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Glycosyl alkoxythioimidates as building blocks for glycosylation: a reactivity study

Sneha C. Ranade, Alexei V. Demchenko *

Department of Chemistry and Biochemistry, University of Missouri – St. Louis, St. Louis, MO 63121, USA

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ABSTRACT

Structural modifications of the leaving group of S-glycosyl *O*-methyl phenylcarbamothioates (SNea) involving change of substituents that express different electronic effects led to a better understanding of how the reactivity of these glycosyl donors can be modified by changing the structure of their leaving groups. Mechanistic studies involving the isolation of departed aglycones were indicative of the direct activation of both *p*-methoxy-SNea and *p*-nitro-SNea leaving groups via the anomeric sulfur rather than the remote nitrogen atom. The presence of an electron donating substituent (*p*-methoxy) has a strong effect on the nucleophilicity of the sulfur atom that becomes more susceptible toward the attack of thiophilic reagents, in particular. This key observation allowed to differentiate the reactivity levels of *p*-methoxy-SNea versus *p*-nitro-SNea and even unmodified SNea leaving groups. The reactivity difference observed in the series of SNea leaving groups is sufficient to be exploited in expeditious oligosaccharide synthesis via selective activation strategies.

1. Introduction

Structural complexity of carbohydrates makes these natural compounds attractive and challenging targets for many synthetic chemists. In spite of the abundance of complex carbohydrates in nature, their isolation and purification are cumbersome. Chemical and enzymatic syntheses are also challenging, and many past and ongoing research efforts have been directed to improve synthetic capabilities to obtain oligosaccharides with high efficiency and yields. The outcome of chemical glycosylation reactions is largely dependent on a variety of factors that include the structure of glycosyl donor, glycosyl acceptor, activator, solvent, temperature, etc.[1–4] Among these, different aspects and components of the glycosyl donor, such as the structure and the mode of activation of the leaving group, the nature of protecting groups, conformation, configuration, etc. all may have a profound effect on stability and reactivity of glycosyl donors and often affect the outcome of glycosylation.

The effect of neighboring protecting groups on reactivity of glycosyl donors and stereoselectivity of their glycosidation has been noticed long time ago.[5] A dedicated study by Fraser-Reid and co-workers generalized the accumulated knowledge and served as the basis for the development of a so-called 'armed–disarmed' strategy for oligosaccharide synthesis.[6] The armed–disarmed strategy has been exploited in a number of ways, and a variety of chemoselective approaches, many of which are based on the previously underappreciated effect of remote protecting groups, have emerged as its extension. These more recent adjustments of the classic armed–disarmed strategy include torsional deactivation,[7–9] tunable reactivity,[10] programmable synthesis,[11] deactivation by a single remote moiety,[12,13] inverse armed–disarmed,[14,15] conformationally superarmed,[16–19] electronically superarmed/superdisarmed,[20–23] and other approaches.[24]

While the electronic effect of both neighboring and remote protecting groups on the reactivity of glycosyl donors has been investigated in a variety of ways,[25–27] the electronic effects originated from the leaving group are much less explored beyond a series of glycosyl halides.[28,29] Roy and co-workers were among the first to observe the differential reactivity of electronically activated *p*-(*N*-acetamido)phenyl thioglycoside versus electronically deactivated *p*-nitrophenyl counterpart. This discovery led to the development of a practical and efficient strategy for oligosaccharide synthesis termed active-latent strategy.[30] The active-latent concept was further extended by Fraser-Reid,[31] Boons,[32] Kim,[33,34] and others,[35–37] but, to the best of our knowledge, only Roy's original approach relies on the reactivity differentiation by electronic properties of the leaving group.

Along similar lines, Kahne et al. demonstrated the difference in reactivity depending on the nature of the substituent at the *para*-position of phenyl sulfoxides.[38] In this study, the reactivity was

* Corresponding author. Tel.: +1 3145167995.
E-mail address: demchenkoa@umsl.edu (A.V. Demchenko).

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observed to decrease in the following order: OMe > H > NO_2. The difference in the reactivity was utilized for the synthesis of Ciclamycin 0 trisaccharide via selective two-step activation in one pot. Similar observations of electronic effect originated from various substituents on the leaving group have been reported by van Boom and co-workers,[39] Hanessian et al.,[40] and our group.[41]

As a part of the ongoing research effort to develop new glycosyl thioimidates as versatile building blocks for chemical[35,36] and enzymatic[42] glycosylation,[43,44] previously we introduced glycosyl alkoxythioimidate donor (SNea, Fig. 1).[45] This leaving group was specifically designed as the bridging intermediate leaving group between glycosyl thiocyanates[46,47] and S-benzoxazolyl (SBox) thioimidates.[48,49] Our anticipation was that the activation profile of the SNea leaving group would be similar to that of both thiocyanates and SBox leaving groups. We were intrigued, however, by a significant discrepancy of results obtained with the SNea donor and the structurally similar SBox donor. The activation profile seemed so drastically different that this even allowed us to develop an orthogonal-like activation[50] of building blocks equipped with SNea (rapidly activated with copper(II) triflate) and SBox (rapidly activated with methyl triflate) leaving groups.[45]

On the other hand, comparative studies between glycosyl thiocyanate and glycosyl SNea donors showed that the activation conditions for these two glycosyl donors are similar.[45] Earlier mechanistic investigations indicated that the SBox leaving group tends to be activated via the anomeric sulfur[51] (direct activation pathway similar to that of alkyl/aryl thioglycosides)[52] regardless of the activation condition chosen. Relying on the similarity of reactivity of SNea and SCN leaving groups we hypothesized that glycosyl SNea donors may follow the remote activation pathway as seen in case of glycosyl thiocyanates (Fig. 1).[46,47] Reported herein is a dedicated study involving a series of building blocks modified with electron-withdrawing and electron-donating substituents at the phenyl group of SNea leaving group that was designed to test this hypothesis. We postulated that the presence of these substituents would have a significant effect on the nucleophilicity of the nitrogen atom. Hence, if the activation of the SNea moiety was indeed taking place via the remote nitrogen, such modifications would significantly impact the reactivity of the respective alkoxythioimidoyl leaving group. We also thought that the effect of such modification on the nucleophilicity of the anomeric sulfur atom (direct activation) would be somewhat weaker due to the remoteness of these two centers.

2. Results and discussion

With these considerations in mind, and to test the hypothesis of the anticipated remote activation of the SNea leaving group via the nitrogen atom, we obtained a series of glycosyl donors: standard SNea donor (**1**),[45] *p*-methoxy-SNea donor (**2**), and *p*-nitro-SNea donor (**3**, Table 1) using earlier established protocols.[45] In order to test the relative reactivity of a new series of glycosyl donors in glycosylation we chose a range of metal triflates that showed excellent results with glycosyl thioimidates and SNea donors in our previous studies.[44] Herein, we tested copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$), bismuth(III) trifluoromethanesulfonate ($Bi(OTf)_3$), and silver(I) trifluoromethanesulfonate (AgOTf). Glycosidation reactions of donor **1** with acceptor **4**[53] in the presence of $Cu(OTf)_2$ or $Bi(OTf)_3$ as promoters were very smooth and completed within 1 h. As a result, disaccharide **5**[54] was isolated in 91% and 95% yields, respectively (entries 1 and 2, Table 1). AgOTf-promoted glycosylation reaction was even faster (30 min) and disaccharide **5** was obtained in 95% yield (entry 3, Table 1).

Encouraged by this strong performance of SNea donor **1**, we turned our attention to investigating the modified donors. When *p*-methoxy-SNea donor **2** was reacted with glycosyl acceptor **4** in the presence of $Cu(OTf)_2$, a similar result to that obtained with standard SNea donor **1** was achieved. The glycosidation required a slightly longer time (2 h for **2** vs 1 h for **1**) and afforded disaccharide **5** in 86% yield (entry 4, Table 1). In case of $Bi(OTf)_3$, the reaction was much faster and completed within 10 min (1 h for **1**) to give disaccharide **5** in 93% yield (entry 5, Table 1). AgOTf-promoted reaction gave 97% of disaccharide **5** in 30 min, which was practically the same reaction time as that recorded for SNea donor **1**. Resultantly, disaccharide **5** was isolated in 97% yield (entry 6, Table 1). As a whole, these comparative glycosylations showed that both SNea **1** and *p*-methoxy-SNea **2** thiocarbamates are excellent glycosyl donors for chemical glycosylation. *p*-Methoxy-SNea derivative **2** showed slightly decreased reactivity in the presence of $Cu(OTf)_2$ and was significantly more reactive in the presence of $Bi(OTf)_3$.

In case of the reaction of *p*-nitro-SNea donor **3** with glycosyl acceptor **4** in the presence of $Cu(OTf)_2$ disaccharide **5** was formed in 90% yield showing somewhat insignificant deviation in reactivity (entry 7, Table 1). The reaction of *p*-nitro-SNea donor **3** with acceptor **4** in the presence of $Bi(OTf)_3$ gave disaccharide **5** in 71% yield (entry 8) in 1 h, similar to that of glycosidation of the standard SNea donor **1**. Interestingly, donor **3** reacted very slowly in the presence of AgOTf, and even after 24 h only trace amount of disaccharide **5** was obtained (entry 9).

Since the results of activations of different leaving groups with metal triflates were somewhat inconclusive, we decided to deepen this study by looking into other activation strategies. In addition, in order to gain the direct proof of the mode of activation, it would be desirable to isolate and establish the structure of the departed aglycones.[55] Although we had had some prior success,[56] elucidation of exact mode of activation using metal-based promoters can be difficult. This is because upon departure, thioimidoyl

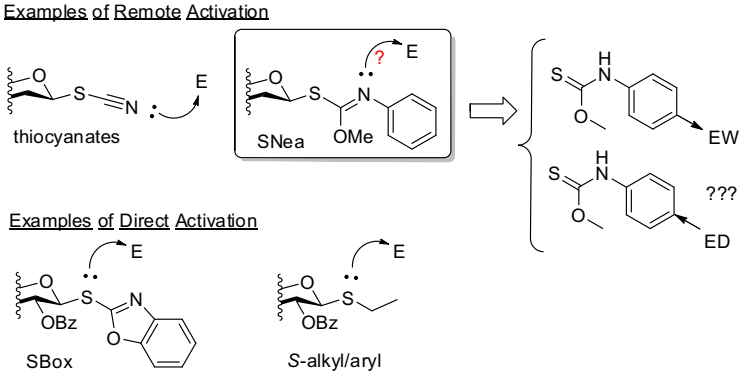
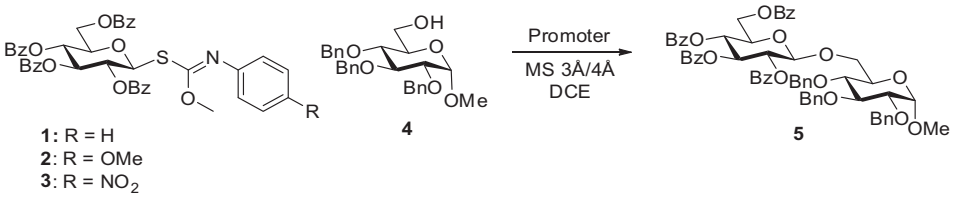
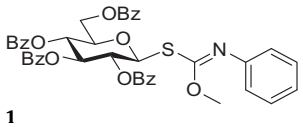
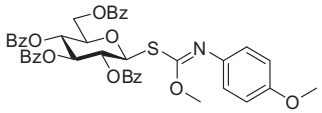
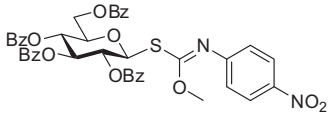


Figure 1. Direct versus remote activation of leaving groups and possible electronic effects.

Table 1
Comparative glycosidations of glycosyl donors **1**–**3** with glycosyl acceptor **4** in the presence of various metal-based promoters



1: R = H
2: R = OMe
3: R = NO_2

Entry	Glycosyl donor	Promoter (3 equiv)	Time	Yield (%) of **5**
1	 **1**	$Cu(OTf)_2$	1 h	91
2	**1**	$Bi(OTf)_3$	1 h	95
3	**1**	AgOTf	30 min	95
4	 **2**	$Cu(OTf)_2$	2 h	86
5	**2**	$Bi(OTf)_3$	10 min	93
6	**2**	AgOTf	30 min	97
7	 **3**	$Cu(OTf)_2$	2 h	90
8	**3**	$Bi(OTf)_3$	2 h	71
9	**3**	AgOTf	24 h	<10

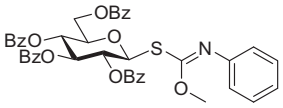
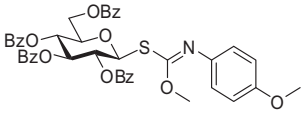
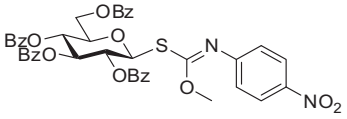
leaving groups often result in the formation of metal inclusion polymers (—M—S—C═N—)$_n$, which are very cumbersome to characterize.[56] Having these considerations in mind, while turning our attention toward studying alternative activation pathways we were particularly interested in those pathways that would allow for gaining a reliable insight into the activation mode of alkoxythioimidates. Hence, promoters used for this extended study included methyl trifluoromethanesulfonate (MeOTf), *N*-iodosuccinimide/trifluoromethanesulfonic acid (NIS/TfOH), and trimethylsilyl trifluoromethanesulfonate (TMSOTf). These reaction conditions were proven successful for determining activation pathways of SBox (MeOTf),[56] STaz (MeOTf, BnBr),[57] SBiz (BnBr),[41] SEt (MeOTf),[52] and ortho-allylphenyl (TMSOTf and NIS/TfOH)[58] leaving groups. We also included molecular iodine (I_2) into the list of promoters to be tested due to our fruitful experience with differentiating armed versus super armed levels of reactivity of various thioglycosides and thioimidates using these reaction conditions.[23]

With this new set of promoters, we were bound to improve our understanding of the activation modes and relative reactivities of glycosyl donors **1**–**3**. The progress of all side-by-side experiments was monitored by TLC, and the reactions were quenched as soon as the acceptor has been consumed. To maintain standard comparison between different glycosyl donors, the incomplete reactions, as judged by TLC, were stopped after 24 h. Previously, we have shown that glycosyl SNea donor **1** reacts quite sluggishly in the presence of 3 equiv of MeOTf.[45] Indeed, reaction of donor **1** with glycosyl acceptor **4** was practically ineffective, and even after 24 h afforded disaccharide **5** in only 12% yield (entry 1, Table 2). The activation of SNea donor **1** was also ineffective in the presence of iodine, wherein no traces of the anticipated product **5** were detected (entry 2). SNea donor **1** was much more reactive in the presence of NIS/TfOH or TMSOTf; these reactions completed in 3–3.5 h. However, disaccharide **5** was formed in modest yields of 45% and 65%, respectively, due to high rates of competing hydrolysis, as judged by accumulation of the corresponding hemiacetal derivative (entries 3 and 4, Table 2). Thus, none of these non-metallic electrophilic promoters offered a reliable activation pathway for glycosidation of SNea donor **1** at the ambient temperature. Lowering the reaction temperature allowed to control the competing hydrolysis and afforded disaccharide **5** in a higher yield. This result, however, cannot be compared with all other experiments performed at room temperature and, hence, is not listed.

Encouragingly, *p*-methoxy-SNea donor **2** was significantly more reactive than its non-substituted SNea counterpart **1**. Both MeOTf and molecular iodine, which were practically ineffective with donor **1**, promoted glycosidations of glycosyl donor **2** with acceptor **4**. These reactions were still rather slow and incomplete even after 24 h, but disaccharide **5** was obtained in 62% and 43% yields, respectively (entries 5 and 6). NIS/TfOH promoted glycosidation of **2** was completed in 30 min, but again yielded disaccharide **5** in a modest yield of 48% due to the competing hydrolysis (entry 7). Similar reaction time was recorded for glycosidation of donor **2** with acceptor **4** in the presence of TMSOTf, but this reaction was much cleaner and afforded disaccharide **5** in 90% yield (entry 8).

Similar to our earlier observations made with metal triflates, *p*-methoxy donor **2** showed over-all higher reactivity in comparison to that of its unmodified SNea counterpart **1** in the presence of non-metallic promoters. While in a series of metal triflates, only $Bi(OTf)_3$ showed a significant level of differentiation between the reactivities of donors **1** and **2**, practically every non-metallic electrophilic promoter was much more effective with *p*-methoxy-SNea donor **2**, as surveyed in Table 2.

Table 2
Comparative glycosidations of donors **1**–**3** with acceptor **4** in the presence of various electrophilic and thiophilic promoters

Entry	Donor	Promoter[a]	Time	Yield (%) of **5**
1		MeOTf	24 h	12
	1			
2	**1**	I_2	24 h	NR[b]
3	**1**	NIS/TfOH	3.5 h	45
4	**1**	TMSOTf	3 h	65
5		MeOTf	24 h	62
	2			
6	**2**	I_2	24 h	43
7	**2**	NIS/TfOH	30 min	48
8	**2**	TMSOTf	30 min	95
9		MeOTf	24 h	10
	3			
10	**3**	I_2	24 h	<10
11	**3**	NIS/TfOH	15 min	85
12	**3**	TMSOTf	1 h	85

[a] 2 equiv of TMSOTf and 3 equiv of all other promoters have been used.
[b] NR: no reaction.

Having completed the comparison of donors **1** and **2**, we turned our attention to studying *p*-nitro-SNea donor **3**. When donor **3** reacted with acceptor **4** in the presence of MeOTf, the reaction was found to be very sluggish, similar to that observed with SNea donor **1**. As a result, disaccharide **5** was isolated in a very modest yield of 10% (entry 9, Table 2). A similar observation was made in case of molecular iodine; the reaction was very slow and gave only traces of disaccharide **5**, even after 24 h (entry 10, Table 2). However, in case of NIS/TfOH, the reaction proceeded rather fast and completed in 15 min affording disaccharide **5** in 85% yield (entry 11, Table 2). A similar result was obtained in the TMSOTf-promoted glycosylation that required 1 h to afford disaccharide **5** in 85% yield (entry 12, Table 2).

From results obtained during the comparative study it is clear that a notable difference in reactivity can be achieved upon modification of the structure of the leaving group. Next, we were bound to extend results obtained in glycosylations promoted with MeOTf to investigating the mechanistic profile of this reaction. A range of experiments were performed to isolate the departed aglycones, the structure of which would help to determine the activation mode of these leaving groups during the glycosylation reaction. For this mechanistic study we obtained acetylated *p*-methoxy-SNea (**6**) and *p*-nitro-SNea (**7**) donors, which were set to react with isopropanol as the glycosyl acceptor in the presence of MeOTf (Scheme 1). These reactions were monitored by TLC and upon disappearance of the glycosyl donor, the reaction mixture was concentrated in vacuo. After that, all components of the reaction have been isolated by column chromatography. Glycosidation of *p*-methoxy-SNea donor **6** afforded isopropyl glycoside **8**;[59,60] also isolated was the departed aglycone that was found to be methylated at sulfur, *O*,*S*-dimethyl (4-methoxyphenyl)carbonimidothioate (**9**). Glycosidation of *p*-nitro-SNea donor **7** afforded isopropyl glycoside **8**. Also isolated was the departed aglycone that was found to be also methylated at sulfur, *S*-methyl (4-nitrophenyl)carbamothioate (**10**). The identity of compounds **9** and **10** was proven by spectral methods. It should be noted that methylation is irreversible as it was determined over the course of our earlier study by performing reaction monitoring by HPLC.[57] Hence, the methylation site should be indicative of the mode of activation of the leaving group.

As aforementioned, it was initially hypothesized that the activation of the SNea leaving group takes place via the remote activation pathway. If this was the case, the presence of electron-donating or electron-withdrawing *p*-phenyl substituents would have a very strong effect on the nucleophilicity of the nitrogen atom and hence affect the overall reactivity of the leaving group. However, our mechanistic study showed that both *p*-methoxy-SNea and *p*-nitro-SNea leaving groups seem to undergo the direct activation pathway. Since some difference in reactivity was still observed, this result indicates that the presence of an electron-donating or electron-withdrawing substituent at the remote *p*-position of the *N*-phenyl ring can also affect the nucleophilicity of the anomeric sulfur. Consequently, due to the presence of the distant electron donating substituent, *p*-methoxy-SNea leaving group is activated more efficiently in comparison with its SNea and *p*-nitro-SNea counterparts. To test the viability of this key observation and gain a more reliable evidence of differential reactivity of glycosyl donors **2** and **3**, a competitive glycosylation reaction depicted in Scheme 2 was planned.

In this experiment, glycosyl donors **2** and **3** were set to compete against each other for a limited amount of glycosyl acceptor **4**, a protocol that became standard in our laboratory to perform direct comparison of reactivity levels of different building blocks.[21,45,58] Since the greatest degree of differentiation was achieved with AgOTf as the promoter (Table 1), we chose to apply these reaction conditions. Upon addition of AgOTf, the reaction between glycosyl donors **2** and **3** and acceptor **4** proceeded smoothly to give disaccharide **5** in 86% yield (Scheme 2). Also recovered was the unreacted glycosyl donor **3**, which was isolated in 83% yield. These results confirm that the *p*-methoxy-SNea donor **2** is indeed significantly more reactive in the presence of AgOTf than its *p*-nitro-SNea counterpart **3**.

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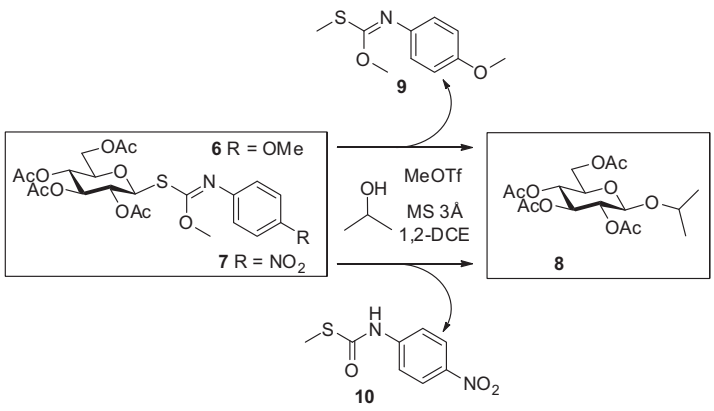
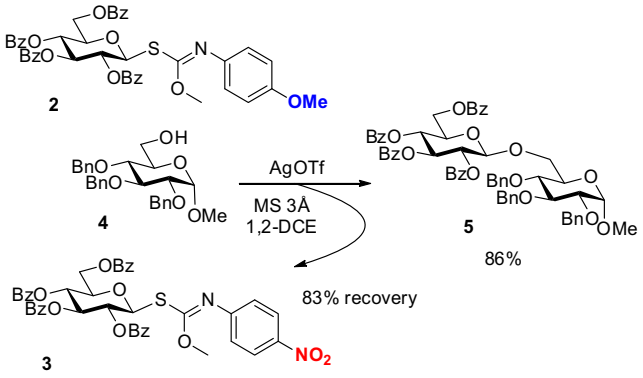


Scheme 1. Mechanism of activation of alkoxythioimidates **6** and **7** with MeOTf.



Scheme 2. Competitive glycosylation involving two glycosyl donors with different reactivities **2** and **3**.

3. Conclusions

Structural modifications of SNea leaving group involving change of substituents that express different electronic effects led to a better understanding of how the reactivity of glycosyl donors can be modified by changing the structure of their leaving groups. Mechanistic studies involving the isolation of departed aglycones were indicative of the direct activation of both *p*-methoxy-SNea and *p*-nitro-SNea leaving groups via the anomeric sulfur. The presence of an electron donating substituent (*p*-methoxy) has a noticeable effect on the nucleophilicity of the distant sulfur atom that becomes more susceptible toward the attack of thiophilic reagents. This key observation allowed to differentiate the reactivity levels of *p*-methoxy-SNea versus *p*-nitro-SNea and even unmodified SNea leaving groups. The reactivity difference observed in the series of SNea leaving groups is sufficient to be exploited in expeditious oligosaccharide synthesis via selective activation strategies.[50]

4. Experimental section

4.1. General remarks

The reactions were monitored by TLC on Kieselgel 60 F_{254} (EM Science). Detection of compounds was achieved using UV light and by charring with 10% sulfuric acid in methanol. Purification by column chromatography was performed on silica gel 60 (EM Science, 70–230 mesh). Removal of solvents was achieved in vacuo at <40 °C using rotary evaporators. CH_2Cl_2 and $ClCH_2CH_2Cl$ were distilled from CaH_2 directly before using for the reactions. Methanol was dried by refluxing with magnesium methoxide, distilled, and stored under argon. Pyridine and acetonitrile were dried by refluxing with CaH_2, distilled, and stored over molecular sieves (3 Å). Molecular sieves (3 Å and 4 Å) used for reactions were crushed and activated in vacuo at 390 °C during 8 h at first and then for 2–3 h at 390 °C prior to application. AgOTf was co-evaporated with toluene (3 × 10 mL) and dried in vacuo for 2–3 h prior to using in reactions. Optical rotations were measured using 'Jasco P-1020' polarimeter. ^{1}H NMR spectra were recorded in $CDCl_3$ at 300 MHz; ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 MHz (Bruker Avance), unless noted otherwise. HRMS determinations were made with the use of JOEL MStation (JMS-700) Mass spectrometer, matrix *m*-nitrobenzyl alcohol, and with NaI as necessary.

4.2. *O*-Methyl (4-methoxyphenyl)carbamothioate

A 1 M solution of NaOMe in methanol (9.1 mL) was added to the flask containing *p*-methoxyphenyl isothiocyanate (0.8 mL, 6.05 mmol) and the resulting mixture was stirred for 15 min at rt. Then, concd aq. HCl (~5 mL) was added till the pH reaches ~4–5. The resulting precipitate was filtered off and rinsed successively with methanol. The combined filtrate (~100 mL) was concentrated in vacuo. The residue containing the title compound was used directly in subsequent transformations. Analytical data for the title compound: R_f = 0.57 (ethyl acetate/hexanes, 3:7, v/v); ^{1}H NMR: δ, 3.81 (s, 1H, OCH_3), 4.12 (s, 1H, OCH_3), 6.87 (dd, 2H, aromatic), 7.16 (dd, 2H, aromatic), 7.41 (br. s, 1H, NH) ppm; ^{13}C NMR: δ, 55.7, 58.9, 114.4 (×2), 124.2, 126.2, 130.0, 157.6, 189.7 ppm; HR-FAB MS $[M]^+$ calcd for $C_9H_{11}NO_2S^+$ 197.0510, found 197.0510.

4.3. *O*-Methyl (4-nitrophenyl)carbamothioate

A 1 M solution of NaOMe in methanol (16.5 mL) was added to the flask containing *p*-nitrophenyl isothiocyanate (2.0 g, 11.1 mmol) and the resulting mixture was stirred for 15 min at rt. Then, concd aq. HCl (~5 mL) was added till the pH reaches ~4–5. The resulting precipitate was filtered off and rinsed successively with methanol. The combined filtrate (~100 mL) was concentrated in vacuo. The residue containing the title compound was used directly in subsequent transformations. The analytical data of the title compound were essentially the same as described previously.[61]

4.4. *S*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl) *O*-methyl (4-methoxyphenyl)carbonimidothioate (2)

O-Methyl (4-methoxyphenyl)carbamothioate (1.1 g, 5.69 mmol) and KOH (212 mg, 3.79 mmol) were added to a

solution of 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide[62] (2.5 g, 3.79 mmol) in dry acetonitrile (30 mL) and the resulting mixture was stirred for 2.5 h at rt. After that, the solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~100 mL) was washed with satd aq. $NaHCO_3$ (15 mL) and water (3 × 15 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–toluene gradient elution) to afford the title compound in 22% yield (650 mg) as a white foam. Analytical data for **2**: R_f = 0.6 (ethyl acetate/toluene, 1:9, v/v); $[\alpha]_D^{30}$ −7.4 (*c* 1, $CHCl_3$); ^{1}H NMR: δ, 3.76 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.25 (m, 1H, $J_{5,6a}$ = 2.9 Hz, $J_{5,6b}$ = 5.7 Hz, H-5), 4.48 (dd, 1H, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.64 (dd, 1H, H-6b), 5.53 (dd, 1H, $J_{2,3}$ = 9.9 Hz, H-2), 5.61 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 5.64 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.94 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 6.64–7.91 (m, 24H, aromatic) ppm; ^{13}C NMR: δ, 55.4, 56.6, 63.2, 69.4, 70.5, 74.1, 77.2, 81.7, 144.3 (×2), 122.3 (×2), 128.3 (×2), 128.4 (×6), 128.5 (×2), 128.7, 128.9, 129.6, 129.8 (×3), 129.9 (×3), 133.2, 133.3, 133.4, 133.5, 139.3, 154.4, 156.4, 164.9, 165.1, 165.7, 166.1 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{43}H_{37}NO_{11}SNa^+$ 798.1985, found 798.1977.

4.5. *S*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl) *O*-methyl (4-nitrophenyl)carbonimidothioate (3)

Sodium salt of *O*-methyl (4-nitrophenyl)carbamothioate (0.426 g, 1.82 mmol) and 15-crown-5 (30.4 μL, 0.15 mmol) were added to a solution of 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide[62] (1.0 g, 1.52 mmol) in dry acetonitrile (10.0 mL) and the resulting reaction mixture was stirred for 45 min at rt. After that, the solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~50 mL) was washed with satd aq. $NaHCO_3$ (10 mL) and water (3 × 10 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–toluene gradient elution) to afford the title compound in 47% yield (560 mg) as a white foam. Analytical data for **3**: R_f = 0.63 (ethyl acetate/toluene, 1:9, v/v); $[\alpha]_D^{30}$ −18.2 (*c* 1, $CHCl_3$); ^{1}H NMR: δ, 3.94 (s, 3H, OCH_3), 4.31 (m, 1H, $J_{5,6a}$ = 2.8 Hz, $J_{5,6b}$ = 5.6 Hz, H-5), 4.54 (dd, 1H, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.69 (dd, 1H, H-6b), 5.56–5.63 (m, 2H, H-1, H-2), 5.70 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 6.01 (dd, 1H, $J_{3,4}$ = 9.1 Hz, H-3), 6.83–8.10 (m, 24H, aromatic) ppm; ^{13}C NMR: δ, 57.2, 63.2, 69.4, 70.5, 74.0, 76.9, 82.0, 122.1 (×2), 125.2 (×2), 128.5 (×2), 128.6 (×3), 128.7 (x 5), 128.8 (×2), 129.7, 129.9 (×3), 130.1 (×3), 133.5, 133.6, 133.8, 133.9, 144.4, 152.6, 155.8, 165.1, 165.3, 165.9, 166.2 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{42}H_{34}N_2O_{12}SNa^+$ 813.1730, found 813.1724.

4.6. *S*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl) *O*-methyl (4-methoxyphenyl)carbonimidothioate (6)

O-Methyl (4-methoxyphenyl)carbamothioate (1.2 g, 5.84 mmol) and NaOH (194 mg, 4.87 mmol) were added to a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[63] (2.0 g, 4.87 mmol) in dry acetonitrile (30 mL) and the resulting reaction mixture was stirred for 1.5 h at rt. After that, the solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~100 mL) was washed with satd aq. $NaHCO_3$ (25 mL) and water (3 × 25 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–toluene gradient elution) to afford the title compound in 35% yield (897 mg) as a white foam. Analytical data for **6**: R_f = 0.48 (ethyl acetate/hexanes, 2:3, v/v), $[\alpha]_D^{30}$ −2.3 (*c* 1, $CHCl_3$), ^{1}H NMR: δ, 1.99, 2.01, 2.02, 2.09 (4 s, 12H, 4×$COCH_3$), 3.75 (m, 1H, $J_{5,6a}$ = 2.4 Hz, $J_{5,6b}$ = 4.8 Hz, H-5), 3.78 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.13 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.25 (dd, 1H, H-6b), 4.99 (dd, 1H, $J_{2,3}$ = 9.1 Hz, H-2), 5.03 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.20–5.27 (m, 2H, H-3, H-1), 6.74–6.84 (m, 4H, aromatic) ppm; ^{13}C NMR: δ, 20.8 (×3), 20.9, 55.6, 56.8, 62.1, 68.2, 69.9, 74.1, 76.2, 81.4, 114.5 (×2), 122.5 (×2), 139.4, 154.6, 156.6, 169.3, 169.5, 170.3, 170.8 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{23}H_{29}NO_{11}SNa^+$ 550.1359, found 550.1371.

4.7. *S*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl) *O*-methyl (4-nitrophenyl)carbonimidothioate (7)

O-Methyl (4-nitrophenyl)carbamothioate (1.2 g, 5.84 mmol) and NaOH (194 mg, 4.87 mmol) were added to a stirring solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[63] (2.0 g, 4.87 mmol) in dry acetonitrile (30 mL) and the resulting reaction mixture was stirred overnight (16 h) at rt. After that, the solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~100 mL) was washed with satd aq. $NaHCO_3$ (25 mL) and water (3 × 25 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–toluene gradient elution) to afford the title compound in 61% yield (1.6 g) as a pale-yellow foam. Analytical data for **7**: R_f = 0.61 (ethyl acetate/hexanes, 2:3, v/v) $[\alpha]_D^{30}$ 11.8 (*c* 1, $CHCl_3$), ^{1}H NMR: δ, 2.00, 2.02, 2.03, 2.10 (4s, 12H, 4× $COCH_3$), 3.78 (m, $J_{5,6a}$ = 2.3 Hz, $J_{5,6b}$ = 5.4 Hz, H-5), 4.03 (s, 3H, OCH_3), 4.14 (dd, 1H, $J_{6a,6b}$ = 12.3 Hz, H-6a), 4.25 (dd, 1H, H-6b), 5.01 (dd, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 5.05 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.25 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 5.25 (d, 1H, $J_{1,2}$ = 10.3 Hz, H-1), 6.91–6.96 (m, 2H, aromatic), 8.14–8.18 (m, 2H, aromatic) ppm; ^{13}C NMR: δ, 20.8 (×3), 20.9, 57.3, 68.1, 69.6, 73.9, 76.4, 81.5, 122.1 (×2), 125.3 (×2), 144.5, 152.6, 155.7, 169.3, 169.5, 170.3, 170.8 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{22}H_{26}N_2O_{12}SNa^+$ 565.1104, found 565.1106.

5. General glycosylation procedures

5.1. Method A—activation with $Cu(OTf)_2$

A mixture of the glycosyl donor (0.038 mmol), glycosyl acceptor (0.03 mmol), and freshly activated molecular sieves (4 Å, 90 mg) in $ClCH_2CH_2Cl$ (0.5 mL) was stirred under argon for 1.5 h at rt. $Cu(OTf)_2$ (41.3 mg, 0.114 mmol) was added and the resulting mixture was stirred for 1–2 h (see Table 1) at rt. After that, the reaction mixture was diluted with CH_2Cl_2, the solid was filtered-off, and rinsed successively with CH_2Cl_2. The combined filtrate (~25 mL) was washed with satd aq. $NaHCO_3$ (5 mL) and water (3 × 5 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–toluene gradient elution) to afford disaccharide **5**.

5.2. Method B—activation with $Bi(OTf)_3$

A mixture containing glycosyl donor (0.038 mmol), glycosyl acceptor (0.03 mmol), and freshly activated molecular sieves (3 Å, 90 mg) in $ClCH_2CH_2Cl$ (0.5 mL) was stirred under argon for 1.5 h at rt. $Bi(OTf)_3$ (74.8 mg, 0.114 mmol) was added and the reaction mixture was stirred for 10 min—2 h (see Table 1) at rt. After that, the reaction mixture was diluted with CH_2Cl_2, the solid was filtered-off, and rinsed successively with CH_2Cl_2. The combined filtrate (~25 mL) was washed with satd aq. $NaHCO_3$ (5 mL) and water (3 × 5 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/toluene gradient elution) to afford the disaccharide **5**.

5.3. Method C—activation with AgOTf

A mixture containing glycosyl donor (0.038 mmol), glycosyl acceptor (0.03 mmol), and freshly activated molecular sieves (3 Å, 90 mg) in $ClCH_2CH_2Cl$ (0.5 mL) was stirred under argon for 1.5 h at rt. Freshly activated AgOTf (29.3 mg, 0.114 mmol) was added and the reaction mixture was stirred for 30 min—24 h (see Table 1) at rt. After that, the reaction mixture was diluted with CH_2Cl_2, the solid was filtered-off, and rinsed successively with CH_2Cl_2. The filtrate (~25 mL) was washed with satd aq. $NaHCO_3$ (5 mL) and water (3 × 5 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/toluene gradient elution) to afford the disaccharide **5**.

5.4. Method D—activation with MeOTf

A mixture containing glycosyl donor (0.038 mmol), glycosyl acceptor (0.03 mmol), and freshly activated molecular sieves (3 Å, 90 mg) in $ClCH_2CH_2Cl$ (0.5 mL) was stirred under argon for 1.5 h at rt. MeOTf (14.2 μL, 0.114 mmol) was added and the reaction mixture was stirred for 24 h (see Table 1) at rt. After that, the reaction mixture was diluted with CH_2Cl_2, the solid was filtered-off, and rinsed successively with CH_2Cl_2. The combined filtrate was washed with satd aq. $NaHCO_3$ (5 mL) and water (3 × 5 mL). The organic layer was separated, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/toluene gradient elution) to afford the disaccharide **5**.

5.5. Method E—activation with molecular I_2

A mixture containing glycosyl donor (0.025 mmol), glycosyl acceptor (0.02 mmol), and freshly activated molecular sieves (3 Å, 60 mg) in $ClCH_2CH_2Cl$ (0.4 mL) was stirred under argon for 1.5 h at rt. Iodine (19.3 mg, 0.076 mmol) was added and the reaction mixture was stirred for 24 h (see Table 1) at rt. After that, the reaction mixture was diluted with CH_2Cl_2, the solid was filtered-off, and rinsed successively with CH_2Cl_2. The combined filtrate (~25 mL) was washed with 10% $Na_2S_2O_3$ (5 mL) and water (3 × 5 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/toluene gradient elution) to afford the disaccharide **5**.

5.6. Method F—activation with NIS/TfOH

A mixture containing glycosyl donor (0.025 mmol), glycosyl acceptor (0.02 mmol), and freshly activated molecular sieves (4 Å, 60 mg) in $ClCH_2CH_2Cl$ (0.4 mL) was stirred under argon for 1.5 h at rt. NIS (17.1 mg, 0.076 mmol) and TfOH (0.7 μL, 0.007 mmol) were added and the reaction mixture was stirred for 15 min—3.5 h (see Table 1) at rt. After that, the reaction mixture was diluted with CH_2Cl_2 (25 mL), the solid was filtered-off, and rinsed with CH_2Cl_2. The filtrate was washed with 10% $Na_2S_2O_3$ (5 mL) and water (3 × 5 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/toluene gradient elution) to afford the disaccharide **5**.

5.7. Method G—activation with TMSOTf

A mixture containing glycosyl donor (0.025 mmol), glycosyl acceptor (0.02 mmol), and freshly activated molecular sieves (4 Å, 60 mg) in $ClCH_2CH_2Cl$ (0.4 mL) was stirred under argon for 1.5 h at rt. TMSOTf (9.0 μL, 0.05 mmol) was added and the reaction mixture was stirred for 30 min—3 h (see Table 1) at rt. After that, the reaction mixture was diluted with CH_2Cl_2, the solid was filtered-off, and then rinsed successively with CH_2Cl_2. The combined filtrate (~25 mL) was washed with satd aq. $NaHCO_3$ (5 mL) and water (3 × 5 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/toluene gradient elution) to afford the disaccharide **5**.

5.7.1. Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (5)

The title compound was synthesized as described in Tables 1 and 2. For example, the synthesis from glycosyl donor **2** (0.038 mmol) and glycosyl acceptor **4** (0.03 mmol) using Method A allowed the title compound in 91% yield. Analytical data for **5** were essentially the same as reported previously.[54]

5.8. Aglycone isolation

5.8.1. *O,S*-Dimethyl (4-methoxyphenyl)carbonimidothioate (9)

The title compound was isolated by column chromatography from the reaction mixture resulted from MeOTf-promoted glycosylation between **6** and isopropanol. Also isolated was isopropyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**8**).[59,60] Analytical data for **9**: R_f = 0.62 (ethyl acetate/toluene, 0.5:9.5, v/v), ^{1}H NMR: δ, 2.34 (s, 3H, SCH_3), 3.79 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.82–6.86 (m, 4H, aromatic) ppm; ^{13}C NMR: δ, 13.7, 55.6, 56.3, 114.5 (×2), 122.7 (×2), 140.8, 156.3, 159.4 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{10}H_{13}NO_2S$ 211.0667, found 211.0663.

5.8.2. *S*-Methyl (4-nitrophenyl)carbamothioate (10)

The title compound was isolated by column chromatography from the reaction mixture resulted from glycosylation between **7** and isopropanol as white solid. Also isolated was compound **8**. Complete analytical data for **10** were reported previously.[64] ^{1}H NMR: δ, 2.27 (s, 3H, SCH_3), 7.59–7.62 (m, 2H, aromatic), 8.06–8.09 (m, 2H, aromatic) ^{13}C NMR: δ, 12.4, 119.6 (×2), 126.1 (×2), 144.3, 146.4, 169.1 ppm.

5.8.3. Competitive glycosylation between glycosyl donor 2 and 3

A mixture of glycosyl donor **2** (40 mg, 0.05 mmol), glycosyl donor **3** (41 mg, 0.05 mmol), glycosyl acceptor **4** (19.5 mg, 0.04 mmol), and freshly activated molecular sieves (3 Å, 120 mg) in 1,2-dichloroethane (0.8 mL) was stirred under argon for 1 h at rt. AgOTf (40 mg, 0.16 mmol) was added and the resulting mixture was stirred for 1.5 at rt. At this time point, glycosyl acceptor **4** had been completely consumed as indicated by TLC (ethyl acetate/toluene, 1:9, v/v). The solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~50 mL) was washed with satd aq. $NaHCO_3$ (5 mL) and water (3 × 5 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–toluene gradient elution) to afford disaccharide **5** in 86% yield. Also isolated was unreacted glycosyl donor **3** (83% yield).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2014.06.025.

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