Indolylthio Glycosides As Effective Building Blocks for Chemical Glycosylation

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INTRODUCTION

Chemical synthesis of glycan sequences of even moderate complexity still remains a considerable challenge. As such, the development of efficient strategies for the oligosaccharide and glycoconjugate synthesis has been a demanding area of research effort worldwide. A vast majority of glycan syntheses is nowadays accomplished using thioglycosides and O-trichloroacetimidates (TCAI).

As a part of the ongoing research effort in our laboratory to develop versatile methods for chemical glycosylation and expedient oligosaccharide synthesis, we became interested in glycosyl thioimidates, glycosyl donors equipped with the SCR₁⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻~-~-~

RESULTS AND DISCUSSION

The thioindole (HSIn) aglycone was obtained from commercially available oxindole (2-indolone) by means of thionation with P₂S₅ in tetrahydrofuran (THF). HSIn was then reacted with a variety of bromide precursors in the presence of potassium carbonate and 18-crown-6 to afford the respective SIn glycosides. Thus, as depicted in Scheme 1, per-benzoylated glucosyl bromide was converted into SIn glycoside 2 in a 63% yield. Per-benzylated glucosyl 3 and galactosyl bromide 5, freshly prepared from the corresponding ethyl thioglycosides, were converted into SIn glycosides 4 and 6 in 60 and 52% yields, respectively. We acknowledge that these yields are far from excellent, but we would like to note that the yields listed herein are after crystallization. For the X-ray structure determination of glucose derivative 2, and galactose derivative 6, crystals of appropriate dimensions were obtained by slow evaporation of ethyl acetate–hexane solutions. Refer to the Experimental Section and the Supporting Information for complete details of the X-ray structure determination of compounds 2 and 6.

With novel SIn glycosides 2, 4, and 6 in hand, we endeavored for investigation of their properties as glycosyl donors. To study the preliminary scope of this approach, we chose model glycosyl acceptors depicted in Figure 1. As possible activators, we decided to rely on the reaction conditions that worked well with thioimidates (AgOTf or AgBF₄) and thioglycosides (NIS/
To our great surprise, no activation took place when we attempted to react SIn donor 2 with reactive primary acceptor 7 in the presence of AgOTf at rt. Even a large excess of 3.0 equiv and prolonged reaction time (24 h) produced no desired disaccharide 11 only in a very modest yield of 36% (entry 5). Moreover, the reaction was very sluggish, appeared as something is hindering the activation of the SIn leaving group, and required 24 h to get to this stage. Increasing the amount of promoters, NIS to 4.0 equiv and TIOH to 0.8 equiv, again appealed as a possible solution. Under these reaction conditions, disaccharide 11 was obtained rather swiftly, in 1 h, in a significantly improved, albeit still unremarkable yield of 60% (entry 6). Further increase in the amount of TIOH to 1.0 equiv turned out to be the most advantageous for this promoter system. As shown in entry 7, disaccharide 11 was obtained in 72% yield. In a further search of the promoters, we replaced AgOTf with AgBF4 (5.0 equiv) to rt, 5 h and obtained disaccharide 11 in 85% yield in 2 h (entry 2). Being encouraged by this outcome, albeit realizing that a large excess of TMSOTf is undesirable, we continued the search of alternative promoter systems.

Glycosidation of SIn donor 2 with acceptor 7 in the presence of 2.0 equiv of NIS and 0.2 equiv of TIOH, a common promoter system used for the activation of alkyl/aryl thioglycosides,24 in 1,2-dichloroethane (1,2-DCE) afforded disaccharide 11 only in a very modest yield of 36% (entry 5). Furthermore, the reaction was very sluggish, appeared as something is hindering the activation of the SIn leaving group, and required 24 h to get to this stage. Increasing the amount of promoters, NIS to 4.0 equiv and TIOH to 0.8 equiv, again appealed as a possible solution. Under these reaction conditions, disaccharide 11 was obtained rather swiftly, in 1 h, in a significantly improved, albeit still unremarkable yield of 60% (entry 6). Further increase in the amount of TIOH to 1.0 equiv turned out to be the most advantageous for this promoter system. As shown in entry 7, disaccharide 11 was obtained in 72% yield. In a further search of the promoters, we replaced AgBF4 with TIOH and TMSOTf. While somewhat similar, this modified promoter system allowed to achieve disaccharide 11 in 77% yield in 1.5 h. A gradual increase in the amounts of promoters (entries 8–10) showed that 4.5 equiv of NIS and 1.0 equiv of TMSOTf are required to achieve this result.

To expand the scope of this reaction, we extended our study to secondary glycosyl acceptors 8–10 (Figure 1). The glycosylation reaction of SIn glucosyl donor 2 with the secondary glycosyl acceptors 8–10 in the presence of Ag2CO3(1.0 equiv) and TMSOTf (4.0 equiv) and conditions that worked best for the primary acceptor 7 (see Table 1) were also successful herein. As shown in Table 2, the corresponding disaccharides 12, 13, and 14 were obtained in commendable yields ranging between 69 and 79% (entries 1–3). Subsequently, we extended our study to glycosylation of per-benzylated donors 4 and 6 with primary and secondary acceptors 7–10. This study included both silver-and iodonium-mediated pathways, and the reaction conditions were adjusted to account for differences in reactivity among the donor and acceptor combinations. Surprisingly, only obtained in 87% yield in 2 h (entry 4). Being encouraged by this outcome, albeit realizing that a large excess of TMSOTf is undesirable, we continued the search of alternative promoter systems.
slightly reduced amounts of promoters were permitted for the activation of supposedly much more reactive (armed) per-benzylated glycosyl donors. Selected key results of this study are summarized in Table 2.

Being marginally more reactive than its per-benzoylated counterpart, benzylated donor 4 could be smoothly activated for the reaction with the primary acceptor 7 with Ag₂CO₃ (1.0 equiv) and the reduced amount of TMSOTf (3.0 equiv). As a result, disaccharide 15 was obtained in 91% yield in 2 h (\(\alpha/\beta = 1.1:1\), entry 4). This series of experiments was performed in dichloromethane as the reaction solvent that would allow us to start reactions at a low temperature (vide infra). Benzylated donor 4 could also be activated with NIS (4.0 equiv) and TIOH (1.0 equiv), essentially the same conditions used for the activation of the per-benzoylated Sn donor. As a result, disaccharide 15 was obtained in 76% yield in 30 min (\(\alpha/\beta = 1:1.2\), entry 5). We then investigated glycosidation of donor 4 with secondary glycosyl acceptors 8–10 in the presence of Ag₂CO₃ and TMSOTf. These reactions were slower, and to achieve faster reactions, we increased the amount of TMSOTf back to 4.0 equiv. To achieve higher yields, these reactions were started at \(-70^\circ C\) and then allowed to slowly warm to rt. This series of experiments produced the corresponding disaccharides 16, 17, and 18 in good yields of 68–81%, albeit unremarkable stereoselectivity (\(\alpha/\beta\) from 1.4:1 to 1:1.1, entries 6–8).

After that, we investigated glycosylations with Sn galactosyl donor 6 with the same series of glycosyl acceptors 7–10. The glycosylation reaction of donor 6 with primary acceptor 7 in the presence of Ag₂CO₃ (1.0 equiv) and TMSOTf (4.0 equiv) afforded disaccharide 19 in 70% yield in 30 min (\(\alpha/\beta = 1:1.3\), entry 9). Decreasing the amount of TMSOTf to 3.0 equiv afforded disaccharide 19 in an increased yield of 82% with practically no change in stereoselectivity (entry 10). This reaction, however, required 3 h to complete, and to achieve practical rates with the secondary acceptors, we
increased the amount to TMSOTf to 4.0 equiv. Like in the case of glucosyl donor 4, glycosylations of galactosyl donor 6 with the secondary glycosyl acceptors 8–10 were started at −70 °C and then allowed to slowly warm to rt. This series of experiments produced the respective disaccharides 20,32 21,33 and 22 in yields ranging between 54 and 75% with preferential α-stereoselectivity (α/β = 1.7−6.0:1, entries 11−13).

After completing these series of experiments, we were still puzzled by the fairly low reactivity of SIn glycosides that required greater excess reagents than even stable alkyl/aryl thioglycosides. The requirement for using excess reagent resulted in unusually prominent side reactions that accompanied many glycosylations. Side products observed included silylated acceptors, hemiacetals, (1→1)-linked disaccharides, and 1,6-anhydro sugars. To gain a better understanding of this glycosylation reaction and uncover its mechanism, we turned our attention to performing a set of experiments monitored by NMR. First, we investigated the activation with NIS. For this purpose, SIn donor 2 was dissolved in CDCl 3, the solution was transferred into a standard 5 mm NMR tube, and the 1H NMR spectrum was recorded (Scheme 2A). NIS (1.0 equiv) was added, and the 1H NMR spectrum was recorded in 15 min, showing the formation of 23 as the only product (Scheme 2B).

While somewhat unanticipated, the formation of such intermediate is not surprising since the 3-position of the indole ring system is strongly nucleophilic and known to react easily with electrophiles of different kinds.35,36 Compound 23 was sufficiently stable to be isolated through column chromatography and fully characterized (see Experimental Section for details). The NH signal in 23 was noted to shift downfield, and the identity of this proton was confirmed by a separate deuterium exchange experiment that indicated the remanence of an exchangeable hydrogen on the N atom of 23 (see the Supporting Information for further details). Upon addition of the second equiv of NIS, the 1H NMR spectrum was recorded in 15 min, showing the formation of 23 as the only product (Scheme 2B).

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As suggested by the 1H NMR spectrum, a partial conversion of compound 23 to a new compound, presumably 24, took place. Only when a total 4.0 equiv of NIS was added to the NMR tube, 1H NMR spectrum recorded after 1 h showed the complete formation of intermediate 24 with no traces of 23 remaining (Scheme 2D). This explains the need for multiple equivalents of NIS to activate the SIn leaving group. The formation of the activated sulfonium intermediate 24 is supported by a δΔ 1.4 ppm downfield chemical shift of the H-1 signal, as indicated in Scheme 2C.

On the basis of the extended NMR monitoring, our current understanding of the NIS-promoted reaction mechanism is as follows. Upon the addition of 4.0 equiv of NIS and TfOH to the reaction mixture containing SIn donor 2 in 1,2-DCE, the first equiv of NIS gets consumed by the electrophilic addition of the iodonium ion at the remote C-3 position of the SIn aglycone to afford the stable intermediate 23 (Scheme 3). The presence of TfOH (or TMSOTf) facilitates the formation of the iodonium ion from NIS. The additional NIS is needed to convert 23 into the activated species 24 that results in the leaving group departure followed by glycosylation. While glycosidation of benzoylated SIn donor 2 proceeds via the intermediacy of the acyloxonium intermediate, leading to complete stereoselectivity, glycosidations of benzylated SIn donors 4 and 6 proceed via the oxacarbenium ion intermediate. The formation of the latter intermediate explains poor stereoselectivity of many uncon-
trolled glycosylations taking place without the assistance of the neighboring group at C-2. 37

To uncover the mechanism of glycosylation reactions proceeding under the cooperative silver salt−Lewis acid catalysis, we set up a series of experiments to monitor the interaction of SIn donor 2 with the promoter system by NMR. For this purpose, donor 2 was dissolved in CDCl₃, the solution was transferred into a standard 5 mm NMR tube, and the ¹H NMR spectrum was recorded (Scheme 4A). TMSOTf (1.0 equiv) was added, and the ¹H NMR spectrum was recorded in 10 min, showing the formation of thioimidate 25 (Scheme 4B). The formation of such a tautomer was somewhat unexpected. The same product was formed with other amounts of TMSOTf (up to 4.0 equiv). Thioimidate 25 was found to be stable in solution for at least 1 h, and it survives conventional aqueous workup and evaporation. However, compound 25 tautomerizes back into SIn glycoside 2 during column chromatography on silica gel.

When Ag₂CO₃ (1.0 equiv) was added to the NMR tube containing 25 produced from 2 with 1 equiv of TMSOTf, compound 25 quickly tautomerizes back to compound 2. Shown in Scheme 4C is a silver complex of 2 wherein the complexation has presumably occurred via the N-atom of indole. This mode of complexation is supported by a δΔ 0.7 ppm downfield chemical shift of the NH signal with practically no other changes observed in comparison to the uncomplexed 2 (Scheme 4A). The analogy is found in the mode of complexation taking place with other thioimidates. Thus, it was previously found that nonaromatic thioimidates, such as S-thiazolinyl (STaz),¹⁰ complex silver and other metals via the nitrogen atom. ³⁸ This mode of complexation is known to result in the remote activation with silver ³⁹,⁴⁰ or temporary deactivation with platinum or palladium salts. ⁴¹ Conversely, aromatic thioimidates such as S-benzoxazolyl (SBox)⁹ and S-benzimidazolyl (SBiz)¹¹ complex silver strictly via the anomeric sulfur.¹² This differential activation, remote versus direct, has allowed us to devise a thioimidate-only orthogonal strategy for oligosaccharide synthesis.³³

When Ag₂CO₃ (1.0 equiv) was added to the NMR tube containing 25 produced from 2 with 2.0 or 4.0 equiv of TMSOTf, imidate 25 remained intact. The ¹H NMR spectrum recorded in 10 min showed the presence of compound 25 only, presumably as a complex with silver due to minor changes in chemical shifts observed (Scheme 2D). Since no glycosylation takes place until multiple equiv of TMSOTf are added, we believe that tautomerization of 2 into 25 needs to have occurred prior to glycosylation under these reaction conditions.

On the basis of extended NMR monitoring, our current understanding of the reaction mechanism of glycosidation of 2 in the presence of TMSOTf and Ag₂CO₃ is as follows. In the presence of excess TMSOTf, glycosyl donor 2 is first tautomerized into its thioimidate counterpart 25 (Scheme 4). We believe that the occurrence of this intermediate is the key to the successful activation to take place under these reaction conditions. While the formation of the 2-Ag complex is possible, there is no feasible pathway for the Sn leaving group activation, neither remotely nor directly (Scheme 5). Silver carbonate then complexes with thioimidate 25 to produce a complex 25-Ag that is not yet sufficiently ionized to cause the leaving group departure.

As proposed in our previous study of the cooperative silver/acid catalysis with glycosyl halides, after the initial interaction of the donor with the silver salt, a strongly ionized species A is produced due to the interaction with an acid. This intermediate will then cause the remote Sn leaving group departure. Depending on the protecting group at C-2, the subsequent glycosylation proceeds via an acyloxonium (SIn donor 2) or oxacarbenium (SIn donors 4 and 6) ion. Different from our previous studies with glycosyl halides, wherein the glycosylations were driven by a strong affinity of silver to halogens and the irreversible formation of the Ag-X bond, the activation of the Sn donors proceeding via the interaction of silver with the N atom is significantly slower. It is also possible

Scheme 4. NMR Experiments with SIn Donor 2 in the Presence of TMSOTf and Ag₂CO₃ to Study the Mechanism
that silver carbonate will react with excess TMSOTf first to generate a loosely bound silver cation species, which are then attacked by the N-atom of thioimidate 25 to produce the ionized intermediate.

Given the specific set of reaction conditions needed for the activation of this new leaving group, the orthogonality of SIn donors with respect to other popular leaving groups, thioglycoside 26 and thioimidate 27 was then investigated. For this purpose, we set up a series of comparative competition experiments wherein 1.0 equiv of Sln donor 4 was set to compete with 1.0 equiv other glycosyl donors for 2.0 equiv of acceptor 7 (Scheme 6). All reactions were stopped after 30 min, and all reaction components were isolated and characterized. First, we set up a comparative competition experiment wherein Sln donor 4 and ethylthio glycoside 26 were set to compete for acceptor 7 in the presence of NIS (1.2 equiv) and TfOH (0.2 equiv). These are typical reaction conditions for the activation of thioglycosides. Indeed, SEt donor 26 reacted entirely, whereas SIn donor 4 was recovered in the form of iodine and SEt adducts 28 and 29 that were isolated in the combined yield of 90% (Scheme 6A). This experiment ultimately confirmed slow and incomplete activation of the SIn glycosides under the reaction conditions common for the activation of alkyl/aryl thioglycosides. Adduct 28 can be readily activated for subsequent glycosylation because it is an intermediate formed as the first step of the interaction of the SIn leaving group with the iodonium promoter. In the competition experiment, it acts as a trap for excess I+ remaining after the activation of the SEt leaving group. Upon this, adduct 29 was formed as a result of trapping the SEt group, and this compound can also be glycosylated under typical conditions for the SIn leaving group activation.

We then set up a comparative competition experiment wherein Sln donor 4 and ethylthio glycoside 26 were set to compete for acceptor 7 in the presence of Ag2CO3 and TMSOTf, newly developed reaction conditions for the activation of SIn glycosides. As a result, SIn donor 4 reacted completely, whereas SEt donor 26 was recovered nearly quantitatively (97% yield, Scheme 6B). This series of experiments demonstrated that SIn glycosides possess different glycosyl donor properties than both thioglycosides and thioimidates to which they are structurally related to.

In summary, we developed a new class of glycosyl donors, indolylthio glycosides. This new glycosyl donor can be activated using a range of activators. Although the activation of the SIn leaving group requires excess reagents, their reactivity profile is interesting. The activation process was studied by NMR, and the increased understanding of the mechanism led to a discovery of orthogonality of the SIn leaving group versus thioglycosides and thioimidates. Further investigation of this leaving group in oligosaccharide synthesis and structural and mechanistic studies are 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. AgOTf was coevaporated at least twice with dry toluene, dried in vacuo, and stored under dark for a better yield of the glycosylated product. Column chromatography was performed on silica gel 60 (70–230 mesh), and reactions were monitored by TLC on Kieselgel 60 F254. The compounds were detected by examination under UV light and by charring with 5% sulphuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. CH2Cl2 and CICH2CH2CH2Cl (1,2-DCE) were distilled from CaH2, 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 with a Jasco P-2000 polarimeter. 1H NMR spectra were recorded in CDCl3 at 300 MHz, and 13C{1H} NMR spectra were recorded at 75 MHz. The 1H NMR chemical shifts are referenced to the central signal of CDCl3 (δH = 7.26 ppm) for solutions in CDCl3. Anomeric purity or anomeric ratios were accessed or calculated by comparing the integration intensities of the relevant signals in their 1H NMR spectra. Anomeric ratios were accessed or calculated by comparing the integration intensities of the relevant signals in their 1H NMR spectra. The 13C NMR chemical shifts are referenced to the central signal of CH2Cl2 (δC = 37.3 ppm). 

The residue was purified by column chromatography on silica gel (ethyl acetate–hexane 5% gradient elution) followed by crystallization from diethyl ether–hexane to afford the title compound as colorless crystals in 64% yield (358 mg, 2.3 mmol). Analytical data for HSIn were in accordance with that previously reported.13 

1H NMR (500 MHz, CDCl3, δ): 6.67 (br. s, 1H, =CH), 7.10 (d, 1H, H-5, J5,6a = 10.8 Hz, C81.8), 7.22 (t, 1H, J5,6a = 10.8 Hz, C81.8), 7.45 (m, 24H, aromatic), 6.60 (br. s, 1H, =CH), 7.10 (d, 1H, J5,6a = 10.8 Hz, C81.8). The resulting mixture was stirred for 4 h at rt. After that, the volatiles were removed under reduced pressure. The residue was dissolved in ethyl acetate (∼200 mL) and washed with water (4 × 50 mL). The organic phase was separated, dried over Na2SO4, and concentrated under reduced pressure. The residue was dried in vacuo for 1 h then dissolved in hot methanol (ca. 50 °C). The resulting solution was allowed to slowly cool to rt to afford the title compound as a yellow crystalline solid in 64% yield (358 mg, 2.3 mmol). Analytical data for HSIn were in accordance with that previously reported.13 

1H Indol-2-yl 2,3,4,6-Tetra-O-benzyl-1-thio-β-D-galactopyranoside (2). HSIn (0.45 g, 3.34 mmol), anhydrous K2CO3 (0.46 g, 3.33 mmol), and 18-crown-6 (0.16 g, 0.61 mmol) were added to a solution of 2,3,4,6-tetra-O-benzyl-α-galactopyranosyl bromide14 (1.2 g, 3.03 mmol) in dry acetone (50 mL), and the resulting mixture was stirred under argon for 50 °C for 3 h. After that, the solids were filtered off through a pad of Celite and 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 (250 mL), and water (2 × 50 mL). The organic phase was separated, dried over Na2SO4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (toluene–ethyl acetate 1% gradient elution) followed by crystallization from diethyl ether–hexane to afford the title compound as colorless crystals in 64% yield (358 mg, 2.3 mmol). Analytical data for HSIn were in accordance with that previously reported.13
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.

**Method B: Glycosylation in the Presence of NIS and TFOH or TMSOTf.** A mixture of a glycosyl donor (0.041–0.044 mmol), a glycosyl acceptor (0.037–0.040 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 (0.165–0.178 mmol) and TFOH (0.041–0.044 mmol) or TMSOTf (0.041 mmol) were added, and the resulting mixture was stirred for the time and temperature indicated in the tables. 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 Na₂S₂O₃ (2×10 mL) and H₂O (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.

**Methyl 6-O-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl)-2,3,4-tri-O-benzyl-a-D-glucopyranoside (11).** The title compound was obtained from donor 2 and acceptor 7 by general glycosylation procedure in 87% yield as a white amorphous solid. Analytical data for 11 was in accordance with that previously reported.²⁰

**Methyl 4-O-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl)-2,3,6-tri-O-benzyl-a-glucopyranoside (12).** The title compound was obtained from donor 2 and acceptor 8 by the general glycosylation procedure in 69% yield as a clear syrup. Analytical data for 12 was in accordance with that previously reported.²⁰

**Methyl 3-O-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl)-2,4,6-tri-O-benzyl-a-D-glucopyranoside (13).** The title compound was obtained from donor 2 and acceptor 9 by the general glycosylation procedure in 78% yield as a clear syrup. Analytical data for 13 was in accordance with that previously reported.¹⁹

**Methyl 2-O-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl)-3,4,6-tri-O-benzyl-a-D-glucopyranoside (14).** The title compound was obtained from donor 2 and acceptor 10 by the general glycosylation procedure in 79% yield as a clear syrup. Analytical data for 14 was in accordance with that previously reported.¹⁹

**Methyl 6-O-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl)-2,3,4-tri-O-benzyl-a-glucopyranoside (15).** The title compound was obtained from donor 4 and acceptor 7 by the general glycosylation procedures in 91% yield (α/β = 1.1:1) as a colorless foam. Analytical data for 15 was in accordance with that previously reported.²⁷

**Methyl 4-O-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl)-2,3,6-tri-O-benzyl-a-D-glucopyranoside (16).** The title compound was obtained from donor 4 and acceptor 8 by the general glycosylation procedure in 66% yield of 16 (α/β = 1.1:1) as a clear syrup. Analytical data for 16 was in accordance with that previously reported.²⁷

**Methyl 3-O-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl)-2,4,6-tri-O-benzyl-a-D-glucopyranoside (17).** The title compound was obtained from donor 4 and acceptor 9 by the general glycosylation procedure in 70% yield (α/β = 1.4:1) as a clear syrup. Analytical data for 17 was in accordance with that previously reported.²⁷

**Methyl 2-O-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl)-3,4,6-tri-O-benzyl-a-D-glucopyranoside (18).** The title compound was obtained from donor 4 and acceptor 10 by the general glycosylation procedure in 81% yield (α/β = 1.2:1) as a colorless foam. Analytical data for 18 was in accordance with that previously reported.²⁷

**Methyl 6-O-(2,3,4,6-Tetra-O-benzyl-D-galactopyranosyl)-2,3,4-tri-O-benzyl-a-D-glucopyranoside (19).** The title compound was obtained from donor 6 and acceptor 7 by the general glycosylation procedure in 70% yield (α/β = 1.1:3) as a clear syrup. Analytical data for 19 was in accordance with that previously reported.²⁷

**Methyl 4-O-(2,3,4,6-Tetra-O-benzyl-D-galactopyranosyl)-3,4,6-tri-O-benzyl-a-D-glucopyranoside (20).** The title compound was obtained from donor 6 and acceptor 8 by the general glycosylation procedure in 54% yield (α/β = 6.0:1) as a clear syrup. Analytical data for 20 was in accordance with that previously reported.²⁷

Methyl 3-O-(2,3,4,6-Tetra-O-benzyl-a-D-galactopyranosyl)-2,4,6-tri-O-benzyl-a-D-glucopyranoside (21). The title compound was obtained from donor 6 and acceptor 9 by the general glycosylation procedure in 62% yield (α/β = 1.7:1) as a clear syrup. Analytical data for 21 was in accordance with that previously reported.

Methyl 2-O-(2,3,4,6-Tetra-O-benzyl-a-D-galactopyranosyl)-3,4,6-tri-O-benzyl-a-D-glucopyranoside (22). The title compound was obtained from donor 6 and acceptor 10 by the general glycosylation procedure in 75% yield (α/β = 2.0:1) as a clear syrup. Analytical data for 22 was in accordance with that previously reported.³⁴

**H NMR Monitoring Experiments.** SIn Glycoside 2 in the Presence of NIS. A solution of donor 2 (0.04 mmol) and NIS (0.040–0.16 mmol) in CDCl₃ (1.0 mL) was stirred in a round-bottom flask under argon for 5 min at rt. The resulting solution was quickly transferred into a standard 5 mm NMR tube, and the ¹H NMR spectrum was recorded at 15, 25, and 60 min time points. The recorded spectra are presented in Scheme 2 and the Supporting Information. SIn Glycoside 2 in the Presence of TMSOTf. A solution of donor 2 (0.0206 mmol) and TMSOTf (0.0206–0.0824 mmol) in CDCl₃ (1.0 mL) was stirred in a round-bottom flask under argon for 5 min at rt. The resulting solution was quickly transferred into a standard 5 mm NMR tube, and the ¹H NMR spectrum was recorded at 15, 25, and 45 min time points. The recorded spectra are presented in Scheme 4 and the Supporting Information.

**Competition Experiments.** Experiment A. A mixture of ethylthio glucoside 26 (26.1 mg, 0.044 mmol), SIn glucoside 4 (30.0 mg, 0.044 mmol), acceptor 7 (41.5 mg, 0.089 mmol), and molecular sieves (3 Å, 80 mg) in 1,2-DCE (1.0 mL) was stirred under argon for 1 h at rt. Triflic acid (8.0 μL, 0.00894 mmol) and NIS (12.1 mg, 0.0536 mmol) were added, and the resulting mixture was stirred under argon for 30 min at rt. The solid was then filtered off through a pad of Celite and rinsed successively with dichloromethane. The combined filtrate (∼30 mL) was washed with 10% aq Na₂S₂O₃ (2×10 mL) and H₂O (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 produce 15 in 98% yield. Also recovered were compounds 28 (HRMS [M + Na]⁺ calc for [C₉H₁₃NO₃SNa⁺] 820.1570, found 820.1596) and 29 (HRMS [M + Na]⁺ calc for [C₉H₁₁NO₃SNa⁺] 754.2637, found 754.2645).

**Experiment B.** A mixture of ethylthio glucoside 26 (26.1 mg, 0.044 mmol), SIn glucoside 4 (30.0 mg, 0.044 mmol), glucosyl acceptor 7 (41.5 mg, 0.089 mmol), and molecular sieves (3 Å, 80 mg) in 1,2-DCE (1.0 mL) was stirred under argon for 1 h at room temperature. Ag₂CO₃ (12.3 mg, 0.044 mmol) was added, and the resulting mixture was stirred for 5 min at rt. After that, TMSOTf (32.4 μL, 0.178 mmol) was added, and the resulting mixture was stirred under argon for 30 min at rt. The reaction was then quenched with triethyl amine (one drop). The solid was filtered off through a pad of Celite and rinsed successively with dichloromethane. The combined filtrate (∼30 mL) was washed with H₂O (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 produce 15 in 96% yield. Also recovered was thioglycoside 26 in 97% yield.

**Experiment C.** A mixture of S-benzoxazolyl glucoside 22 (15892 mg, 30.1 mg, 0.045 mmol), SIn glucoside 4 (30.0 mg, 0.044 mmol), glucosyl acceptor 7 (41.5 mg, 0.089 mmol), and molecular sieves (3 Å, 80 mg) in 1,2-DCE (1.0 mL) was stirred under argon for 1 h at rt. After that, freshly activated AgOTf (10.7 mg, 0.089 mmol) was added, and the resulting mixture was stirred under argon for 20 min 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 H₂O (2 x 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 produce 15 in 96% yield. Also recovered was Sn derivative 4 in 90% yield.

**X-ray Crystal Structure Determination for Compounds 2 and 6.** The obtained crystals were mounted on a MiTeGen cryoloop in random orientations. For compound 2, preliminary examination and data collection were performed using a Bruker X8 Kappa Apex II single-crystal X-ray diffractometer equipped with an Oxford Cryostream LT device. All data were collected using graphite monochromated Mo K radiation (~0.71073 Å) from a fine focus sealed tube X-ray source. Preliminary unit cell constants were determined with a set of 36 narrow frame scans. Typical data sets consist of combinations of τ and ϕ scan frames with a typical scan width of 0.5 and counting time of 10 s/frame at a crystal to a detector distance of 4.0 cm.

For compound 6, preliminary examination and data collection were performed using a Bruker Venture Duo Photon-II single-crystal X-ray diffractometer equipped with an Oxford Cryostream LT device. Data sets were collected using an Incoatec µs microfocus source (Cu) with multilayer mirror optics. Preliminary unit cell constants were determined from a set of 180° fast ϕ scan frames (1 s exposure, 1 scan). Typical data sets consist of combinations of τ and ϕ scan frames with a typical scan width of 1.0 and counting time of 1 to 5 s/frame at a crystal to detector distance of 3.7 cm.

The collected frames were integrated using an orientation matrix determined from the narrow frame scans. Apex II and SAINT software packages were used for data collection and data integration. Analysis of the integrated data did not show any decay. Final cell constants were determined by the global refinement of reflections harvested from the complete data set. Collected data were corrected for systematic errors using SADABS based on the Laue symmetry using equivalent reflections.

Structure solution and refinement were carried out using the SHELXTL- PLUS software package. The structures were solved by direct methods and refined successfully in the monoclinic space group, P2₁. Full matrix least-squares refinements were carried out by minimizing Σ[(Fo - Fc)²]. The non-hydrogen atoms were refined anisotropically to convergence. All hydrogen atoms were treated using an appropriate riding model (AFIX m3). Absolute structure determinations were carried out by fast Fourier transformations.

**Supporting Information**

This material is available free of charge via the Internet at The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00943.

**X-Ray crystal structure determination for compound 2 (CIF)**

**X-Ray crystal structure determination for compound 6 (CIF)**

Additional monitoring experiments, NMR spectra for all new and selected known compounds, and X-ray structure determination data are listed in the Supporting Information.

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