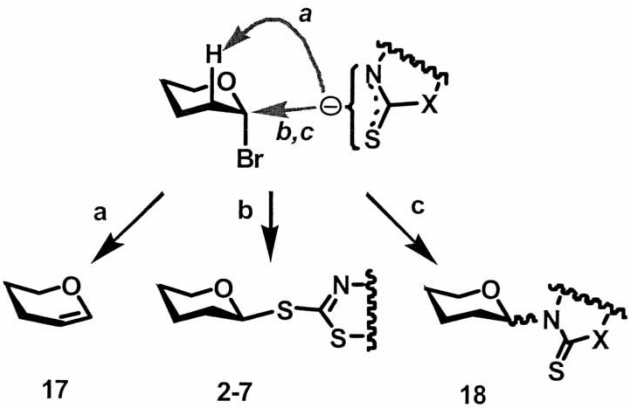
SM—starting material

Although the reaction conditions reported here are optimized to favor the glycosylation at the softer sulfur atom (S-glycosylation), some of these coupling reactions were significantly compromised by competitive side processes. Among those, β-elimination resulting in the formation of a 1,2-dehydro (glycal) derivative **17a, b** and/or N-glycosylation resulting in the formation of a corresponding N-linked derivative (**18a–d**) were found to be the most common (Sch. 1). Moreover, **17a** or **17b** was obtained as a major product in the syntheses of **4a, 4b, 5a, 5b, 7a**, and **7b** with the isolated yields ranging from 36% (entry 8) to 70% (entry 15). Although the corresponding per-acetylated N- linked derivatives (**18a–d**, see Fig. 4) were only obtained in the attempted synthesis of **4a** from **14** (entry 7) as a major product (**18a**), they were often detected in the reaction mixtures.

Glycosidation and Hydrolytic Stability Studies

Glycosidation of perbenzoylated thioimidates **4b, 6b**, and **7b** were studied under essentially the same reaction conditions as previously investigated for the glycosidations of SBox (**2b**) and STaz (**3b**) glycosides.[8–10] Although novel derivatives appear to be somewhat less efficient glycosyl donors than either **2b** or **3b**, these results are in line with many other glycosylation methods.[2] Thus, while typical yields for the synthesis of **20**[22] in glycosylations of **19**[23] with **2a** and **3a** were in the range of 94% to 97% (Table 2, entries 1–4), the yields achieved with either **4b, 6b**, or **7b** were consistently lower (51% to 81%, entries 5–10). The use of per-acetylated glycosyl donors was found to be impractical due to a competing process of the 2-O-acetyl moiety migration from a glycosyl donor to the 6-OH of the glycosyl acceptor **19**.[24]

Per-acetylated derivatives **2a, 3a, 4a, 6a**, and **7a** were studied under acid hydrolysis conditions (synthesis of **21**, Fig. 5). Reaction conditions selected for



Scheme 1

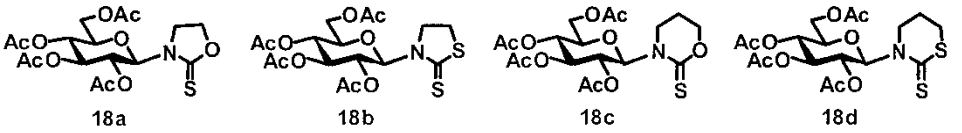
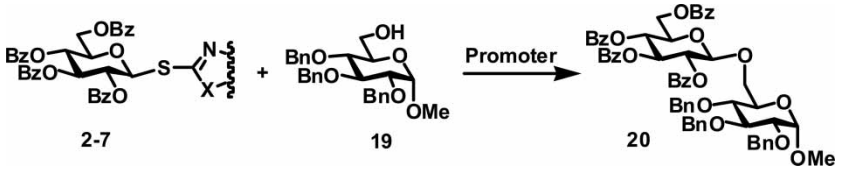


Figure 4

this purpose were essentially the same as those previously reported for the hydrolysis of S-ethyl or S-phenyl glycosides (**22**[25] or **23**,[26] respectively, Fig. 5). The first procedure involved hydrolysis in the presence of N-iodosuccinimide (2 equiv.) and TfOH (0.1–0.2 equiv). in wet CH_2Cl_2.[27] Under these reaction conditions **2a, 22**, and **23** were rapidly converted into the hemiacetal **21**[28]; these reactions required 15, 2, and 20 min, respectively, whereas the hydrolysis of **3a, 4a, 6a**, and **7a** was significantly slower and required 16, 2, 16, and 48 hr, respectively.

The second procedure involved hydrolysis in the presence of N-bromosuccinimide (2 equiv.) in aqueous acetone.[29] Under these reaction conditions **22** was hydrolyzed in 5 min, **3a, 7a**, and **23** were hydrolyzed in 3 to 5 hr, while **2a** and **6a** were significantly more resistant: their hydrolysis was sluggish and the reaction was not completed even in 48 hr. These observations clearly illustrate that S-ethyl or S-phenyl glycosides are significantly more susceptible under hydrolytic conditions than their thioimidoyl counterparts. In the long run, this advantageous feature of thioimidates may become an important factor in their application as building blocks in convergent oligosaccharide synthesis.

Table 2: Glycosylation of **19** with per-benzoylated glycosyl donors **2**–**7**: synthesis of **20.**



Entry	Donor	Promoter	Time	Yield	Ref
1	**2b**	AgOTf	5 min	94%	(9)
2	**2b**	MeOTf	1 hr	95%	(9)
3	**3b**	AgOTf	16 hr	97%	(10)
4	**3b**	MeOTf	2 hr	97%	(10)
5	**4b**	AgOTf	5 min	60%	
6	**4b**	MeOTf	3.5 hr	81%	
7	**6b**	AgOTf	16 hr	79%	
8	**6b**	MeOTf	2 hr	67%	
9	**7b**	AgOTf	30 min	65%	
10	**7b**	MeOTf	16 hr	51%	

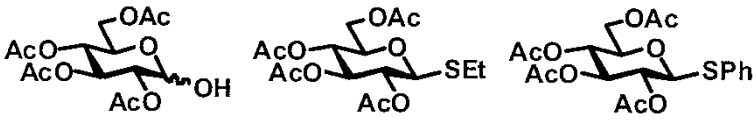


Figure 5

CONCLUSIONS

We investigated a number of novel thioimidoyl glycosides, which can be obtained from anomeric acetates and halides. In case of glycosidation of somewhat more basic oxygen-containing heterocyclic aglycones, the isolated yields were compromised due to competing side processes, namely β-elimination and N-glycosylation. The glycosyl donor properties of these derivatives were studied in comparison to other glycosyl donors of this class, SBox and STaz glycosides. Hydrolytic stability studies have clearly demonstrated that the glycosyl thioimidates are more stable compounds overall than their S-ethyl and S-phenyl counterparts.

EXPERIMENTAL

General Methods

Column chromatography was performed on silica gel 60 (EM Science, 70–230 mesh); reactions were monitored by TLC on Kieselgel 60 F_{254} (EM Science). The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol or $KMnO_4$ solution in EtOH. Solvents were removed under reduced pressure at $<40^{\circ}C$. CH_2Cl_2, $(ClCH_2)_2$, and MeCN were distilled from CaH_2 directly prior to application. MeOH was dried by refluxing with magnesium methoxide, distilled, and stored under argon. Pyridine was dried by refluxing with CaH_2 and then distilled and stored over molecular sieves (3Å). Molecular sieves (3Å), used for reactions, were crushed and activated in vacuo at 390°C during 8 hr in the first instance and then for 2 to 3 hr at 390°C directly prior to application. AgOTf (Acros) was coevaporated with toluene (3×10 mL) and dried in vacuo for 2 to 3 hr directly prior to application. Optical rotations were measured at Jasco P-1020 polarimeter. UV-VIS spectra were recorded at HP 8452A Diode Array Spectrophotometer. ^1H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra were recorded at 75 MHz (Bruker Avance). HRMS determinations were made with the use of JEOL MStation (JMS-700) Mass Spectrometer.

Preparation of thioimidates 4–7. General procedure for the synthesis of 4a, 5a, 6a, and 7a. ***Method A.*** A mixture of 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose (**14**, 0.128 mmol), a thiol (**9**, **10**, or **13**, 0.192 mmol), and activated

molecular sieves 3 Å (100 mg) in dry CH_2Cl_2 (1.0 mL) was stirred under an atmosphere of argon for 30 min at rt. TMSOTf (0.192 mmol) was then added dropwise and the reaction mixture was kept for 45 min at rt. After that, additional amounts of thiol (0.192 mmol) and TMSOTf (0.192 mmol) were added and the reaction mixture was kept for 1 hr at reflux (45°C). Upon completion, the mixture was diluted with CH_2Cl_2, the solid was filtered off, and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with aq. NaOH (2×15 mL) and water (3×10 mL), and the organic layer was separated, dried, and concentrated in vacuo. The residue was purified by crystallization from CH_2Cl_2/ether/hexane or by column chromatography on silica gel (ethyl acetate/toluene elution) to afford a corresponding thioimidate.

General procedure for the synthesis of 4a, 5a, 6a, and 7a. *Method B.* KOH (4.2 mmol) was added to a solution of **9, 10**, or **13** (4.2 mmol) in a distilled acetone. The reaction mixture was refluxed at 60°C for 3 hr, then concentrated in vacuo and dried to afford the corresponding potassium salts as white solids, which were sufficiently pure to be used in subsequent applications. A potassium salt (4.5 mmol) was added to a stirred solution of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (**15**, 3.0 mmol) in dry acetone or MeCN (20 mL). The reaction mixture was stirred under argon for 1 hr at rt. Upon completion, the mixture was diluted with toluene (20 mL) and washed with water (10 mL), 1% aq. NaOH (10 mL), and water (3×10 mL), and the organic phase was separated, dried, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane elution) to afford a corresponding thioimidate.

4,5-Dihydrooxazol-2-yl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (4a) was prepared as white crystals from **15** (Method B) in 34% yield. Analytical data for **4a**: $R_f = 0.44$ (acetone/toluene, 2/3, v/v); m.p. +126–129°C (CH_2Cl_2/ether/hexane); $[\alpha]_D^{24} -3.0°$ (c = 0.3, $CHCl_3$); UV: $\lambda_{max} = 272$ nm; ^{1}H NMR: δ 5.37 (d, 1H, $J_{1,2} = 10.4$ Hz, H-1), 5.24 (dd, 1H, $J_{3,4} = 9.2$ Hz, H-3), 5.15 (dd, 1H, $J_{2,3} = 9.2$ Hz, H-2), 5.15 (dd, 1H, $J_{4,5} = 9.9$ Hz, H-4), 4.40 (m, 2H, CH_2O), 4.29 (dd, 1H, $J_{5,6a} = 4.6$ Hz, $J_{6a,6b} = 12.5$ Hz, H-6a), 4.15 (dd, 1H, $J_{5,6b} = 2.2$ Hz, H-6b), 3.92 (dd, 2H, CH_2N), 3.85 (m, 1H, H-5), 2.08, 2.06, 2.05, 2.03 (4s, 12H, $4 \times COCH_3$) ppm; ^{13}C NMR: δ 171.03, 170.44, 169.75 ($\times 2$), 163.04, 83.67, 76.85, 74.24, 74.49, 70.13, 68.29, 62.11, 55.15, 21.12 ($\times 2$), 21.00, 20.95 ppm; HR-FAB MS $[M + Na]^+$ calcd. for $C_{17}H_{23}NNaO_{10}S$ 456.0940, found 456.0947. **2,3,4,6-Tetra-O-acetyl-1-N-(4,5-dihydro-2-thione-oxazol-3-yl)-β-D-glucopyrano- sylamine** (**18a**) was isolated as a sole product in the attempt of the synthesis of **4a** from **14** (80%, Method A) and as a side product in the synthesis of **4a** from **15** (24%, Method B). Analytical data for **18a**: $R_f = 0.41$ (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{26} + 26.8°$ (c = 1.13, $CHCl_3$); UV: $\lambda_{max} = 300$ nm; ^{1}H NMR: d, 5.82 (d, 1H, $J_{1,2} = 9.4$ Hz, H-1), 5.43

(dd, 1H, $J_{3,4} = 9.4$ Hz, H-3), 5.08 (dd, 1H, $J_{4,5} = 9.4$ Hz, H-4), 5.07 (dd, 1H, $J_{2,3} = 9.5$ Hz, H-2), 4.44–4.62 (m, 2H, CH_2O), 4.28 (dd, 1H, $J_{5,6a} = 4.9$ Hz, $J_{6a,6b} = 12.5$ Hz, H-6a), 4.11 (dd, 1H, $J_{5,6b} = 1.8$ Hz, H-6b), 3.77–3.99 (m, 3H, H-5, CH_2N), 2.03, 2.05, 2.06, 2.09 (4s, 12H, 4 × $COCH_3$) ppm; ^{13}C NMR: d, 189.44, 170.71, 170.54, 169.90, 169.78, 84.17, 74.61, 72.74, 68.78, 68.18, 67.70, 61.91, 43.06, 20.93, 20.86 (×2), 20.77 ppm.

5,6-Dihydro-4H-1,3-oxazin-2-yl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (5a) could not be obtained by either Method A or B. **2,3,4,6-Tetra-O-acetyl-1-N-(5,6-dihydro-4H-2-thione-1,3-oxazin-3-yl)-β-D-glucopyranosylamine** (**18c**) was isolated as a colorless film in the attempt of the synthesis of **5a** from **15** (27%, Method B). Analytical data for **18c**: $R_f = 0.50$ (acetone/toluene, 1/3, v/v); $[\alpha]_D^{26}$ +.25.7° (c = 1.25, $CHCl_3$); UV: $\lambda_{max} = 300$ nm; ^{1}H NMR: d, 6.77 (d, 1H, $J_{1,2} = 9.4$ Hz, H-1), 5.43 (dd, 1H, $J_{3,4} = 9.6$ Hz, H-3), 5.14 (dd, 1H, $J_{2,3} = 9.5$ Hz, H-2), 5.05 (dd, 1H, $J_{4,5} = 9.6$ Hz, H-4), 4.20–4.37 (m, 3H, H-6a, CH_2O), 4.12 (dd, 1H, $J_{5,6b} = 1.9$ Hz, $J_{6a,6b} = 12.5$ Hz, H-6b), 3.89–3.94 (m, 1H, H-5), 3.51 (dd, 2H, CH_2N), 2.13–2.16 (m, 2H, CCH_2C), 2.02, 2.05, 2.07, 2.09 (4s, 12H, 4 × $COCH_3$) ppm; ^{13}C NMR: d, 188.57, 170.74, 170.65, 169.90, 169.84, 87.34, 74.55, 72.96, 68.47, 68.25, 68.15, 61.95, 40.46, 21.15, 20.97 (×2), 20.78 (×2) ppm; HR-FAB MS $[M + Na]^+$ calcd for $C_{18}H_{25}NNaO_{10}S$ 470.1097, found 470.1090.

Benzothiazol-2-yl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (6a) was prepared as white crystals from **14** (Method A) or **15** (Method B) in 85% or 99% yield, respectively. Analytical data for **6a**: $R_f = 0.38$ (ethyl acetate – toluene, 3/7, v/v); m.p. +121–124°C (CH_2Cl_2/ether/hexane); $[\alpha]_D^{25}$ +34.7° (c = 1.04, $CHCl_3$); UV: $\lambda_{max} = 276$ nm; ^{1}H NMR: δ, 7.40–8.00 (m, 4H, aromatic), 5.59 (d, 1H, $J_{1,2} = 10.2$ Hz, H-1), 5.33 (dd, 1H, $J_{3,4} = 9.2$ Hz, H-3), 5.25 (dd, 1H, $J_{2,3} = 9.2$ Hz, H-2), 5.19 (dd, 1H, $J_{4,5} = 10.0$ Hz, H-4), 4.32 (dd, 1H, $J_{5,6a} = 4.9$ Hz, $J_{6a,6b} = 12.5$ Hz, H-6a), 4.19 (dd, 1H, $J_{5,6b} = 1.9$ Hz, H-6b), 3.94 (m, 1H, H-5), 2.05, 2.05, 2.05, 2.03 (4s, 12H, 4 × $COCH_3$) ppm; ^{13}C NMR: δ 170.98, 170.47, 169.78, 162.28, 153.11, 136.21, 126.79 (×2), 125.45, 122.76 (×2), 121.43 (×2), 84.41, 74.17, 70.10, 68.50, 62.26, 21.09, 20.97 (×2) ppm; HR-FAB MS $[M + Na]^+$ calcd. for $C_{21}H_{23}NNaO_9S_2$ 520.0712, found 520.0717.

5,6-Dihydro-4H-1,3-thiazin-2-yl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (7a) was prepared as white crystals from **14** (Method A) or **15** (Method B) in 84% or 22% yield, respectively. Analytical data for **7a**: $R_f = 0.53$ (ethyl acetate-toluene, 3/7, v/v); m.p. +102–104°C (CH_2Cl_2/ether/hexane); $[\alpha]_D^{24}$ +9.2° (c = 1.03, $CHCl_3$); UV: $\lambda_{max} = 274$ nm; ^{1}H NMR: δ, 5.55 (d, 1H, $J_{1,2} = 10.5$ Hz, H-1), 5.27 (dd, 1H, J3,4 = 9.2 Hz, H-3), 5.08–5.15 (m, 2H, $J_{2,3} = 9.2$ Hz, H-2, 4), 4.27 (dd, 1H, $J_{5,6a} = 4.3$ Hz, $J_{6a,6b} = 12.4$ Hz,

H-6a), 4.13 (dd, 1H, $J_{5,6b} = 2.2$ Hz, H-6b), 3.74–3.84 (m, 3H, H-5, CH_2N), 3.08 (m, 2H, CH_2S), 2.08, 2.05, 2.02, 2.02 (4s, 12H, $4 \times COCH_3$) 1.95 (m, 2H, CCH2C), ppm; ^{13}C NMR: δ, 171.04, 170.49, 169.76 ($\times$2), 152.59, 81.02, 74.50, 69.49, 68.54, 62.27, 48.98, 30.06, 28.16, 20.86, 20.81, 20.72 ($\times$2), 20.48 ppm; HR-FAB MS$[M + Na]^+$ calcd. for $C_{18}H_{25}NNaO_9S_2$ 486.0868, found 486.0876.

2,3,4,6-Tetra-O-acetyl-1-N-(5,6-dihydro-4H-2-thione-1,3-thiazin-3-yl)-b-D-glucopyranosylamine (18d) was isolated as a side product in the synthesis of **7a** from **15** (18%, Method B). Analytical data for **18d**: $R_f = 0.42$ (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{26}$ +40.6° (c = 1.02, $CHCl_3$); UV: $\lambda_{max} = 296$ nm; ^{1}H NMR: d, 7.08 (d, 1H, $J_{1,2} = 9.3$ Hz, H-1), 5.41 (dd, 1H, $J_{3,4} = 9.5$ Hz, H-3), 5.16 (dd, 1H, $J_{2,3} = 9.4$ Hz, H-2), 5.10 (dd, 1H, H-4), 4.26 (dd, 1H, $J_{5,6a} = 4.9$ Hz, $J_{6a,6b} = 12.5$ Hz, H-6a), 4.13 (dd, 1H, $J_{5,6b} = 2.1$ Hz, H-6b), 3.87–3.92 (m, 1H, H-5), 3.41–3.66 (m, 2H, CH_2N), 2.92 (dd, 2H, CH_2S), 2.16–2.25 (m, 2H, CCH_2C), 2.01, 2.04, 2.05, 2.08 (4s, 12H, $4 \times COCH_3$) ppm; ^{13}C NMR: d, 197.03, 170.73, 170.43, 169.89, 169.81, 87.74, 74.52, 72.91, 68.77, 68.33, 61.99, 44.29, 31.87, 22.71, 20.96, 20.86, 20.76 ($\times$2) ppm.

General procedure for the synthesis of 4b, 5b, 6b, and 7b. KOH (4.2 mmol) was added to a solution of **9, 10, 12**, or **13** (4.2 mmol) in a distilled acetone. The reaction mixture was refluxed at 60°C for 3 hr, then concentrated in vacuo and dried to afford the corresponding potassium salts as white solids, which were sufficiently pure to be used in subsequent applications. A potassium salt (4.5 mmol) and 18-crown-6 (0.45 mmol) were added to a stirred solution of 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranosyl bromide (**16**, 3.0 mmol) in dry acetone or MeCN (20 mL). The reaction mixture was stirred under argon for 1 hr at rt. Upon completion, the mixture was diluted with toluene (20 mL) and washed with water (10 mL), 1% aq. NaOH (10 mL), and water (3×10 mL), and the organic phase was separated, dried, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/toluene elution) to afford a corresponding thioimidate.

4,5-Dihydrooxazol-2-yl 2,3,4,6-tetra-O-benzoyl-1-thio-β-D-glucopyranoside (4b) was obtained as white crystals in 23% yield. Analytical data for **4b**: $R_f = 0.41$ (acetone-toluene, 1/4, v/v); m.p. +82–84°C (CH_2Cl_2/ether/hexane); $[\alpha]_D^{24}$ +48.1° (c = 1.0, $CHCl_3$); UV: $\lambda_{max} = 274$ nm; ^{1}H NMR: δ, 7.20–8.00 (m, 20H, aromatic), 5.93 (dd, 1H, $J_{3,4} = 9.2$ Hz, H-3), 5.56–5.69 (m, 3H, H-1, 3, 4), 4.56 (dd, 1H, $J_{5,6a} = 2.8$ Hz, $J_{6a,6b} = 12.3$ Hz, H-6a), 4.43 (dd, 1H, $J_{5,6b} = 5.2$ Hz, H-6b), 4.13–4.28 (m, 3H, H-5, CH_2O), 3.74 (m, 2H, CH_2N) ppm; ^{13}C NMR: δ, 166.00, 165.63, 165.13, 165.06, 162.58, 133.43, 133.24, 133.03, 129.91 ($\times$2), 129.76 ($\times$4), 129.66 ($\times$3), 128.97, 128.64 ($\times$2), 128.37 ($\times$2), 128.33 ($\times$2), 128.25, 128.17 ($\times$2), 125.24, 85.52, 73.96, 70.23, 69.34, 69.19, 62.93, 54.58, 29.64, 21.39 ppm; HR-FAB MS $[M + Na]^+$ calcd. for $C_{37}H_{31}NNaO_{10}S$ 704.1566, found 704.1573.

5,6-Dihydro-4H-1,3-oxazin-2-yl 2,3,4,6-tetra-O-benzoyl-1-thio-β-D-glucopyranoside (5b) was obtained as a colorless film in 12% yield. Analytical data for **5b**: $R_f = 0.40$ (acetone-toluene,/9, v/v); $[\alpha]_D^{25}$ +25.1° (c = 0.25, $CHCl_3$); UV: $\lambda_{max} = 274$ nm; ^{1}H NMR: δ, 7.10–8.00 (m, 20H, aromatic), 5.90 (dd, 1H, $J_{2,3} = 8.7$ Hz, H-2), 5.55–5.64 (m, 3H, H-1, 3, 4), 4.54 (dd, 1H, $J_{5,6a} = 2.9$ Hz, $J_{6a,6b} = 12.2$ Hz, H-6a), 4.40 (dd, 1H, $J_{5,6b} = 5.3$ Hz, H-6b), 4.04–4.21 (m, 3H, H-5, CH_2O), 3.33 (m, 2H, CH_2N), 1.76 (m, 2H, CCH_2C) ppm; ^{13}C NMR: δ, 166.30, 165.91, 165.41, 165.34, 133.72, 133.53, 133.32, 130.22, 130.07 (×2), 130.05 (×4), 130.01 (×3), 129.96, 129.94 (×2), 129.01 (×2), 128.93 (×2), 128.71, 128.66, 128.62 (×2), 128.54, 87.74, 83.81, 75.05, 70.49 (×2), 69.94, 63.22, 54.88, 29.93 ppm; HR-FAB MS $[M + Na]^+$ calcd. for $C_{37}H_{31}NNaO_{10}S$ 704.1566, found 704.1573.

Benzothiazol-2-yl 2,3,4,6-tetra-O-benzoyl-1-thio-β-D-glucopyranoside (6b) was obtained as cream crystals in 88% yield. Analytical data for **6b**: $R_f = 0.49$ (ethyl acetate-hexanes, 2/3, v/v); m.p. +212–214°C (CH_2Cl_2/ether/hexane); $[\alpha]_D^{25}$ +58.6° (c = 1.03, CH_2C_{l2}); UV: $\lambda_{max} = 276$ nm; ^{1}H NMR: δ, 7.20–8.10 (m, 24H, aromatic), 6.08 (dd, 1H, $J_{3,4} = 9.4$ Hz, H-3), 5.95 (d, 1H, $J_{1,2} = 10.2$ Hz, H-1), 5.71–5.79 (m, 2H, $J_{2,3} = 9.4$ Hz, H-2, 4), 4.71 (dd, 1H, $J_{5,6a} = 2.1$ Hz, $J_{6a,6b} = 11.8$ Hz, H-6a), 4.42–4.55 (m, 2H, H-5, 6b) ppm; ^{13}C NMR: δ, 166.49, 166.11, 165.66, 165.62, 62.57, 153.05, 134.00, 133.95 (×2), 133.77 (×2), 133.49 (×2), 130.38 (×2), 130.31 (×2), 130.18 (×2), 130.02, 129.04 (×2), 129.02 (×2), 128.98 (×3), 128.89 (×2), 128.79 (×2), 128.75, 126.67, 125.21, 122.64, 121.36, 84.62, 74.30, 70.81, 69.76, 63.64 ppm; HR-FAB MS $[M + Na]^+$ calcd. for $C_{41}H_{31}NNaO_9S_2$ 768.1338, found 768.1323.

5,6-Dihydro-4H-1,3-thiazin-2-yl 2,3,4,6-tetra -O-benzoyl-1-thio-β-D-glucopyranoside (7b) was prepared from **16** in 18% yield. Alternatively it was prepared from **7a** as follows: 0.1 N solution of NaOMe in MeOH was added dropwise until pH 9 to the solution of **7a** (0.4 g, 0.863 mmol) in MeOH (20 mL). The reaction mixture was kept for 3 hr at rt and then neutralized (pH 7) by the addition of Dowex (H^+). The resin was filtered off, washed with MeOH (5 × 5 mL), and the combined filtrate (35 mL) was concentrated in vacuo and dried. The stirring solution of the residual white solid (0.27 g, 0.914 mmol) in pyridine (16 mL) was cooled to 0°C and benzoyl chloride (1.05 mL, 9.146 mmol) was added dropwise. The temperature was allowed to gradually increase and the reaction mixture was left stirring for 16 h at rt. Upon completion, the reaction was quenched by slow dropwise addition of MeOH (5 mL), concentrated in vacuo and then coevaporated with toluene (3 × 10 mL). The residue was then diluted with CH_2Cl_2 (35 mL) and washed with water (20 mL); the combined filtrate was then washed with $NaHCO_3$ (20 mL), water (20 mL), 1 N aqueous HCl (20 mL), and water (3 × 20 mL); and the organic layer was separated, dried, and concentrated in vacuo. The

residue was purified by silica gel column chromatography (ethyl acetate/toluene) followed by crystallization from CH_2Cl_2/ether/hexane to afford **7b** as cream crystals in 72% yield. Analytical data for **7b**: $R_f = 0.49$ (acetone-toluene,1/9, v/v); m.p. +93–95°C (CH_2Cl_2/ether/hexane); $[\alpha]_D^{25}$ +78.6° (c = 1.03, $CHCl_3$); UV: $\lambda_{max} = 276$ nm; ^{1}H NMR: δ, 7.10–8.00 (m, 20H, aromatic), 5.93 (dd, 1H, $J_{3,4} = 9.4$ Hz, H-3), 5.85 (d, H, $J_{1,2} = 10.4$ Hz, H-1), 5.53–5.65 (m, 2H, $J_{2,3} = 9.4$ Hz, H-2, 4), 4.56 (dd, 1H, $J_{5,6a} = 4.6$ Hz, $J_{6a,6b} = 12.2$ Hz, H-6a), 4.41 (dd, 1H, $J_{5,6b} = 5.6$ Hz, H-6b), 4.20 (m, 1H, H-5) ppm; ^{13}C NMR: δ, 166.52, 166.18, 165.62, 152.89, 134.07, 133.95, 133.87, 133.68, 130.64 (×2), 130.48 (×3), 130.46 (×3), 130.37 (×2), 129.69, 129.45, 129.05 (×2), 128.94 (×3), 128.72 (×4), 81.26, 76.85, 20 74.72, 70.37, 69.99, 63.69, 48.94, 28.07, 20.67 ppm; HR-FAB MS $[M + Na]^+$ calcd. for $C_{38}H_{33}NNaO_9S2$ 734.1494, found 734.1481.

Synthesis of the disaccharide 20. General AgOTf-promoted glycosylation procedure. A mixture a glycosyl donor (0.11 mmol), **19** (0.10 mmol), and freshly activated molecular sieves (3Å, 200 mg) in $(ClCH_2)_2$ (2 mL) was stirred under an atmosphere of argon for 1.5 hr. Freshly conditioned AgOTf (0.22 mmol) was added and the reaction mixture was stirred for 5 min to 16 hr (see Table 2) at rt, then diluted with CH_2Cl_2; the solid was filtered off and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with 20% aq. $NaHCO_3$ (15 mL) and water (3 × 10 mL), and the organic phase was separated, dried, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate-hexane gradient elution) to afford **20**, analytical data for which were essentially the same as those previously reported.[22]

General MeOTf-promoted glycosylation procedure. A mixture the glycosyl donor (0.11 mmol), **19** (0.10 mmol), and freshly activated molecular sieves (3Å, 200 mg) in $(ClCH_2)_2$ (2 mL) was stirred under an atmosphere of argon for 1.5 hr. MeOTf (0.22 mmol) was added and the reaction mixture was stirred for 1 to 16 h (see Table 2) at rt, then diluted with CH_2Cl_2; the solid was filtered off and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with 20% aq. $NaHCO_3$ (15 mL) and water (3 × 10 mL), and the organic phase was separated, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate-hexane gradient elution).

Comparative hydrolytic stability studies. Synthesis of 21. General NIS/TfOH-promoted leaving group hydrolysis. A mixture of **2a, 3a, 4a, 6a**, **7a**, **22**, or **23** (0.10 mmol), N-iodosuccinimide (0.20 mmol), and TfOH (0.01–0.02 mmol) in CH_2Cl_2-water (95/5 v/v, 2.5 mL) was stirred for 2 to 48 h. The reaction mixture was then diluted with CH_2Cl_2 (25 mL) and

washed with 20% aq. $NaHSO_3$ (15 mL), and water (3 × 10 mL), and the organic phase was separated, dried, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate-hexane gradient elution) to afford **21**, analytical data for which was essentially the same as those previously reported.[28]

General NBS-promoted leaving group hydrolysis. A mixture of **2a, 3a, 4a, 6a**, **7a**, **22**, or **23** (0.10 mmol) and N-bromosuccinimide (0.20 mmol) in acetone-water (9/1 v/v, 2.5 mL) was stirred for 5 min to 48 hr. The reaction mixture was then diluted with CH_2Cl_2 (25 mL) and washed with 20% aq. $NaHCO_3$ (15 mL) and water (3 × 10 mL), and the organic phase was separated, dried, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate- hexane gradient elution) to afford **21**.

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