Special Collection

N-Alkylated Analogues of Indolylthio Glycosides as Glycosyl Donors with Enhanced Activation Profile

Ganesh Shrestha,[a] Matteo Panza,[a] Yashapal Singh,[a] Keith J. Stine,[a] and Alexei V. Demchenko*[a, b]

While studying indolylthio glycosides, previously we determined their activation profile that required large excess of activators. This drawback was partially addressed in the present study of N-alkylated SInR derivatives. The activation process was studied by NMR and the increased understanding of the mechanism led to a discovery of different activation pathways taking place with SIn versus SInR derivatives. Also investigated was orthogonality of the SInR leaving groups versus thioglycosides and selective activation of thioimidates over SInR glycosides.

Introduction

Chemical synthesis of glycans and glycoconjugates remains challenging to chemists, and even advanced strategies and technologies can address this challenge only in part.[1] While most syntheses of glycans are accomplished using thioglycosides or O-imidates as glycosyl donors, the development of new efficient methods for chemical glycosylation remains a vibrant area of scientific quest. Following early work by Zinner, Mukaiyama, and Hanessian, our lab became interested in glycosyl thioimidates, glycosyl donors equipped with the $SCR_1=NR_2$ leaving group.[2] Among these, S-benzoxazolyl (SBox),[3] S-thiazolinyl (STaz),[4] and S-benzimidazolyl (SBiz)[5] imidates showed great levels of versatility and efficacy, both for single step glycosylations and expeditious strategies for glycan assembly.[6]

Our recent endeavor was dedicated to studying (1H-indol-2-yl)thio (S-indolyl, SIn) glycosides.[7] These compounds are structurally similar both to thioglycosides and to thioimidates, but in terms of reactivity act as neither due to their unusual activation profile. In fact, SIn glycosides were found to be fully orthogonal in respect to ethylthio glycosides.[7] This is because of very different reaction conditions required for their glycosidation and/or activation pathways taking place with the SIn glycosides in respect to other structurally similar compounds. The activation of the SIn leaving group for glycosylation persistently demanded large amounts of reagents, regardless of

the activation method employed. For example, the activation required 5.0 equiv. of $AgBF_4$ versus typical 2—3 equiv. used for the activation of thioimidates.[8] Also N-iodosuccinimide (NIS, 4.5 equiv) and TMSOTf (1.0 equiv) or TfOH were needed for the SIn leaving group activation versus a typical NIS (2.0 equiv) and TMSOTf or TfOH (0.2 equiv) needed for the activation of alkyl/aryl thioglycosides.[9] Cooperative silver catalysis required Ag_2CO_3 (1.0 equiv) and TMSOTf (3.0—4.0 equiv), whereas only catalytic TMSOTf was needed in all of our previous applications of this reaction.[10]

These results were indicative of side processes that were taking place leading to the unusually high consumption of reagents. Reaction monitoring showed that in the presence of NIS, SIn glycosides only start to react upon consumption of 3.0 equiv. of NIS, and the formation of intermediates **A** and **B** shown in Scheme 1A has been proven by NMR. A similar study

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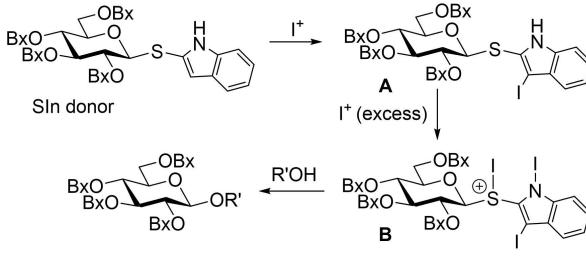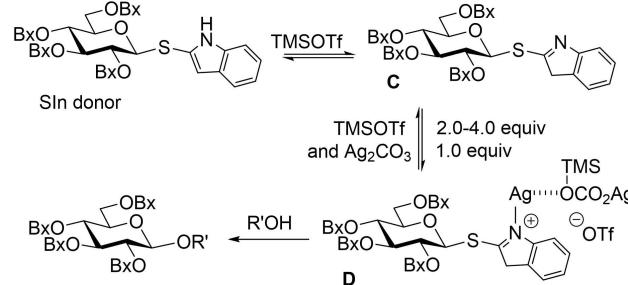
Scheme 1. A summary of previous mechanistic studies with SIn glycosyl donors.

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performed in the presence of the silver salt and TMSOTf showed that the SIn leaving group should first tautomerize into a thioimidate **C**, and then be activated via intermediate **D** (Scheme 1B). This stepwise pathway was used to explain the demand for multiple equivalents of TMSOTf. With acquiring preliminary understanding of the mechanistic pathways, we wondered whether blocking the nitrogen atom of the SIn leaving group would help to decrease the amounts of reagents required for the activation and hence allow for a more benign glycosylation reaction. Reported herein is our first attempt to modify the SIn leaving group by introducing a stable *N*-alkyl substituent.

Results and Discussion

We have selected atom economical methyl and allyl protecting groups for this study. As shown in Scheme 2, *N*-substituted thioindoles were prepared from the respective *N*-substituted oxindoles[11] via thionation with P_2S_5 in tetrahydrofuran (THF).[12] *N*-Methyl thioindole and *N*-allyl thioindole were obtained in 88% and 65% yield, respectively. The leaving groups were then introduced by reactions of the respective *N*-alkylated thioindoles with glycosyl bromides in the presence of potassium carbonate and 18-crown-6 (18-C-6) in dry acetone. Thus, per-*O*-benzoylated glucosyl bromide **1**[13] was converted into SinMe glucosyl donor **2** in 88% yield. Similarly, per-*O*-acetylated SinMe derivative **4** was prepared from acetobromoglucose **3** in 60% yield. Per-*O*-benzylated SinMe glucosyl donor **5** was prepared from acetylated derivative **4** using conventional deacetylation — benzylation sequence. This two-step reprotection accomplished in 86% yield served as an indication that the new N-alkylated leaving groups are sufficiently stable to withstand strongly basic reaction conditions associated with these transformations. SinAll glucosyl donors **6** and **8** were prepared in 78% and 61% ($\alpha/\beta = 1.6:1$) from glucosyl bromides **1** and **7**, respectively. SinAll galactosyl donor **10** and mannosyl donor **12** were synthesized from the corresponding per-*O*-benzoylated glycosyl bromides **9** and **11**, in 88% (separable α,β-mixture) and 67% (α-anomer), respectively (Scheme 2).[13] We do not know what triggered the formation of compound **10** as a mixture of anomers. Such factors as relatively higher reactivity of compounds of the D-galacto series and/or post S-glycosylation anomerization could have been driving forces of this process.

With the novel SinR derivatives in hand, we probed their potential as glycosyl donors with primary glycosyl acceptor **13**.[14] The key results of this preliminary study are summarized in Table 1. We chose to explore the same activators as those used for regular (NH) thioindole glycosyl donors, *i.e.* NIS/TfOH, NIS/TMSOTf and Ag_2CO_3/TMSOTf.[7] Glycosidation of donor **2** with acceptor **13** in the presence of 3.0 equiv. NIS and 0.8 equiv. TfOH was somewhat sluggish (19 h) and disaccharide **14**[15] was obtained in a modest yield of 60% (entry 1). Reaction performed in the presence of 4.0 equiv. of NIS and 1.0 equiv. of TfOH rapidly (15 min) afforded disaccharide **14** in 75% yield (entry 2). Reaction in the presence of 4.5 equiv. of NIS and 1.0 equiv. of TMSOTf was even faster (10 min), and disaccharide **14**
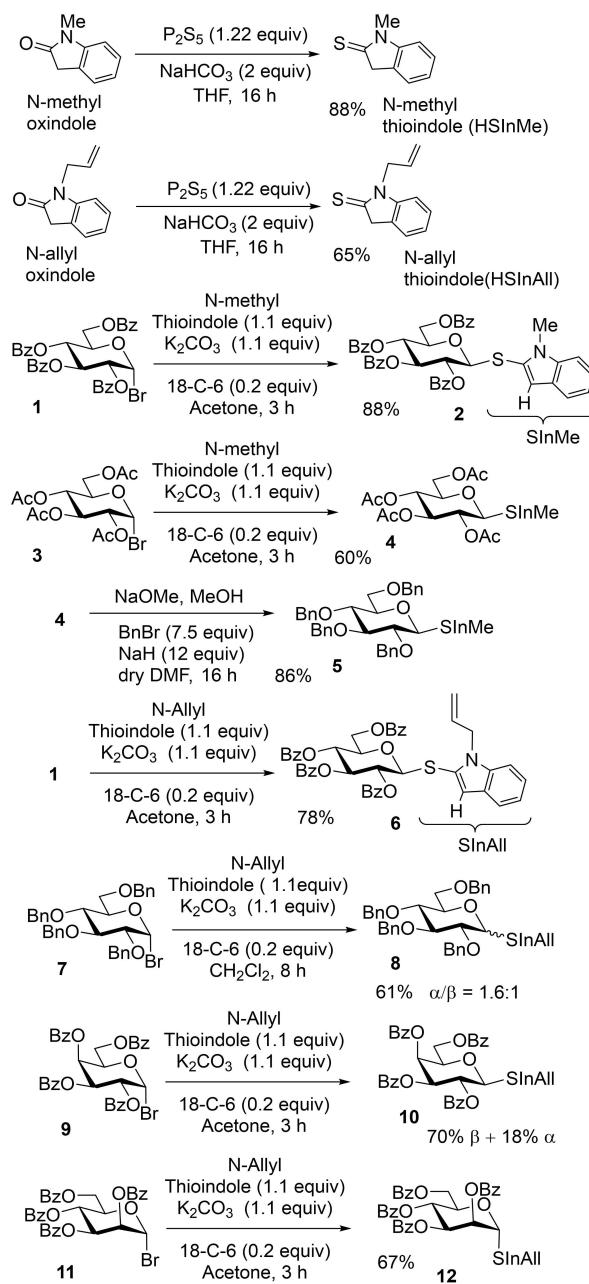

Scheme 2. Synthesis of protected SInMe and SInAll glycosides **2**, **4–6**, **8**, **10**, and **12**.

was obtained in 83% yield (entry 3). Glycosidation of donor **2** in the presence of 0.8 equiv. of Ag_2CO_3 and 4.0 equiv. of TMSOTf led to the formation of disaccharide **14** in 70% yield in 3.5 h (entry 4).

It should be noted that while the results of these reactions were generally good, we saw no significant difference between the new *N*-methylated leaving group and the previously investigated SIn glycosides. A similar level of reagent consumption was observed, and all our attempts to perform reaction in the presence of lower amounts of activators resulted in sluggish reactions and/or low yields. Therefore, we turned our attention to studying glycosidation of *N*-allylated donor **6**

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Table 1. Optimization of glycosidations of SInMe donor **2** and SInAll donor **6** with 6-OH acceptor **13**.

Entry	Conditions [equiv.]	Yield of 14
1	**2**, NIS (3.0), TfOH (0.8), rt, 19 h	60%
2	**2**, NIS (4.0), TfOH (1.0), rt, 15 min	75%
3	**2**, NIS (4.5), TMSOTf (1.0), rt, 10 min	83%
4	**2**, Ag$_2$CO$_3$ (0.8), TMSOTf (4.0), rt, 3.5 h	70%
5	**6**, NIS (2.0), TMSOTf (0.2), rt,16 h	29%
6	**6**, NIS (3.0), TMSOTf (0.8), rt, 2 h	68%
7	**6**, NIS (3.0), TMSOTf (1.0), rt, 1 h	89%
8	**6**, NIS (3.0), TfOH (0.4), rt, 24 h	52%
9	**6**, NIS (3.0), TfOH (0.8), rt, 24 h	69%
10	**6**, NIS (3.0), TfOH (1.0), rt, 24 h	73%
11	**6**, NIS (3.2), TfOH (1.0), rt, 1 h	94%
12	**6**, Ag$_2$CO$_3$ (1.0), TMSOTf (4.0), rt, 1 h	79%

Figure 1. Standard glycosyl acceptors used in this study.

with glycosyl acceptor **13** (Table 1). Starting with glycosylation in the presence of 2.0 equiv. of NIS and 0.2 equiv. of TMSOTf, typical conditions for the activation of alkyl/aryl thioglycosides, the activation of the SinAll leaving groups was sluggish and inefficient. Disaccharide **14** was obtained in only 29% yield in 16 h (entry 5). A steady increase of the amount of reagents led to improved outcomes of these reactions. Thus, reactions performed with 3.0 equiv. of NIS and 0.8 or 1.0 equiv. of TMSOTf rapidly (1—2 h) afforded disaccharide **14** in 68% or 89% yield (entries 6 and 7). We then attempted glycosylation in the presence of 3.0 equiv. of NIS and 0.4 equiv. of TfOH. In this case, disaccharide **14** was obtained in 52% yield in 24 h (entry 8). Keeping the amount of NIS constant (3.0) and increasing the amount of TfOH to 0.8 and 1.0 equiv. allowed us to improve yields of disaccharide **14** to 69% and 73%, respectively (entries 9 and 10). These somewhat slow reactions were stopped after 24 h. The optimal conditions were found to be 3.2 equiv. of NIS and 1.0 equiv. of TfOH which afforded disaccharide **14** in 94% in 1 h (entry 11). Glycosidation of donor **6** in the presence of 0.8 equiv. of Ag$_2$CO$_3$ and 4.0 equiv. of TMSOTf led to the formation of disaccharide **14** in 79% yield in 1 h (entry 12).

Based on the preliminary experimentation, we chose NIS/TfOH activation conditions for both donors **2** and **6** in the ratios depicted in entries 2 and 11 (Table 1), respectively, to perform further studies. This selection was made solely based on the amount of NIS needed, which was lower in case of TfOH versus TMSOTf (compare entries 2 and 3). For expanding the scope of this reaction, we chose glycosyl donors **2**, **5**, **6**, **8**, **10**, and **12** (Scheme 2) and standard primary acceptor **13** as well as secondary glycosyl acceptors **15—17**[14] depicted in Figure 1. The results of this study are summarized in Table 2.
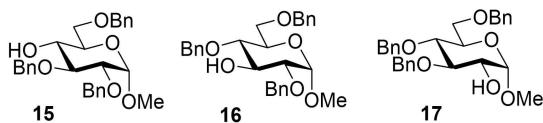
Glycosidation of per-O-benzoylated SinMe glucosyl donor **2** with glycosyl acceptors **15—17** gave the respective β-linked disaccharides **18—20**[14—16] in 79—85% yield (entries 1—3). Glycosylation of acceptor **13** with per-O-benzylated SinMe donor **5** in the presence of NIS (4.0 equiv) and TfOH (1.0) was swift (10 min) and efficient. As a result, disaccharide **21** was obtained in 92% yield in 10 min (entry 4). The high reactivity of per-O-benzylated (armed) donor **5** allowed us to decrease the amount of NIS to 3.0 equiv. In this case, a slower reaction (20 min) and a reduced yield (83%) for the formation of disaccharide **21** were recorded (entry 5). Glycosidation of SinMe donor **5** with secondary glycosyl acceptors **15—17** gave the respective disaccharides **22—24** in 61—69% yields and poor stereoselectivity (entries 6—8). The low yields were attributed to the formation of unidentified side products. The reactions with donor **5** lack stereoselectivity due to a non-participating benzyl substituent at C-2.

Glycosidation of per-O-benzoylated SinAll glucosyl donor **6** with acceptors **15—17** was conducted in the presence of NIS (3.5 equiv) and TfOH (1.0 equiv). These reactions required 45 min—3 h to produce the respective β-linked disaccharides **18—20** in 68—87% yields (entries 9—11). Glycosidations of per-O-benzylated SinAll glucosyl donor **8** with acceptors **13** and **15—17** were conducted in the presence of a reduced amount of NIS (3.2 equiv) and TfOH (1.0 equiv). There reactions required only 10—20 min to afford the respective β-linked disaccharides **21—24** in 75—84% yields (entries 12—15). The lack of stereoselectivity in these reactions was also due to a non-participating benzyl ether substituent at C-2 of the donor.

We then turned to investigating glycosylations with benzoylated N-allyl galactosyl and mannosyl donors **10** and **12**, respectively. Glycosidation of galactosyl donor **10** with acceptor **13** in the presence of 3.2 equiv. of NIS and 1.0 equiv. of TfOH afforded β-linked disaccharide **25**[17] in 85% yield in 1 h (entry 16). Moving towards glycosylations with less reactive, secondary acceptors **15—17** we decided to increase the amount of NIS to 3.5 equiv. keeping the amount of TfOH constant. This slight modification paid off, and the corresponding β-linked disaccharides **26—28**[18] were swiftly (1 h) obtained in excellent yields of 92—96% (entries 17—19). Glycosidation of mannosyl donor **12** with acceptor **13** in the presence of 3.2 equiv. NIS and 1.0 equiv. TfOH afforded α-linked disaccharide **29**[17] in 88% yield in 1.5 h (entry 20). Like in case of the galactosyl donor, we decided to increase the amount of NIS to 3.5 equiv. keeping the amount of TfOH constant for glycosylations of less reactive secondary glycosyl acceptors **14—16**. As a result, the corresponding α-linked disaccharides **30—32**[17,19] were obtained in 89—93% yields in 2.5 h (entries 21—23).

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Table 2. Expanding the scope of glycosylation with SInR donors: synthesis of disaccharides **18–32**. Yields and product ratios are invisible in the PDF file for all entries with the figure
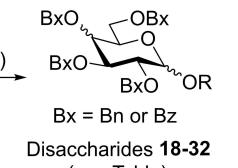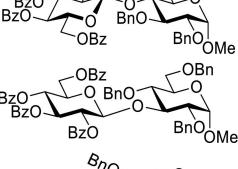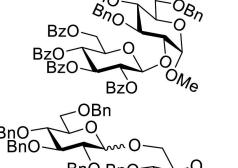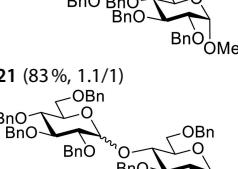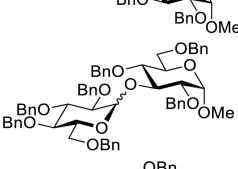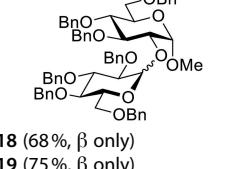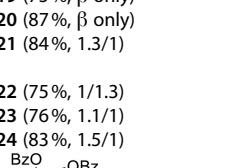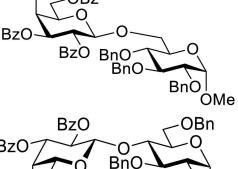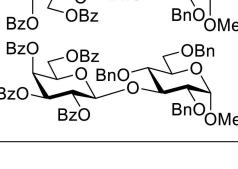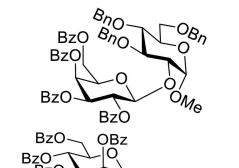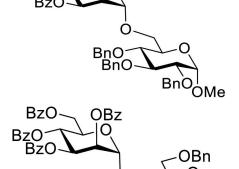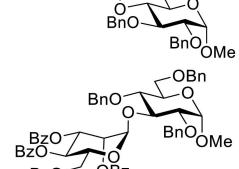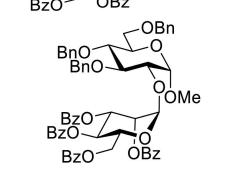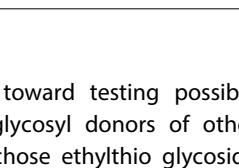
Glycosyl donors **2**, **5**, **6**, **8**, **10** and **12** (Scheme 1)
NIS (see Table) and TfOH (1.0 equiv)
MS 3Å, 1,2-DCE
ROH (0.8 equiv)
Glycosyl acceptors **13**, **15-17** (Figure 2)
Bx = Bn or Bz
Disaccharides **18-32** (see Table)

Entry	Donor + Acceptor, amount of NIS, time	Product (Yield, α/β ratio)
1	**2** (SInMe) + **15**, NIS (4.0 equiv), 45 min	
2	**2** + **16**, NIS (4.0 equiv), 45 min	
3	**2** + **17**, NIS (4.0 equiv), 15 min	
4	**5** (SInMe) + **13**, NIS (4.0 equiv), 10 min	
5	**5** + **13**, NIS (3.0 equiv), 20 min	**21** (83%, 1.1/1)
6	**5** + **15**, NIS (4.0 equiv), 15 min	
7	**5** + **16**, NIS (4.0 equiv), 15 min	
8	**5** + **17**, NIS (4.0 equiv), 15 min	
9	**6** (SInAll) + **15**, NIS (3.5 equiv), 3 h	**18** (68%, β only)
10	**6** + **16**, NIS (3.5 equiv), 1 h	**19** (75%, β only)
11	**6** + **17**, NIS (3.5 equiv), 45 min	**20** (87%, β only)
12	**8** (SInMe) + **13**, NIS (3.2 equiv), 10 min	**21** (84%, 1.3/1)
13	**8** + **15**, NIS (3.2 equiv), 20 min	**22** (75%, 1/1.3)
14	**8** + **16**, NIS (3.2 equiv), 10 min	**23** (76%, 1.1/1)
15	**8** + **17**, NIS (3.2 equiv), 10 min	**24** (83%, 1.5/1)
16	**10** (SInAll) + **13**, NIS (3.2 equiv), 1 h	
17	**10** + **15**, NIS (3.5 equiv), 1 h	
18	**10** + **16**, NIS (3.5 equiv), 1 h	

Table 2. continued

Glycosyl donors **2**, **5**, **6**, **8**, **10** and **12** (Scheme 1)
NIS (see Table) and TfOH (1.0 equiv)
MS 3Å, 1,2-DCE
ROH (0.8 equiv)
Glycosyl acceptors **13**, **15-17** (Figure 2)
Bx = Bn or Bz
Disaccharides **18-32** (see Table)

Entry	Donor + Acceptor, amount of NIS, time	Product (Yield, α/β ratio)
19	**10** + **17**, NIS (3.5 equiv), 1 h	
20	**12** (SInAll) + **13**, NIS (3.2 equiv), 1.5 h	
21	**12** + **15**, NIS (3.5 equiv), 2.5 h	
22	**12** + **16**, NIS (4.0 equiv), 2.5 h	
23	**12** + **17**, NIS (3.5 equiv), 2.5 h	

Next, we advanced our studies toward testing possible orthogonality of SInR donors with glycosyl donors of other series. For this experimentation, we chose ethylthio glycoside **33**[20] and Sbox imidate **34**.[21] In such comparative study, 1.0 equiv. of a thioindolyl glycoside (SInMe **5** or SInAll **8**) were set to complete with 1.0 equiv. of other donors (**33** or **34**) for 2.0 equiv. of the primary glycosyl acceptor **13**. First competitive reaction was set between donor **5** and ethylthio glycoside **33** in the presence of NIS (1.2 equiv) and TfOH (0.2 equiv), conditions that are suitable for the activation of thioglycosides. Indeed, SEt donor **33** was consumed completely in 5 h while SInMe donor **5** was recovered as its SEt adduct **35** in 86% yield (Scheme 3). The formation of this adduct is a result of a capturing the departed leaving group. Disaccharide **21** was obtained in 95% yield that was calculated based on the acceptor recovery. A similar reaction of SInAll donor **8** and SEt donor **33** with glycosyl acceptor **13** led to a complete activation of SEt donor **33** while donor **8** was recovered as its SEt adduct **36** in 91% yield (Scheme 3). Disaccharide **21** was obtained in 98% yield. It should be noted that excellent yields obtained for the formation of disaccharide **21** is attributed, in part, to excess of donors used in these reactions.

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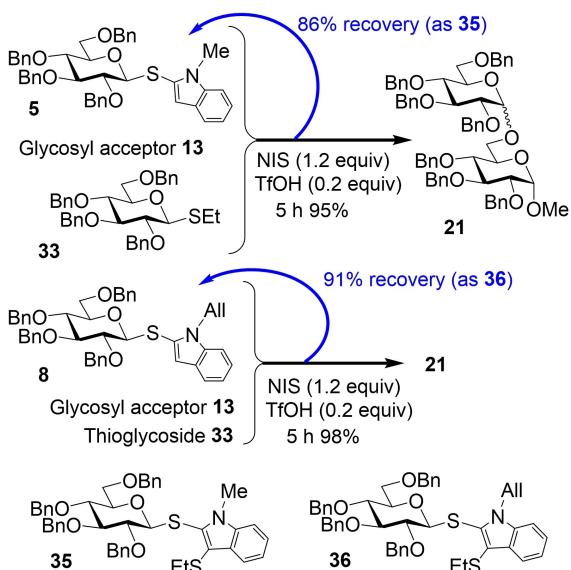
Scheme 3. Competition experiments between SInR and SEt that led to preferential activation of thioglycoside **33**.

Another competitive set of reactions was performed in the presence of Ag$_2$CO$_3$ and TMSOTf promoter system. Thioglycoside donor **33** was expected to remain unreactive under these reaction conditions. Indeed, the competitive reaction between donors **5** and **33** led to complete consumption of donor **5** in 15 min. SEt donor **33** was recovered in 92% yield, and disaccharide **21** was isolated in 98% yield (Scheme 4). A similar competition between donors **8** and **33** led to complete consumption of donor **8** in 15 min. As a result, donor **33** was recovered in 94% yield and disaccharide **21** was isolated in 99% yield (Scheme 4). These experiments signified that the thioindole analogs show entire orthogonality in respect to common ethylthio glycosides.

We also conducted competition experiments between thioindolyl glycosides and Sbox imidate **34** in the presence of
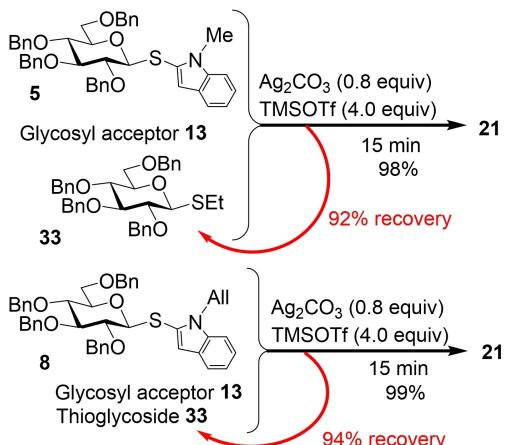
2.0 equiv. of AgOTf as promoter. These reaction conditions are standard for the activation of Sbox glycosides,[22] but unmodified SIn glycosides reacted very slowly, even in the presence of a large access of AgOTf.[7] Thus, a competition reaction between SinMe donor **5** and Sbox donor **34** resulted in a complete consumption of donor **34** in 5 min. As a result, donor **5** was recovered in 91% yield, and disaccharide **21** was obtained in 98% yield (Scheme 5). A similar competition reaction between SinAll donor **8** and Sbox donor **34** led to complete consumption of donor **34** in 5 min. Unreacted donor **8** was recovered in 95% yield, and disaccharide **21** was isolated in 99% yield (Scheme 5).

To gain understanding of the glycosylation reaction mechanism we performed a set of experiments monitored by NMR. First, we investigated the activation in the presence of NIS. For this purpose, SinAll donor **6** was dissolved in CDCl$_3$, the solution was transferred into a standard 5 mm NMR tube, and ^{1}H NMR spectrum was recorded (Scheme 6). NIS (1.0 equiv) was added and ^{1}H NMR spectrum was recorded in 25 min showing the formation of iodine adduct **37** as the only product. A similar experiment performed with SinMe donor **2** cleanly produced analogous adduct **38** (structure shown in Scheme 7, see the SI for the experiment details). Intermediates **37** and **38** are stable compounds, can be purified by column chromatography, were fully characterized by NMR, and their identity was confirmed by mass spectrometry.

Corrected Scheme 7 has been provided as a chemdraw file. The changes in part A, wherein all Bx have been replaced with Bz

To uncover the mechanism of glycosylation reaction proceeding under the cooperative silver salt-Lewis acid catalysis we also set up a series of NMR experiments. For this purpose, SinAll donor **6** was dissolved in CDCl$_3$, the solution was transferred into a standard 5 mm NMR tube, and ^{1}H NMR spectrum was recorded. TMSOTf (1.0 equiv) was added and ^{1}H NMR spectrum was recorded in 10 min showing the formation of TMS-adduct **39** (structure shown in Scheme 7, see the SI for the experiment details). A similar experiment performed with SinMe donor **2** produced analogous adduct **40** (structure shown

Scheme 4. Competition experiments between SInR and SEt that led to the preferential activation of SInMe **5** or SInAll **8**.
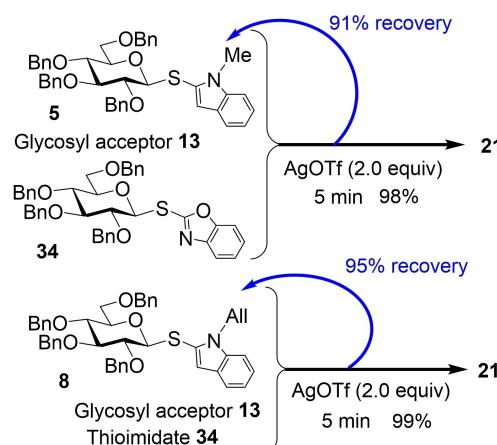

Scheme 5. Competition experiments between SInR and SBox building blocks that led to the preferential activation of SBox donor **34**.

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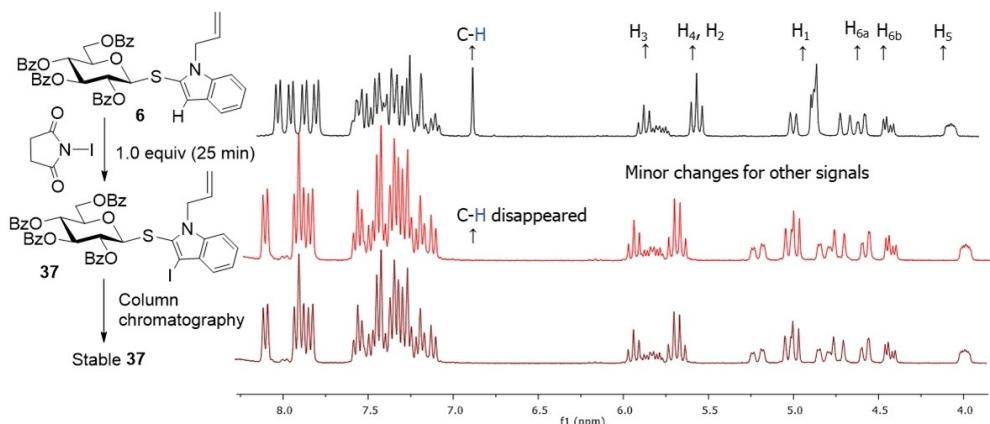
Scheme 6. NMR experiment with SInAll donor **6** in the presence of NIS (1.0 equiv) to observe the formation of **37**.
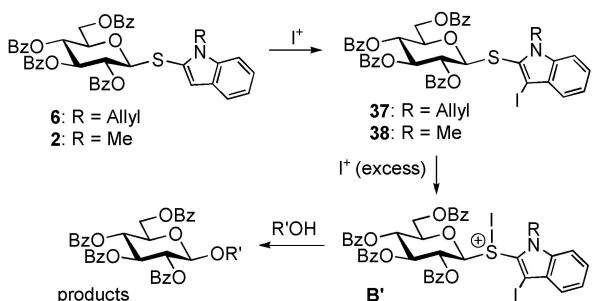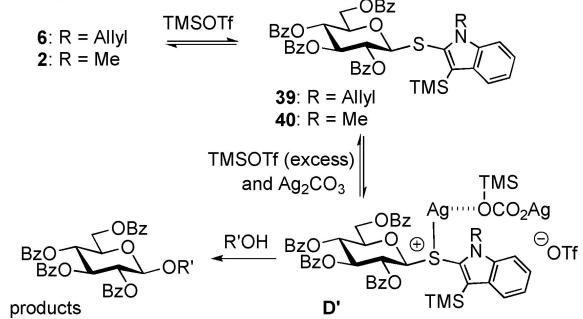
Scheme 7. Plausible mechanistic pathways for the activation of SInR glycosyl donors.

in Scheme 7). Intermediates **39** and **40** are relatively unstable compounds that produced very elusive NMR spectra. Upon attempt to purify them by column chromatography, they reverted to the respective starting materials **6** and **2**.

Based on this NMR monitoring our current understanding of the NIS-promoted reaction mechanism for the activation of SinR derivatives is as follows. Upon addition of NIS and TfOH to the reaction mixture containing SinAll donor **6** or SinMe donor **2** in 1,2-DCE, the first equivalent of NIS gets consumed by the electrophilic addition of the iodonium ion at the C-3 position of the SinR aglycone to afford stable intermediates **37** or **38**, respectively (Scheme 7A). The presence of TfOH facilitates the formation of the iodonium ion from NIS. The additional NIS is

needed to convert **37/38** into the activated species **B'** that results in the leaving group departure followed by glycosylation.

Note the key difference between intermediate **B'** and intermediate **B** that was observed with unprotected SIn derivatives in our previous work (Scheme 1). This difference explains the reduced amount of NIS that was typically required for the activation of SinR donors (3.2 equiv) versus their unprotected SIn counterparts (4.5 equiv). While glycosidation of benzoylated SinR donors proceeds via the intermediacy of the acyloxonium intermediate leading to complete stereoselectivity, glycosidations of benzylated SinR donors proceed via oxacarbenium ion intermediate. The formation of the latter intermediate explains poor stereoselectivity of many uncontrolled glycosylations taking place without the assistance of the neighboring group at C-2.

Based on NMR monitoring our current understanding of the reaction mechanism of glycosidation of SinR donors **6** or **2** in the presence of TMSOTf and Ag_2CO_3 is as follows. Upon addition of the promoters to the reaction mixture containing SinAll donor **6** or SinMe donor **2** in 1,2-DCE, the first equivalent of TMSOTf gets consumed by the electrophilic addition of TMS at the C-3 position of the SinR aglycone to afford elusive intermediates **39** or **40**, respectively (Scheme 7B). This step represents the key difference from the activation of unprotected SIn donors that were first tautomerized into its thioimidate counterpart (refer to Scheme 1). Silver carbonate then complexes with adducts **39/40** to produce respective silver complexes, which become strongly ionized in the presence of access TMSOTf. In should be noted that the resulting intermediate **D'** signifies a drastic activation difference from the analogous intermediate **D** observed with SIn derivatives (see Scheme 1). Whereas SinR donors are activated via the anomeric sulfur, following the direct activation pathway, like in thioglycosides, SIn donors are activated via the endocyclic nitrogen atom of the leaving group, which represents the remote activation pathway, like in thioimidates.

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Conclusions

We presented an extended study of a new class of glycosyl donors, indolylthio glycosides. Previously we observed that while the activation profile of the SIn leaving group is interesting, most reactions required large excess of reagents. This drawback was partially addressed in the present study of N-alkylated SInR derivatives. The activation process was studied by NMR, and the increased understanding of the mechanism led to a discovery of different activation pathways taking place with SIn versus SInR derivatives. We also investigated orthogonality of the SInR leaving groups versus thioglycosides. Further investigation of the leaving groups of this class in application to the synthesis of glycans is currently underway in our laboratory.

Experimental Section

General. The reactions were performed using commercial reagents and the ACS-grade solvents used for reactions were purified and dried in accordance with standard procedures. Column chromatography was performed on silica gel 60 (70–230 mesh), reactions were monitored by TLC on Kieselgel 60 F254. The compounds were detected by examination under UV light and by charring with 5% sulfuric acid in methanol. Solvents were removed under reduced pressure at $<40\,°C$. CH_2Cl_2 and $ClCH_2CH_2Cl$ (1,2-DCE) were distilled from CaH_2 directly prior to application. Molecular sieves (3 Å), used for reactions, were crushed and activated in vacuo at $390\,°C$ for 8 h in the first instance and then for 2–3 h at $390\,°C$ directly prior to application. Optical rotations were measured at 'Jasco P-2000' polarimeter. ^1H NMR spectra were recorded in $CDCl_3$ at 300 MHz, ^{13}C NMR spectra were recorded at 75 MHz. The ^1H NMR chemical shifts were referenced to tetramethyl silane (TMS, $\delta\,H=0$ ppm) or $CDCl_3$ ($\delta\,H=7.26$ ppm) for ^1H NMR spectra for solutions in $CDCl_3$. The ^{13}C NMR chemical shifts were referenced to the central signal of $CDCl_3$ ($\delta\,C=77.00$ ppm) for solutions in $CDCl_3$. HR FAB-MS determinations were made with the use of JEOL MStation (JMS-700) Mass Spectrometer.

Synthesis of HSInR aglycones

1-Methylindoline-2-one (N-methyl oxindole). The title compound was prepared from Isatin as previously described.[11] Analytical data for N-methyl oxindole were in accordance with that previously reported.[11]

1-Methylindoline-2-thione (N-methyl thioindole, HSInMe). The title compound was obtained following the previously described procedure,[12] which was modified as follows. N-Methyl oxindole (4.0 g, 27.2 mmol) was dissolved in dry tetrahydrofuran (100 mL) under argon. P_2S_5 (7.37 g, 33.16 mmol) was added followed by a portionwise addition of sodium bicarbonate (4.57 g, 54.6 mmol), and the resulting mixture was stirred under argon for 16 h at rt. After that, the volatiles were removed under reduced pressure. The residue was dissolved in ethyl acetate (400 mL) and washed with water (3×50 mL). The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate – hexane 10% gradient elution) to afford the title compound in 88% yield. Analytical data for HSInMe: $R_f=0.45$ (ethyl acetate/hexane, 2/3, v/v); ^1H NMR (300 MHz): δ 3.57 (s, 3H, NCH_3), 4.02 (s, 2H, CH_2), 6.93–7.34 (m, 4H, aromatic) ppm; $^{13}C\{^1H\}$ NMR (75 MHz): δ 30.9, 48.7, 109.3, 123.6, 124.0, 127.7, 128.7, 146.2, 200.6 ppm; ESI-TOF $[M+H]^+$: calcd for $[C_9H_{10}NS]^+$ 164.0528; found: 164.0532.

1-Allylindolin-2-one (N-allyl oxindole). The title compound was prepared from Isatin using previously described procedure.[11] Analytical data for N-allyl oxindole were in accordance with that previously reported.[11]

1-Allylindolin-2-thione (N-allyl thioindole, HSInAll). N-allyl oxindole (2.0 g, 11.54 mmol) was dissolved in dry tetrahydrofuran (40 mL) under argon. P_2S_5 (3.12 g, 14.08 mmol) was added followed by a portionwise addition of sodium bicarbonate (1.93 g, 23.08 mmol), and the resulting mixture was stirred under argon for 16 h at rt. After that, the volatiles were removed under reduced pressure. The residue was dissolved in ethyl acetate (300 mL) and washed with water (3×40 mL). The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate – hexane 10% gradient elution) to afford the title compound in 65% yield. Analytical data for HSInAll: $R_f=0.50$ (ethyl acetate-hexane, 1/4, v/v); ^1H NMR (300 MHz): δ 4.06 (s, 2H, $CH_2C=S$), 4.81 (d, 2H, NCH_2), 5.19-5.25 (m, 2H, $=CH_2$), 5.79–5.91 (m, 1H, $CH=$), 6.92–7.30 (m, 4H, aromatic) ppm; $^{13}C\{^1H\}$ NMR (75 MHz): δ 46.2, 48.6, 109.8, 118.0, 123.5, 123.8, 127.4, 128.5, 129.2, 145.2, 200.5 ppm. ESI-TOF $[M+H]^+$: calcd for $[C_{11}H_{12}NS]^+$ 190.0685; found: 190.0690.

Synthesis of SInR Glycosides

1-Methylindolyl 2,3,4,6-tetra-O-benzoyl-1-thio-β-D-glucopyranoside (2). HSInMe (0.33 g, 2.02 mmol), anhydrous K_2CO_3 (0.28 g, 2.02 mmol), and 18-crown-6 (0.10 g, 0.37 mmol) were added to a solution of 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranosyl bromide[23] (**1**, 1.21 g, 1.83 mmol) in dry acetone (32 mL), and the resulting mixture was stirred under argon at $50\,°C$ for 3 h. After that, the solids were filtered off through a pad of Celite, rinsed successively with CH_2Cl_2, and the combined filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (~150 mL), washed with 10% aq. $NaHCO_3$ (25 mL), and water (2×25 mL). The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (toluene - ethyl acetate 1% gradient elution) to afford the title compound as a white amorphous solid in 88% yield (1.17 g, 1.615 mmol). Analytical data for **2**: $R_f=0.3$ (ethyl acetate/diethyl ether, 4/6, v/v); $[\alpha]_D^{22}$ -20.0 (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz): δ 3.73 (s, 3H, NCH_3), 4.06-4.12 (m, 1H, $J_{5,6a}=5.3$, $J_{5,6b}=2.4$ Hz, H-5), 4.43 (dd, 1H, $J_{6a,6b}=12.2$ Hz, H-6a), 4.59 (dd, 1H, H-6b), 4.89 (d, 1H, $J_{1,2}=9.9$ Hz, H-1), 5.51–5.59 (m, 2H, $J_{2,3}=9.5$ Hz, H-2, 4), 5.91 (dd, 1H, $J_{3,4}=9.5$ Hz, H-3), 6.89 (s, 1H, $=CH$), 7.11–7.56 (m, 24H, aromatic) ppm; $^{13}C\{^1H\}$ NMR (75 MHz): δ 30.1, 62.8, 68.9, 70.4, 74.0, 76.3, 86.7, 109.9, 112.3, 112.4, 119.7, 120.8, 122.9, 125.1 (x2), 126.9 (x2), 128.2, 128.3, 128.4 (x3), 128.5 (x2), 128.6 (x2), 129.0, 129.3, 129.5, 129.6 (x2), 129.7 (x2), 129.8 (x2), 133.1, 133.2, 133.4, 138.6, 164.9 (x2), 165.7, 166.0 ppm; ESI-TOF $[M+Na]^+$: calcd for $[C_{43}H_{35}NO_9SNa]^+$ 764.1925; found: 764.1916.

1-Methylindolyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (4). HSInMe (1.3 g, 8.02 mmol), anhydrous K_2CO_3 (1.11 g, 8.02 mmol), and 18-crown-6 (0.38 g, 1.46 mmol) were added to a solution of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide[23] (**3**, 3.00 g, 1.83 mmol) in dry acetone (50 mL), and the resulting mixture was stirred under argon at rt for 4 h. After that, the solids were filtered off through a pad of Celite, rinsed successively with CH_2Cl_2 and the combined filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (300 mL), washed with 10% aq. $NaHCO_3$ (30 mL) and water (2×30 mL). The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane - ethyl acetate 10% gradient elution) to afford the title compound as a white amorphous solid in 60% yield (2.15 g, 4.36 mmol). Analytical data for **4**: $R_f=0.45$ (ethyl acetate/hexane, 3/7, v/v); $[\alpha]_D^{22}$ -36.2 (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz): δ

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1.92–2.15 (m, 12 H, 4×CH₃CO), 3.57-3.62 (m, 1H, H-5), 3.78 (s, 3H, NCH₃) 4.10-4.11 (m, 2H, H-6a, 6b), 4.51 (d, 1H, $J_{1,2}$ = 9.9 Hz, H-1), 4.90-5.05 (m, 2H, H-2, 4), 5.18 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 6.86 (s, 1H, =CH, indole), 7.09-7.62 (m, 4H, aromatic) ppm; ¹³C{¹H} NMR (75 MHz): δ 20.4 (x2), 20.5, 20.7, 30.1, 61.6, 67.7, 69.7, 73.7, 75.6, 85.9, 109.8, 112.2 (x2), 119.7, 120.8, 122.9, 124.8, 126.8, 138.5, 169.2 (x2), 170.1, 170.3 ppm; ESI-TOF $[M+Na]^+$: calcd for $[C_{23}H_{27}NO_9SNa]^+$ 516.1299; found: 516.1308.

1-Methylindolyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside (5). Compound **4** (2.0 g, 4.05 mmol) was dissolved in minimum amount of methanol (~25 mL), a 1 M solution of NaOMe in MeOH was added until pH > 9, and the resulting mixture was stirred for 1 h at rt. The reaction mixture was neutralized with Dowex (H⁺), the resin was filtered off, and rinsed successively with MeOH. The combined filtrate (~75 mL) was concentrated under reduced pressure, and the residue was dried in *vacuo* for 2 h. The crude residue was dissolved in dry DMF (24 mL), NaH (1.94 g, 48.66 mmol) was added portionwise, followed by the dropwise addition of benzyl bromide (3.61 mL, 30.41 mmol), and the resulting mixture was stirred for 16 h at rt. The reaction mixture was poured into ice-water (50 mL) and stirred for 30 min. The mixture was extracted with ethyl acetate/ diethyl ether (1:1, v/v, 3×100 mL), and the combined organic extract was washed with water (2×50 mL). The organic phase was separated, dried with Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate – hexane, 5% gradient elution) to afford the title compound as a white amorphous solid in 86% yield (2.4 g, 3.49 mmol). Analytical data for **5**: R_f = 0.55 (ethyl acetate/ hexane, 3/7, v/v); $[\alpha]_D^{22}$ −10.9 (c = 1.0, CHCl₃); ¹H NMR (300 MHz): δ 3.33 (dd, 1H, $J_{6a,6b}$ = 10.1 Hz, H-6a), 3.46-3.74 (m, 5H, H-2, 3, 4, 5, 6b), 3.80 (s, 3H, NCH₃), 4.41–4.53 (m, 4H, H-1, 3×CHPh), 4.43 (d, 1H, ²J = 10.8 Hz, CHPh), 4.81–4.89 (m, 3H, 3×CHPh), 5.02 (d, ²J = 10.3 Hz, CHPh), 6.87 (s, 1H, =CH, indole), 7.03–7.31 (m, 24H, aromatic) ppm; ¹³C{¹H} NMR (75 MHz): δ 30.3, 68.6, 73.2 (x2), 74.8, 74.4, 75.2, 78.6, 80.4, 86.5, 88.2 (x2), 109.7, 110.9, 119.5, 120.5, 122.5, 126.9 (x2), 127.1 (x2), 127.5 (x3), 127.6 (x2), 127.8 (x2), 128.0 (x2), 128.3 (x3), 137.8 (x4), 137.9 (x2), 138.2 (x2), 138.4 (x2), ppm; ESI-TOF $[M+H]^+$: calcd for $[C_{43}H_{43}NO_5SNa]^+$ 708.2754; found: 708.2748.

1-Allylindolyl 2,3,4,6-tetra-O-benzoyl-1-thio-β-D-glucopyranoside (6). HSInAll (0.47 g, 2.5 mmol), anhydrous K₂CO₃ (0.35 g, 2.5 mmol), and 18-crown-6 (0.12 g, 0.46 mmol) were added to a solution of 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranosyl bromide[13] (**1**, 1.50 g, 2.27 mmol) in dry acetone (40 mL), and the resulting mixture was stirred under argon for 3 h at 50 °C. After that, the solids were filtered off through a pad of Celite, rinsed successively with CH₂Cl₂, and the combined filtrate was concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (~150 mL), washed with 10% aq. NaHCO₃ (25 mL) and water (2×25 mL). The organic phase was separated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (toluene - ethyl acetate 1% gradient elution) to afford the title compound as a white amorphous solid in 78% yield (1.33 g, 1.71 mmol). Analytical data for **6**: R_f = 0.6 (ethyl acetate/ toluene, 0.5/9.5, v/v); $[\alpha]_D^{22}$ −4.3 (c = 1.0, CHCl₃); ¹H NMR (300 MHz): δ 4.00-4.10 (m, 1H, $J_{5,6a}$ = 5.5, $J_{5,6b}$ = 2.3 Hz, H-5), 4.45 (dd, 1H, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.61 (dd, 1H, H-6b), 4.66–5.00 (m, 5H, H-1, NCH₂, =CH₂), 5.56–5.62 (m, 2H, H-2, 4), 5.73–5.83 (m, 1H, CH=), 5.90 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 6.90 (s, 1H, =CH, indole), 7.07–8.01 (m, 24H, aromatic) ppm; ¹³C{¹H} NMR (75 MHz): δ 45.7, 62.8, 68.9, 70.4, 73.9, 76.3, 86.8, 110.4, 112.5 (x2), 115.9, 119.9, 120.8, 123.0, 125.1, 127.1, 128.2, 128.3 (x2), 128.4 (x4), 128.5 (x2), 128.9, 129.3, 129.5 (x2), 129.6 (x2), 129.7 (x2), 129.8 (x2), 133.1, 133.2, 133.4 (x2), 133.5, 137.8, 164.9 (x2), 165.6, 165.9 ppm; ESI-TOF $[M+Na]^+$: calcd for $[C_{45}H_{37}NO_9SNa]^+$ 790.2081; found: 790.2074.

1-Allylindolyl 2,3,4,6-tetra-O-benzyl-1-thio-α-D-glucopyranoside (8). Ethyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside[20] (**33**,

1.10 g, 1.88 mmol) and freshly activated molecular sieves (3 Å, 0.75 g) in CH₂Cl₂ (50 mL) were stirred under argon for 1 h at rt. Bromine (0.12 mL, 2.26 mmol) was added, and the resulting mixture was stirred for 20 min at rt. After that, the volatiles were removed under reduced pressure, the residue was co-evaporated with dry toluene (2×20 mL), and dried in *vacuo* for 2 h. The residue containing crude 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl bromide **7** was dissolved in CH₂Cl₂ (10 mL), HSInAll (0.39 g, 2.07 mmol), anhydrous K₂CO₃ (0.29 g, 2.068 mmol), and 18-crown-6 (0.1 g, 0.37 mmol) were added, and the resulting mixture was stirred under argon for 8 h at rt. The solids were filtered off through a pad of Celite and rinsed successively with CH₂Cl₂. The combined filtrate (~150 mL) as washed with water (30 mL), 10% aq. NaHCO₃ (25 mL), and water (2×30 mL). The organic phase was separated, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene 2% gradient elution) to afford the title compound as a white amorphous solid in 61% yield (0.82 g, 1.15 mmol, α/β = 1.6:1). A small sample of α-**8** was separated for characterization purposes. Analytical data for α-**8**: R_f = 0.50 (ethyl acetate/ hexane, 3/7, v/v); $[\alpha]_D^{22}$ 68.8 (c = 1.0, CHCl₃); ¹H NMR (300 MHz): δ 3.59-3.71 (m, 3H, H-3, 5, 6b), 3.84–3.97 (m, 2H, H-2, 4), 4.38–4.42 (m, 1H, H-6a), 4.46-5.07 (m, 12H, =CH₂, NCH₂, 8×CHPh), 5.49 (d, 1H, $J_{1,2}$ = 4.4 Hz, H-1), 5.82–5.91(m, 1H, CH=), 6.79 (s, 1H, =CH indole), 7.07–7.51 (m, 24H, aromatic) ppm; ¹³C{¹H} NMR (75 MHz): δ 45.6, 45.8, 67.9, 68.2, 68.6, 71.7, 72.4, 73.3 (x2), 74.8, 75.0, 75.3, 75.6, 75.7, 76.0, 77.1, 78.8, 79.4, 80.7, 82.2, 86.6, 88.0, 88.5, 110.0, 110.1, 110.4, 110.5, 111.5, 115.8, 116.1, 119.7, 120.2, 120.3, 120.5, 120.6, 122.2, 122.5, 127.2, 127.6 (x4), 127.8 (x7), 128.2 (x4), 128.3 (x7), 133.4, 133.5, 133.7, 133.8, 137.4, 137.5, 137.7, 137.8, 137.9, 138.0, 138.2, 138.4 ppm; ESI-TOF $[M+H]^+$: calcd for $[C_{45}H_{45}NO_5SNa]^+$ 734.2916; found: 734.2927. Selected ¹H NMR (300 MHz) data for β-**8**: 3.33 (dd, H-5), 3.48–3.58 (m, H-2, 6a, 6b), 3.37–3.71 (m, H-3, 4), 4.39 (d, H-1), 5.82–5.91 (m, CH=), 6.89 (s, =CH indole), 7.07-7.51 (m, aromatic) ppm.

1-Allylindolyl 2,3,4,6-tetra-O-benzoyl-1-thio-α- and β-D-galacto-pyranoside (α-10 and β-10). HSInAll (0.79 g, 4.20 mmol), anhydrous K₂CO₃ (0.58 g, 4.20 mmol) and 18-crown-6 (0.20 g, 0.76 mmol) were added to a solution of 2,3,4,6-tetra-O-benzoyl-α-D-galactopyranosyl bromide[13] (**9**, 2.50 g, 3.80 mmol) in dry acetone (66 mL), and the resulting mixture was stirred under argon for 3 h at 50 °C. After that, the solids were filtered off through a pad of Celite, rinsed successively with CH₂Cl₂, and the combined filtrate was concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (~250 mL), washed with 10% aq. NaHCO₃ (30 mL) and water (2× 30 mL). The organic phase was separated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (toluene - ethyl acetate 1% gradient elution) to afford separate anomers of the title compound as white amorphous solid. Eluted first was α-**10** (18% yield, 0.53 g, 0.685 mmol) followed by elution of β-**10** (70% yield, 2.04 g, 2.66 mmol). Analytical data for α-**10**: R_f = 0.55 (ethyl acetate/ toluene, 0.5/9.5, v/v); $[\alpha]_D^{22}$ −4.20 (c = 1.0, CHCl₃); ¹H NMR (300 MHz): δ 4.48 (dd, 1H, $J_{6a,6b}$ = 11.6 Hz, H-6a), 4.61–4.68 (m, 3H, H-6b, NCH₂), 4.77–5.02 (m, 2H, =CH₂), 5.27 (dd, 1H, $J_{5,6a}$ = 5.2 Hz, H-5), 5.65-5.77 (m, 1H, =CH), 5.88–6.02 (m, 3H, CH=, H-1, 2, 3), 6.13 (m, 1H, =CH, H-4), 6.78 (s, 1H, =CH indole), 7.00–8.07 (m, 24H, aromatic) ppm; ¹³C{¹H} NMR (75 MHz): δ 45.5, 62.6, 68.3, 68.5, 68.8, 38.9, 86.8, 109.9, 111.8, 116.3, 119.8, 120.5, 122.7, 125.7, 127.3, 128.2, 128.4 (x2), 128.5 (x2), 128.6, 128.8 (x4), 128.9, 129.3, 129.7, 129.8 (x2), 129.9 (x4), 132.9, 133.0, 133.2 (x2), 133.6 (x2), 137.6, 165.3, 165.4, 165.5, 166.1 ppm; ESI-TOF $[M+Na]^+$: calcd for $[C_{45}H_{37}NO_9SNa]^+$ 790.2081; found: 790.2033. Analytical data for β-**10**: R_f = 0.50 (ethyl acetate/ toluene, 0.5/9.5, v/v); $[\alpha]_D^{22}$ −6.3 (c = 1.0, CHCl₃); ¹H NMR (300 MHz): δ 4.30-4.36 (m, 2H, $J_{5,6b}$ = 8.5, $J_{6a,6b}$ = 13.3 Hz, H-5, 6a), 4.57 (m, 1H, H-6b), 4.73–4.94 (m, 3H, H-1, NCH₂),

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5.00–5.07 (m, 2H, =CH$_2$), 5.59 (dd, 1H, H-3), 5.77–5.97 (m, 3H, $J_{2,3}$ = 6.9 Hz, H-2, 4, CH=), 7.05–8.03 (m, 25H, =CH indole, aromatic) ppm; ^{13}C{^{1}H} NMR (75 MHz): δ 45.8, 62.3, 67.7, 67.9, 72.9, 75.1, 85.8, 110.6, 113.3, 115.9, 119.9, 121.2, 123.0, 124.3, 127.2, 128.2, 128.4 (x5), 128.5 (x2), 128.6 (x2), 129.1, 129.2, 129.6 (x5), 129.7 (x4), 133.2, 133.3 (x2), 133.6, 138.1, 165.0, 165.1, 165.4, 165.9 ppm; ESI-TOF [M+ Na]$^+$: calcd for [C$_{45}$H$_{37}$NO$_9$SNa]$^+$ 790.2081; found: 790.2076.

1-Allyllindolyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-α-D-mannopyranoside (12). HSInAll (0.79 g, 4.20 mmol), anhydrous K$_2$CO$_3$ (0.58 g, 4.20 mmol) and 18-crown-6 (0.20 g, 0.76 mmol) were added to a solution of 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide[13] (11, 2.50 g, 3.80 mmol) in dry acetone (66 mL), and the resulting mixture was stirred under argon for 3 h at 50 °C. After that, the solids were filtered off through a pad of Celite, rinsed successively with CH$_2$Cl$_2$, and the combined filtrate was concentrated under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$ (~250 mL), washed with 10% aq. NaHCO$_3$ (30 mL) and water (2×30 mL). The organic phase was separated, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (toluene - ethyl acetate 1% gradient elution) to afford the title compound as a white amorphous solid in 67% yield (1.91 g, 2.54 mmol). Analytical data for **12**: R$_f$ = 0.55 (ethyl acetate/ toluene, 0.5/9.5, v/v); [α]$_D^{22}$ −49.0 (c = 1.0, CHCl$_3$); ^{1}H NMR (300 MHz): 4.00-4.03 (m, 1H, $J_{5,6a}$ = 5.1 Hz, H-5), 4.49 (dd, 1H, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.71–4.90 (m, 3H, H-6b, NCH$_2$), 5.01–5.09 (m, 3H, H-1, =CH$_2$), 5.56 (dd, 1H, $J_{3,4}$ = 3.0 Hz, H-3), 5.88–6.04 (m, 3H, H-4, =CH$_2$), 6.19 (dd, 1H, $J_{2,3}$ = 2.7 Hz, H-2), 6.92 (s, 1H, =CH indole), 7.08–8.07 (m, 24H, aromatic) ppm; ^{13}C{^{1}H} NMR (75 MHz): δ 45.7, 62.9, 66.2, 71.1 72.6, 86.7, 110.3, 111.5 (x2), 115.9, 119.9, 120.8, 123.0, 126.9, 127.2, 127.7, 128.2, 128.4 (x2), 128.5 (x3), 128.6 (x3), 128.8, 129.6 (x3), 129.7 (x4), 129.9 (x2), 133.1, 133.2, 133.4 (x2), 133.7, 133.8, 137.8, 165.2, 165.3, 165.5, 166.0 ppm; ESI-TOF [M+Na]$^+$: calcd for [C$_{45}$H$_{37}$NO$_9$SNa]$^+$ 790.2081; found: 790.2073.

Synthesis of Disaccharides

General procedure for glycosylation in the presence of NIS and TfOH or TMSOTf. A mixture of a glycosyl donor (0.040–0.044 mmol), a glycosyl acceptor (0.036–0.039 mmol), and molecular sieves (3 Å, 80 mg) in 1,2-DCE or DCM (1.0 mL) was stirred under argon for 1 h at rt. After that, NIS (0.122–0.182 mmol) and TfOH (0.040 mmol) or TMSOTf (0.040 mmol) were added, and the resulting mixture was stirred for the time indicated in Tables at rt. The solid was filtered off through a pad of Celite and rinsed successively with dichloromethane. The combined filtrate (~30 mL) was washed with 10% aq. Na$_2$S$_2$O$_3$ (2×10 mL) and H$_2$O (2×10 mL). The organic phase was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution). If necessary, further purification was accomplished by size-exclusion column chromatography on Sephadex LH-20.

General procedure for glycosylation in the presence of Ag$_2$CO$_3$ and TMSOTf. A mixture of a glycosyl donor (0.040–0.044 mmol), a glycosyl acceptor (0.036–0.039 mmol), and molecular sieves (3 Å, 80 mg) in 1,2-DCE or DCM (1.0 mL) was stirred under argon for 1 h at rt. Ag$_2$CO$_3$ (0.035–0.042 mmol) and TMSOTf (0.168–0.175 mmol) were added, and the resulting mixture was for the time indicated in Tables at rt. The solid was filtered off through a pad of Celite and rinsed successively with dichloromethane. The combined filtrate (~30 mL) was washed with H$_2$O (2×10 mL). The organic phase was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution) to afford the corresponding disaccharide. If necessary, further purification was accomplished by size-exclusion column chromatography on Sephadex LH-20.

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (17). The title compound was obtained from donor **2** and acceptor **13**[14] by general glycosylation procedure in 75% yield as a white amorphous solid. Analytical data for **17** was in accordance with that previously reported.[15]

Methyl 4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (18). The title compound was obtained from donor **2** and acceptor **15**[14] by the general glycosylation procedure in 79% yield as a clear syrup. Analytical data for **18** was in accordance with that previously reported.[15]

Methyl 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (19). The title compound was obtained from donor **2** and acceptor **16**[14] by the general glycosylation procedure in 80% yield as a clear syrup. Analytical data for **19** was in accordance with that previously reported.[14]

Methyl 2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (20). The title compound was obtained from donor **2** and acceptor **17**[14] by the general glycosylation procedure in 85% yield as a clear syrup. Analytical data for **20** was in accordance with that previously reported.[16]

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (21). The title compound was obtained from donor **5** and acceptor **13** by the general glycosylation procedures in 92% yield (α/β = 1.2/1) as a colorless foam. Analytical data for **21** was in accordance with that previously reported.[24]

Methyl 4-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (22). The title compound was obtained from donor **5** and acceptor **15** by the general glycosylation procedure in 61% yield (α/β = 1/1.2) as a clear syrup. Analytical data for **22** was in accordance with that previously reported.[25]

Methyl 3-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (23). The title compound was obtained from donor **5** and acceptor **16** by the general glycosylation procedure in 69% yield (α/β = 1.2/1) as a clear syrup. Analytical data for **23** was in accordance with that previously reported.[26]

Methyl 2-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (24). The title compound was obtained from donor **5** and acceptor **17** by the general glycosylation procedure in 67% yield (α/β = 1.2/1) as a colorless foam. Analytical data for **24** was in accordance with that previously reported.[27]

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (25). The title compound was obtained from donor **10** and acceptor **13** by general glycosylation procedure in 85% yield as a white amorphous solid. Analytical data for **25** was in accordance with that previously reported.[17]

Methyl 4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (26). The title compound was obtained from donor **10** and acceptor **15** by the general glycosylation procedure in 92% yield as a colorless amorphous solid. Analytical data for **26** was in accordance with that previously reported.[18]

Methyl 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (27). The title compound was obtained from donor **10** and acceptor **16** by the general glycosylation procedure in 96% yield as a colorless amorphous solid. Analytical data for **27**: R$_f$ = 0.5 (ethyl acetate/ toluene, 0.5/9.5, v/v); [α]$_D^{22}$ 5.1 (c = 1.0, CHCl$_3$); ^{1}H NMR (300 MHz): δ 3.25 (s, 3H, CH$_3$), 3.36 (dd, 1H, $J_{2,3}$ = 3.5 Hz, H-2), 3.56–3.70 (m, 4H, H-4, 5, 6a, 6b), 4.16

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(d, 1H, ^2J = 12.1 Hz, C*H*Ph), 4.29-4.46 (m, 9H, H-1, 3, 5', 6a', 6b', 4× C*H*Ph), 5.28 (d, 1H, ^2J = 10.4 Hz, C*H*Ph), 5.50 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1'), 5.67 (dd, 1H, $J_{3',4'}$ = 7.5 Hz, H-3'), 5.87 (dd, 1H, $J_{2',3'}$ = 9.1 Hz, H-2'), 5.99 (dd, 1H, H-4'), 7.06–8.00 (m, 35H, aromatic) ppm; ^{13}C{^{1}H} NMR (75 MHz): δ 55.0, 61.4, 68.0, 68.3, 69.5, 70.5, 70.8, 71.6, 73.5, 73.7, 74.8, 75.1, 78.5, 80.6, 97.6, 97.7, 100.9, 127.5, 127.7 (x4), 128.0 (x4), 128.3 (x3), 128.4 (x5), 128.5 (x2), 128.7, 128.9, 129.3, 129.4, 128.8, 133.2, 137.8, 137.9, 138.5, 165.2, 165.4, 165.5, 165.6 ppm; ESI-TOF [M + Na]$^+$: calcd for [C$_{62}$H$_{58}$O$_{15}$Na]$^+$ 1065.3668; found: 1065.3629.

Methyl 2-O-(2,3,4,6-tetra-O-benzoyl-β-D-galactopyranosyl)-3,4,6-tri-O-benzyl-α-D-glucopyranoside (28). The title compound was obtained from donor 10 and acceptor 17 by general glycosylation procedure in 96% yield as a colorless amorphous solid. Analytical data for 28: R$_f$ = 0.50 (ethyl acetate/ toluene, 0.5/9.5, v/v); [α]$_D^{22}$ 53.3 (c = 1.0, CHCl$_3$); ^{1}H NMR (300 MHz): δ 3.42 (s, 3H, CH$_3$), 3.60–3.74 (m, 4H, H-4, 5, 6a, 6b), 3.97 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 4.33-4.67 (m, 9H, H-5', 6a', 6b', 6×C*H*Ph), 5.09 (d, 1H, $J_{1,2}$ = 2.3 Hz, H-1), 5.15 (d, 1H, $J_{1',2'}$ = 8.1 Hz, H-1'), 5.58 (dd, 1H, $J_{3',4'}$ = 2.8 Hz, H-3'), 5.95–5.99 (m, 2H, H-2', 4'), 6.97–8.08 (m, 35H, aromatic) ppm; ^{13}C{^{1}H} NMR (75 MHz): δ 55.3, 55.4, 62.2, 68.1, 68.4, 69.6, 69.9, 71.4, 72.1, 73.4, 74.9, 75.2, 80.8, 82.2, 99.4, 102.7, 127.0 (x3), 127.5, 127.6, 127.7 (x3), 127.8, 128.0 (x4), 128.1 (x9), 128.5 (x6), 128.8, 128.9, 129.1, 129.7 (x5), 130.0 (x2), 133.2, 137.9, 138.0, 138.4, 165.0, 165.5, 165.6, 166.0 ppm; ESI-TOF [M + Na]$^+$: calcd for [C$_{62}$H$_{58}$O$_{15}$Na]$^+$ 1065.3668; found: 1065.3627.

Methyl 6-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (29). The title compound was obtained from donor 12 and acceptor 13 by general glycosylation procedure in 70% yield as a white amorphous solid. Analytical data for 29 was in accordance with that previously reported.[17]

Methyl **4-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-2,3,6-tri-O-benzyl-α-D-glucopyranoside (30).** The title compound was obtained from donor 12 and acceptor 15 by the general glycosylation procedure in 80% yield as a clear syrup. Analytical data for 30 was in accordance with that previously reported.[17]

Methyl 3-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-2,4,6-tri-O-benzyl-α-D-glucopyranoside (31). The title compound was obtained from donor 12 and acceptor 16 by the general glycosylation procedure in 93% yield as a clear syrup. Analytical data for 31 was in accordance with that previously reported.[19a]

Methyl 2-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-3,4,6-tri-O-benzyl-α-D-glucopyranoside (32). The title compound was obtained from donor 12 and acceptor 17 by the general glycosylation procedure in 92% yield as a clear syrup. Analytical data for 32 was in accordance with that previously reported.[19b]

Competition experiments

Experiment A. A mixture of ethylthio glucoside 33 (26.0 mg, 0.044 mmol), methyl thioindolyl glucoside 5 (30.0 mg, 0.044 mmol), acceptor 13 (40.6 mg, 0.087 mmol), and 3 Å molecular sieves (80 mg) in dichloroethane (1.0 mL) was stirred under argon for 1 h at rt. After that, triflic acid (0.78 μL, 0.0087 mmol) was added followed by the addition of NIS (11.8 mg, 0.0524 mmol), and the resulting mixture was stirred for 5 h at rt. The solid was filtered off through a pad of Celite, rinsed successively with dichloromethane, and the combined filtrate (~30 mL) was washed with 10% aq. Na$_2$S$_2$O$_3$ (2×10 mL). The organic phase was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/ hexane 5% gradient elution). The unreacted donor 5 was isolated as SEt adduct 35 in 86% yield. Analytical data for 35: R$_f$ = 0.55 (ethyl acetate/ hexane, 3/7, v/v); ^{1}H NMR (300 MHz): δ 1.14 (t, 3H, CH$_2$C*H$_3$*), 2.71-2.80 (m, 2H, C*H$_2$*CH$_3$), 3.26 (m, 1H, H-5), 3.54–

3.66 (m, 5H, H-2, 3, 4, 6a, 6b), 3.86 (s, 3H, NCH$_3$), 4.39–4.57 (m, 4H, H-1, 3×C*H*Ph,), 4.79 (d, 1H, ^2J = 11.5 Hz, C*H*Ph), 4.86–4.93 (m, 3H, 3× C*H*Ph), 5.17 (d, 1H, ^2J = 10.4 Hz, C*H*Ph), 7.14–7.81 (m, 24H, aromatic) ppm; ^{13}C{^{1}H} NMR (75 MHz): δ 15.1, 30.8, 68.8, 73.9, 75.0, 75.6, 75.8, 78.7, 81.7, 86.6, 89.9, 110.1, 113.7, 114.1, 120.1, 120.2, 120.3, 120.4, 123.5, 127.6 (x4), 127.7 (x4), 127.9 (x4), 128.3 (x4), 128.4 (x6), 133.8, 137.9, 138.0, 138.4 ppm; ESI-TOF [M + H]$^+$: calcd for [C$_{45}$H$_{47}$NO$_5$S$_2$Na]$^+$ 768.2788; found: 768.2743.

A competition experiment with allyl thioindolyl glucoside 8 (30 mg, 0.042 mmol) instead of donor 5 was performed in a similar manner. The unreacted donor 8 was obtained as SEt adduct 36 in 91% yield. Analytical data for 36: R$_f$ = 0.50 (ethyl acetate/ hexane, 3/7, v/v); ^{1}H NMR (300 MHz): δ 3.54–3.70 (m, 2H, H-3, 5), 3.83–3.98 (m, 3H, H-2, 4, 6a), 4.31–4.38 (m, 4H, H-6b, 3×C*H*Ph), 4.69–4.86 (m, 5H, NCH$_2$, 3× C*H*Ph), 5.00–5.10 (m, 4H, =CH$_2$, 2×C*H*Ph), 5.82–5.91 (m, 2H, $J_{1,2}$ = 4.7 Hz, H-1, CH=), 7.15–7.76 (m, 24H, aromatic) ppm; ^{13}C{^{1}H} NMR (75 MHz): δ 15.1, 29.7, 30.7, 46.7, 68.3, 68.8, 72.5, 72.6, 73.5, 75.3, 75.8, 79.6, 82.3, 89.2, 110.6, 113.4, 116.5, 119.8, 120.5, 123.2, 127.6, 127.9, 128.0, 128.1, 128.3, 128.4, 130.2, 133.3, 133.8, 137.5, 137.8, 137.9, 138.1, 138.7 ppm; ESI-TOF [M + H]$^+$: calcd for [C$_{47}$H$_{49}$NO$_5$S$_2$Na]$^+$ 794.2944; found: 794.2945.

Experiment B. A mixture of ethylthio glucoside 33 (26.0 mg, 0.044 mmol), methyl thioindolyl glucoside 5 (30 mg, 0.044 mmol), glucosyl acceptor 13 (40.6 mg, 0.087 mmol), and 3 Å molecular sieves (80 mg) in dichloroethane (1.0 mL) was stirred under argon for 15 min at rt. After that, Ag$_2$CO$_3$ (9.6 mg, 0.035 mmol) and TMSOTf (31.6 μL, 0.175 mmol) were added, and the resulting mixture was stirred under argon for 15 min at rt. The reaction was quenched with triethyl amine (~0.2 mL), the solid was filtered off through a pad of Celite, rinsed successively with dichloromethane, and the combined filtrate (~30 mL) was washed with 10% aq. Na$_2$S$_2$O$_3$ (2×10 mL). The organic phase was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/ hexane 5% gradient elution). The unreacted donor 33 was recovered in 92% yield and its identity was confirmed by ^{1}H NMR and mass spectroscopy. A competition experiment with allyl thioindolyl glucoside 8 (30 mg, 0.042 mmol) instead of donor 5 was performed in a similar manner. The unreacted donor 33 was recovered in 94% yield and its identity was confirmed by ^{1}H NMR and mass spectroscopy.

Experiment C. A mixture of S-benzoxazolyl glucoside 34 (29.5 mg, 0.044 mmol), methyl thioindolyl glucoside 5 (30.0 mg, 0.044 mmol), glucosyl acceptor 11 (40.6 mg, 0.087 mmol), and 3 Å molecular sieves (80 mg) in dichloroethane (1.0 mL) was stirred under argon for 1 h at rt. After that, freshly activated AgOTf (22.5 mg, 0.087 mmol) was added, and the resulting mixture was stirred for 5 min at rt. The solid was filtered off through a pad of Celite, rinsed successively with dichloromethane, and the combined filtrate (~ 30 mL) was washed with H$_2$O (2×10 mL). The organic phase was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/ hexane 5% gradient elution). The unreacted donor 5 was recovered in 91% yield and its identity was confirmed by ^{1}H NMR and mass spectroscopy. A competition experiment with allyl thioindolyl glucoside 8 (30 mg, 0.042 mmol) instead of donor 5 was performed in a similar manner. The unreacted donor 8 was recovered in 95% yield and its identity was confirmed by ^{1}H NMR and mass spectroscopy.

1H NMR monitoring experiments

A typical experiment in the presence of NIS. A solution of SInMe donor 2 (0.0404 mmol) or SInAll donor 6 (0.0391 mmol) and NIS

(0.0391-0.1173 mmol) in CDCl$_3$ (1.0 mL) was stirred in a RB flask under argon for 30 min at rt. The resulting solution was transferred into a standard 5 mm NMR tube and ^{1}H NMR spectra recorded at 10 min, 1 h, 16 h timepoints or as needed. The recorded spectra are presented in the SI. Analytical data for intermediate **37**: R$_f$ = 0.6 (ethyl acetate/ toluene, 0.5/9.5, v/v); ^{1}H NMR (300 MHz): δ 3.95–3.98 (m, 1H, $J_{5,6a}$ = 5.7 Hz, H-5), 4.42 (dd, 1H, $J_{6a,6b}$ = 11.9 Hz, H-6a), 4.56 (dd, 1H, H-6b), 4.69–5.22 (m, 5H, H-1, NCH$_2$, =CH$_2$), 5.62–5.72 (m, 2H, H-2, 4), 5.77–5.86 (m, 1H, CH=), 5.92 (dd, 1H, $J_{3,4}$ = 9.4 Hz, H-3), 7.09-7.94 (m, 24H, aromatic) ppm; ^{13}C{^{1}H} NMR (75 MHz): δ 47.8, 62.8, 69.1, 70.6, 73.1, 74.5, 76.3, 88.5, 111.3, 116.6, 121.2, 122.5, 124.6, 128.3 (x2), 128.4 (x2), 128.5 (x2), 128.6 (x2), 128.9 (x2), 129.3 (x2), 129.7 (x4), 129.9 (x2), 130.0 (x2), 130.2 (x2), 133.2 (x2), 133.3 (x2), 133.4, 137.9, 165.1, 165.3, 165.7, 165.9 ppm; ESI-TOF [M + Na]$^+$: calcd for [C$_{45}$H$_{36}$INO$_9$SNa]$^+$ 916.1048; found: 916.0990. Analytical data for intermediate **38**: R$_f$ = 0.3 (ethyl acetate/ diethyl ether, 2/3, v/v); ^{1}H NMR (300 MHz): δ 3.85 (s, 3H, NCH$_3$), 3.96–4.00 (m, 1H, $J_{5,6a}$ = 5.9, H-5), 4.41 (dd, 1H, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.56 (dd, 1H, H-6b), 4.93 (d, 1H, $J_{1,2}$ = 10.1 Hz, H-1), 5.62–5.70 (m, 2H, H-2, 4), 5.92 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 7.09–7.95 (m, 24H, aromatic) ppm; ^{13}C{^{1}H} NMR (75 MHz): δ 32.1, 63.0, 69.1, 70.6, 71.9, 73.7, 76.2, 88.9, 110.5, 120.8, 121.9, 124.3, 128.3 (x2), 128.4 (x4), 128.5 (x2), 128.6 (x2), 128.9 (x2), 129.3 (x2), 129.6 (x2), 129.8 (x2), 130.2 (x2), 130.4 (x2), 133.3, 133.5 (x2), 138.5, 165.1, 165.3, 165.7, 165.9 ppm; ESI-TOF [M + Na]$^+$: calcd for [C$_{43}$H$_{34}$INO$_9$SNa]$^+$ 890.0896; found: 890.0832.

A typical experiment in the presence of TMSOTf. A solution of SInMe donor **2** (0.0404 mmol) or SInAll donor **6** (0.0391 mmol) and TMSOTf (0.040–0.1564 mmol) in CDCl$_3$ (1.0 mL) was stirred in a RB flask under argon for 5 min at rt. The resulting solution was transferred into a standard 5 mm NMR tube and ^{1}H NMR spectra recorded at 10 min, 30 min, 1 h, 16 h timepoints or as needed. The recorded spectra are presented in the SI.

Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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