

Glycoside Synthesis | Very Important Paper |

Glycosylations of Simple Acceptors with 2-O-Acyl L-Idose or L-Iduronic Acid Donors Reveal Only a Minor Role for Neighbouring-Group Participation

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Abstract: Several L-idose and L-iduronic acid glycosyl donors (mostly thioglycosides but also halides and trichloroacetimidates) with acyl protecting groups at the C-2 position were prepared and evaluated in glycosylation reactions with simple acceptors. In glycosaminoglycan oligosaccharide syntheses in the literature, the presence of C-2 acyl protecting groups in L-ido-configured glycosyl donors generally results in exclusive formation of 1,2-*trans* glycosidic linkages, a finding that has typically been attributed to neighbouring-group participation. However, glycosylations of simple alcohols with L-ido-configured donors (particularly thioglycosides), reported here, generally displayed incomplete stereocontrol and gave mixtures of the 1,2-*trans* and 1,2-*cis* products, suggesting that neighbour-

Introduction

Glycosaminoglycans (GAGs) are complex, highly sulfated polysaccharides that play important roles in mammalian physiology as well as in numerous disease processes such as angiogenesis, metastasis, inflammation and viral infections, to name a few. The monosaccharide L-iduronic acid (IdoA) is a key component of the GAGs heparin, heparan sulfate (HS) and dermatan sulfate (DS) where it is found $\alpha(1\rightarrow 4)$ -linked to D-glucosamine (for heparin/HS)^[1] or $\alpha(1\rightarrow 3)$ -linked to *N*-acetyl-D-galactosamine (for DS).^[2] The unusual conformational flexibility of IdoA is thought to contribute to the biological activity of GAGs by facilitating binding interactions with a range of structurally diverse proteins.^[2,3] The synthesis of IdoA building blocks^[4] is of great current interest for synthetic access to well-defined GAG oligosaccharides which are essential for biological studies to identify therapeutically useful sequences and for elucidating structureactivity relationships.[5]

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ing-group participation has lesser importance in these reactions. Glycosyl donors and reaction conditions were identified that gave improved, but not exclusive, selectivity for the desired α -L-anomer (1,2-*trans*) as the major product. Interestingly, glycosylations under the same reaction conditions with more complex monosaccharide acceptors gave exclusively the expected 1,2-*trans* products. The role of neighbouring-group participation in these glycosylations was explored with density functional theory (DFT) calculations, which revealed that the nonstereoselective addition of the acceptor alcohol to the intermediate oxocarbenium ion is competitive with the stereospecific addition of the acceptor to the acyloxonium ion intermediate.

As non-reducing end IdoA is found in GAGs only in α -L-glycosidic linkages, generally the IdoA or L-idose (Ido) glycosyl donors required for GAG oligosaccharide synthesis are prepared^[4,5b,5c] with an acyl protecting group at C-2 to ensure exclusive formation of the desired α (1,2-*trans*) glycosidic linkage. The 1,2-trans stereoselectivity has been generally thought to arise from neighbouring-group participation. Glycosylation reactions with glycosyl donors bearing a "participating" acyl protecting group at C-2 are generally thought to occur via the initial formation of a short-lived positively charged oxocarbenium ion formed upon dissociation of the anomeric leaving group (Scheme 1).^[6] Immediate intramolecular attack by the C-2 protecting group leads to the formation of an acyloxonium ion intermediate which blocks approach of the acceptor from the bottom face and thus prevents formation of the 1,2-cis glycosidic product. Direct nucleophilic attack by the acceptor alcohol on C-1 of the acyloxonium ion gives the 1,2-trans glycosidic product (Scheme 1, pathway a), while attack at the carbonyl carbon leads to the formation of an orthoester byproduct (pathway d). The stereoselectivity of the reaction is also influenced by factors such as leaving group, solvent, activation system, additives and protecting groups on the donor and acceptor. Occasionally, significant amounts of 1,2-cis-linked glycosides are also obtained (pathway c), mostly when the acceptor alcohols are unreactive, and/or if the participating substituents at C-2 are poorly nucleophilic.^[7]

Many \L -Ido-configured donors bearing acyl groups at C-2 and which adopt or are locked in the ${}^{1}C_{4}$ conformation in solu-

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Scheme 1. Mechanism for glycosylation with a glycosyl donor bearing an acyl participating group at C-2 (adapted from ref.[6b]).

tion, have been utilized in GAG oligosaccharide synthesis^[5] and in the majority of cases the glycosyl acceptor has been a secondary alcohol on a suitably protected D-glucosamine (or Dgalactosamine) derivative. In these cases the glycosylation reactions generally give the expected α -L-linked 1,2-trans glycosylation products exclusively. There have also been many examples of the synthesis of GAG oligosaccharides with an IdoA residue at the reducing end,^[8] generally as a glycoside of a reactive primary or secondary alcohol (e.g., methanol, 2-propanol, etc) or as part of an aliphatic linker. The required glycosylation reactions of IdoA or Ido glycosyl donors with acyl (participating) protecting groups at C-2 with such simple alcohols have also generally been reported to give exclusively the desired α -L-glycosides.^[8] Interestingly, however, there have been some cases where the reported stereochemical outcomes of the reactions have been, unexpectedly, moderate to poor.^[9] However, there have been no investigations into the reasons for the observed selectivities, nor any systematic studies on these types of glycosylation reactions. Herein, we describe the results of our own studies on the glycosylation reactions of a variety of Ido or IdoA donors bearing participating protecting groups at C-2 with simple alcohol acceptors. In most cases, a mixture of anomers was obtained rather than the expected 1,2-trans glycoside, indicating that the reaction did not proceed exclusively via an acyloxonium ion intermediate. We report DFT calculations that show that non-stereoselective attack by the acceptor on the intermediate oxocarbenium ion is competitive with the stereoselective reaction of the acceptor with the acyloxonium ion.

Results and Discussion

Glycosylations Using Glycosyl Halide Donors

As part of a broader project aimed at the synthesis of IdoA derivatives as probes for HS-degrading enzymes involved in

mucopolysaccharidosis disorders, synthetic access was required to simple glycosides of Ido or IdoA. Initial efforts were directed towards the preparation of methyl α -L-idopyranosides such as 6 via the Koenigs-Knorr reaction (Scheme 2). The well-known Koenigs-Knorr method uses heavy metal salts, mainly silver or mercury salts, as promoters and glycosyl halides (usually bromides) as the glycosyl donors. Thus, bromide 3 was chosen as the target glycosyl halide. Acetolysis of the 1,6-anhydrosugar $\mathbf{1}^{[10]}$ gave glycosyl acetate $\mathbf{2}^{[11]}$ in 98% yield with an α/β anomeric ratio of 1.6:1. The anomeric configurations of Ido or IdoA glycosides obtained throughout this study were determined by a combination of NMR techniques. Anomers with the α -L configuration generally displayed long range coupling from H-1 to H-3 which was readily discernible in COSY spectra, whereas their β anomeric counterparts did not. On the other hand, only the β anomers displayed an nOe correlation between H-1 and H-5 in 1D NOESY spectra. Another trend that was apparent for a β anomer was the chemical shift of C-5 in the ¹³C NMR spectrum which was shifted significantly downfield relative to the α anomer, often by > 5 ppm.

Glycosyl acetate **2** was treated with 30 % HBr in acetic acid at room temperature. However, the desired bromide **3** proved to be unstable and could not be isolated due to hydrolysis to the hemiacetal **4**, which was isolated in 74 % yield. Treatment of compound **2** with bromotrimethylsilane^[12] in anhydrous DCM at 0 °C also led to the hemiacetal **4**. Despite earlier reports^[11,13] of the successful synthesis of **3** using titanium tetrabromide, in our hands the bromide **3** was found to be highly reactive and unstable. Hung has also reported that a similar L-idosyl bromide is unstable and is readily hydrolyzed to the hemiacetal.^[14]

The use of glycosyl chloride **5** as a glycosyl donor was then investigated. Although the reactivity of glycosyl chlorides is lower than glycosyl bromides as glycosyl donors, their thermal







Scheme 2. Preparation and glycosylations with halide and trichloroacetimidate L-ido glycosyl donors.

and chemical stabilities are higher. Compound 5 was synthesized according to the procedure reported by Zhang and coworkers,^[15] wherein acetate 2 was treated with thionyl chloride and tin tetrachloride, producing chloride 5 in good yield (88 %, 10:1 α/β) which was then used directly in the next step without further purification. Upon subjecting chloride 5 to Koenigs-Knorr reaction conditions with Ag₂CO₃ as promoter, two products were obtained. The desired methyl glycoside 6 was isolated exclusively as the α -anomer in 17 % yield but the major product of the reaction was the orthoester 7 (34 %). The identities of the products were determined by NMR spectroscopy and mass spectrometry (both m/z 433 [M + Na]⁺). The ¹H NMR spectrum of the orthoester 7 had two sets of signals due to the presence of two diastereoisomers in a ratio of 10:3. Hung has also reported the formation of orthoester as the major product on subjecting a similar α -L-glycosyl chloride to glycosylation with methanol using AgOTf as promoter.^[14] Similarly, Whitfield^[9b] reported that glycosylation of methanol with a related IdoA-configured glycosyl bromide also gave orthoester as the major product and interestingly, the β -L-glycoside as a minor product with no trace of α -L-glycoside.

Sugar 1,2-orthoesters are often undesired byproducts in the Koenigs–Knorr glycosylation with donors carrying 1,2-*trans* C-2 acetyl protecting groups. Formation of orthesters in this case suggests that the reaction proceeds via an acyloxonium intermediate. Subsequent nucleophilic attack on C-1 by methanol leads to the formation of the methyl glycoside **6** and the nucleophilic attack on the newly formed acyloxonium carbon leads to the formation of the 1,2 orthoester **7**. Orthoesters can often be converted into their corresponding glycosides under Lewis acid catalysis.^[16] Treatment of **7** with a catalytic amount of TMSOTf in the presence of methanol led to the isolation of methyl glycoside **6**. However, due to partial conversion and decomposition of starting material, **6** was isolated in poor yield (25 %). Jacquinet et al.^[9a] have previously reported that glycos-

ylation of methanol with a related IdoA-configured orthoester as a glycosyl donor results in a mixture of anomeric methyl glycosides ($\alpha/\beta = 2$:1), suggesting that reaction through an oxocarbenium ion intermediate is a viable pathway.

Glycosylation Using Glycosyl Trichloroacetimidates

Glycosyl trichloroacetimidates are commonly used as powerful glycosyl donors owing to their ease of synthesis and stability at room temperature.^[17] The activation is accomplished using catalytic amounts of Lewis acids such as TMSOTf or BF₃•OEt₂.^[18] Hemiacetal 4 was thus converted into the corresponding trichloroacetimidate donor 8^[19] by treatment with trichloroacetonitrile and cesium carbonate as the base (Scheme 2). Trichloroacetimidate 8 was obtained in 48 % yield as a mixture of anomers (2:1, α/β). However, the reaction was capricious and yields within the range 35-48 % were obtained upon scaling up. The use of other bases (K₂CO₃, DBU) did not improve yields. In all cases TLC of the reaction did not indicate any significant decomposition. Thus the low yield is presumably the result of decomposition of the trichloroacetimidate during work up and purification. The subsequent glycosylation of donor 8 at 0 °C with TMSOTf as the promoter gave the methyl glycoside 6 in good yield (83 %) but with poor selectivity (α/β = 1.2:1), suggesting that in this case reaction does not proceed exclusively via an acyloxonium ion intermediate. Kusumoto and co-workers reported the exclusive formation of the α -anomer of glycoside 6 in 72 % yield using BF₃·OEt₂ as a promoter.^[19a] Owing to the modest yield in our hands for the synthesis of donor 8 this reaction was not pursued further and attention was turned to thioglycoside donors.

Glycosylation Using Thioglycoside Donors

Amongst the various glycosyl donors, thioglycosides are one of the most popular because of their stability and ease of prepara-







Scheme 3. Synthesis of L-ido thioglycoside donors 9, 10 and 15 and glycosylation with 10.

tion.^[20] Thioglycosides of L-idose and L-idoA derivatives are commonly used as glycosyl donors with various acceptors for GAG oligosaccharide synthesis. When reacting L-ido-configured thioglycoside donors containing participating protecting groups with simple alcohols such as methanol, the formation of anomeric mixtures is not unprecedented.^[9d] Ethyl thioglycoside 9 was initially chosen for investigation and was prepared from compound 2 in moderate yield (49 %) by treatment with ethanethiol in the presence of BF₃•OEt₂ (Scheme 3). Tabeur et al.^[9c] and Codée et al.^[21] have previously reported the synthesis of compound 9 in 95 % and 79 % yield, respectively, under the same reaction conditions. The moderate yield obtained could be attributed to the decomposition (detected by TLC) of either the starting material 2 or the thioglycoside 9. Despite having a participating group at C-2, an anomeric mixture (2:1 α/β) was obtained. Phenylthioglycoside 10^[9c] was subsequently synthesized in 79 % yield with anomeric ratio of 10:1 α/β via the reaction of 2 with thiophenol and BF₃·Et₂O at 0 °C. This is a considerable improvement in both yield and selectivity compared with the synthesis of 9.

Glycosylation of **10** with methanol in dichloromethane in the presence of NIS and catalytic TMSOTf at room temperature, afforded methyl glycoside **6** in 79 % yield with an anomeric ratio of 3.3:1 α/β (Scheme 3). Further experiments were then performed in an effort to increase selectivity for the desired α -anomer. Thus, the effect of reaction temperature on the anomeric selectivity of the reaction was studied (Table 1). Decreasing the temperature to 0 °C gave a 1:1 mixture of anomers. However, increasing the temperature to 35 °C led to a 10-fold increase in the α -anomeric ratio (30:1 α/β).

Fügedi and co-workers^[22] have reported the direct synthesis of L-ido-configured thioglycosyl donors via the 1,6-anhydrosugar 1 with exclusive α selectivity.^[9d,22] Anhydrosugar 1 was thus converted into the partially or fully protected derivatives 11^[23] and 13^[24] (Scheme 2). Subsequent thiolysis of 11 and 13 with trimethyl(phenylthio)silane in the presence of zinc iodide led to the formation of the thioglycosides 12^[25] and 14 in excellent yield (77–81 %) exclusively as the α anomers.^[25] The selectivities obtained for the preparation of 9, 10, 12 and 14, although not directly comparable because of the nature of the

Table 1.	Summary of	of glycosylation	outcomes	with	different	thioglycoside	donors.
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Entry	Donor	Acceptor	Conditions ^[a]	Product (% yield)	α/β ratio ^[b]
1	10	MeOH	NIS-TMSOTf, 0 °C, 3 h	6 (80)	1:1
2	10	MeOH	NIS-TMSOTf, room temp., 2 h	6 (79)	3.3:1
3	10	MeOH	NIS-TMSOTf, 35 °C, 0.8 h	6 (82)	30:1
4	10	MeOH	NIS-TfOH, –78 °C to r.t., 24 h	6 (n.d.)	1.7:1
5	15	MeOH	Ph ₂ SO/Tf ₂ O	16 (10)	1:0
6	17	MeOH	NIS-TMSOTf, r.t., 2 h	18 (90)	1:1
7	17	MeOH	NIS-TMSOTf, 0 °C, 6 h	18 (88)	1.3:1
8	17	MeOH	NIS-TMSOTf, 35 °C, 0.5 h	18 (78)	1.2:1
9	17	MeOH	NIS-TMSOTf, DCE, 65 °C, 0.5 h	18 (72)	1.2:1
10	19	MeOH	NIS-TMSOTf, r.t., 1 h	20 (80)	1.7:1
11	19	<i>n</i> BuOH	NIS-TMSOTf, r.t., 2 h	21 (51)	2:1
12	19	22	NIS-TMSOTf, r.t., 0.5 h	23 (75)	1:0
13	19	MeOH	NIS-TfOH, –78 to 0 °C, 3 h	25 (68)	2:1
14	19	<i>n</i> BuOH	NIS-TfOH, –78 to 0 °C, 7 h	26 (82)	3.2:1
15	19	<i>i</i> PrOH	NIS-TfOH, –78 to 0 °C, 7 h	27 (77)	2.8:1
16	24	nBuOH	NIS-TfOH, –78 to 0 °C, 6 h	28 (85)	3.8:1
17	24	<i>i</i> PrOH	NIS-TfOH, –78 to 0 °C, 6 h	29 (78)	5.6:1

[a] All reactions carried out in DCM unless otherwise indicated. [b] Anomeric ratio determined by ¹H NMR spectroscopy.



starting materials, indicate that the nature of both the nucleophile and the Lewis acid are important factors in determining anomeric selectivity in reactions to form L-ido thioglycosides. Subsequent C-6 oxidation of compound **14** with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and iodobenzene diacetate (BAIB), followed by esterification of the resulting carboxyl group with methyl iodide and potassium hydrogen carbonate gave the methyl ester **15** in good yield (68 % over two steps).

Donor 15 was subjected to alvcosvlation using NIS-TMSOTF as the promoter at room temperature (Scheme 3). However, only the starting material was isolated after several hours of reaction. Glycosyl donor 15 is a disarmed donor, due to the presence of the electron-withdrawing methyl ester at C-5. The more powerful promoter system of diphenyl sulfoxide (Ph₂SO) and triflic anhydride in the presence of the hindered base 2,4,6tri-tert-butylpyrimidine (TTBP) was then investigated.^[26] The glycosylation was performed according to the protocol reported by Crich and Smith,^[27] wherein a 1:1 mixture of thioglycoside and Ph₂SO was cooled to -75 °C in DCM in the presence of TTBP. This mixture was then treated with 1.1 equivalents of triflic anhydride (Tf₂O), and, after 5 min, the acceptor (methanol) was added and the reaction stirred at this temperature for 30 min. Unfortunately, this strategy of glycosylation gave the α -methyl glycoside **16** in a poor yield (10 %) due to extensive decomposition of the glycosyl donor 15 as detected by TLC and it was unclear whether any β -glycoside had also formed during the reaction. This donor was therefore not investigated further.

Having failed to obtain the desired α -L-methyl glycoside **16** in sufficient yield, glycosylation using the armed non-oxidized analogue 14 was investigated. Firstly, the free 6-OH group was protected with a temporary protecting group in order to avoid self-condensation of the substrate under glycosylation conditions. The tert-butyldimethylsilyl (TBDMS) ether was chosen as a temporary protecting group for 6-OH of 14 (Scheme 4). The silvl ether 17 obtained in 97 % yield, was subjected to glycosylation using NIS-TMSOTf as a promoter system at room temperature to obtain the methyl glycoside 18 in an excellent yield of 90 % with an anomeric ratio of 1:1 α/β . During the glycosylation reaction, the C-6 silvl ether protecting group was also cleaved, possibly during work-up. Attempts were then made to optimize the formation of the α -anomer (summarized in Table 1). Anomeric mixtures were obtained under all of the reaction conditions studied. Decreasing the temperature of the reaction to 0 °C increased the time required for completion of the reaction and also slightly increased the amount of α -anomer formed



(1.3:1). Upon increasing the reaction temperature to 35 °C or 65 °C, the reaction time decreased and a slight decrease in the fraction of α -anomer was seen (1.2:1). However, the change in anomeric ratio was not significant in either case, in contrast to the reactions with donor **10** which showed a dramatic improvement in α -selectivity upon increasing the temperature.

A glycosylation reaction was next performed with glycosyl donor 19 (Scheme 5), obtained as a gift from Alchemia Ltd and used as a building block for their generic synthesis of fondaparinux where it gives exclusively the $\boldsymbol{\alpha}$ glycoside with mono- or disaccharide acceptors.^[28] The only previous report of this compound was in a patent application^[28] where no analytical data were given, and where the structure was depicted incorrectly as the β -L-glycoside. Compound **19** was thus fully characterized by 1D and 2D NMR and MS experiments, and confirmed to be the α -L-glycoside. There was no correlation between H-1 and H-5 in the NOESY spectrum, while a W-coupling between H-1 and H-3 was apparent in the ¹H and COSY spectra. The thioglycoside 19 differs from the other donors considered earlier in having a locked conformation due to the 4,6-O-isopropylidene protecting group. This feature might have an impact on the stereochemical outcome of glycosylation as C-2 participation would likely result in a strained acyloxonium ion



Scheme 5. Glycosylations with donors 19 and 24.



Scheme 4. Glycosylations with L-ido thioglycoside donors 15 and 17.





intermediate. On subjecting the thioglycoside **19** to glycosylation at room temperature with NIS/TMSOTf an anomeric mixture of the methyl glycoside **20** was obtained (1.7:1 α/β) in 80 % yield. The isopropylidene group was removed under these reaction conditions, presumably post-glycosylation, to afford methyl glycoside **20**. A similar result was obtained upon reaction with *n*-butanol at room temperature to give **21** in moderate yield (51 %, 2:1 α/β). Glycosylation of the more complex monosaccharide acceptor **22**^[28] under the same conditions gave as anticipated, only the α -methyl glycoside **23** in good yield (75 %), although once again the isopropylidene group was removed.

It was next decided to change the promoter system for glycosylation to NIS/TfOH and to conduct the reaction at -78 °C with warming up to -20 or 0 °C as necessary. This protocol is commonly used for HS oligosaccharide synthesis with thioglycoside donors^[29] and it has recently become the preferred method for thioglycoside activation in our laboratory (unpublished results). Thus donor 19 was reacted under these conditions with methanol, resulting in the formation of 25 in 68 % yield. The stereoselectivity ($\alpha/\beta = 2:1$) was similar but the isopropylidene group remained intact. The reaction was then repeated with *n*-butanol and 2-propanol as the acceptors, the latter to see if there was any difference in selectivity when using a secondary alcohol other than one on a monosaccharide acceptor. There has been a previous report of the glycosylation of an IdoA donor with 2-propanol resulting in a mixture of anomers.^[9e] The reactions were also repeated using the donor 24 wherein the C-2 participating group was replaced with a more sterically demanding pivalate group, which has been reported^[8a] to improve glycosylation outcomes with IdoA donors compared with their acetate congeners. The results are summarized in Table 1. In all cases the glycoside was obtained in good yield (77-85 %) but always as a mixture of anomers, although with improved selectivity towards the desired α anomer. The

best selectivity (α/β = 5.6:1) was obtained when using the less reactive secondary alcohol 2-propanol as the acceptor combined with donor **24** containing the C-2 pivalate group. The NIS-TfOH promoter system was also applied to the glycosylation of donor **10** with MeOH (Table 1, entry 4), but no advantage in selectivity was observed.

Although various L-idoA donors are known to give high stereoselectivity in reactions with complex glycosyl acceptors, the formation of anomeric mixtures containing a high proportion of β -glycoside is not unprecedented in glycosylations with simple acceptors such as methanol or 2-propanol.^[9] The results of our investigations described above provide numerous new examples of this phenomenon, suggesting that glycosylations of L-idose and L-idoA donors bearing a "participating group" do not always proceed via nucleophilic attack on the acyloxonium intermediate. In order to gain insight into the relevance of the acyloxonium intermediate in these glycosylations, we performed a density functional theory study. Calculations with the M06-2X functional^[30] were performed on the model system shown in Scheme 6 (details of the computational methods are given in the supporting information). Here, the pyranose ring has the same substitution pattern at C-2 and C-6 as in our thioglycosides 9 and 10, while the C-3 and C-4 substituents have been replaced by H atoms for simplicity. Methanol is used as the glycosyl acceptor.

The computations indicate that the oxocarbenium ion **31** would rapidly cyclize to form acyloxonium ion **32**. Oxocarbenium ion **31** is predicted to adopt a ^{2,5}*B* boat conformation, while acyloxonium ion **32** is predicted to prefer a twisted ^{0,3}*B* boat (Figure 1). The barrier to cyclization of **31** is almost negligible (**TS1**, $\Delta G^{\ddagger} \approx 1$ kcal/mol) and the cyclic acyloxonium ion **32** is 9.5 kcal/mol more stable than **31**. Hence, in a rapidly equilibrating mixture of these two cationic intermediates, the acyloxonium ion **32** would be the dominant, almost exclusive, component.



Scheme 6. Energetics of several pathways for glycosylation of the model thioglycoside **30**, computed with M06-2X/6-311+G(d,p)//M06-2X/6-31G(d) in SMD implicit dichloromethane. ΔG in kcal/mol. Note that the structures drawn only depict the general stereochemical features and not the exact conformations of the pyranose ring in each structure.







Figure 1. Structures of intermediates and transition states in the model glycosylation reaction of **30**, calculated with M06-2X/6-31G(d) in SMD implicit dichloromethane. Distances in [Å].

The reaction of acyloxonium ion 32 with methanol may proceed via the S_N2 transition state TS2 with a barrier of 12.8 kcal/ mol (relative to 32). In TS2, the pyranose ring of 32 is changing from the $^{O,3}B$ boat into a $^{1}C_{4}$ chair. This process is stereospecific, leading to the 1,2-*trans* glycoside α -33. Intermediate 32 cannot directly react with methanol to give the anomeric glycoside β -**33.** A possible route to β -**33** would involve the conversion of 32 back to 31 followed by attack of methanol on the lower face of the oxocarbenium carbon (TS4). Our computations indicate that once 32 has opened to 31, attack on either the top or bottom face by methanol does not pass through a well-defined transition state. However, the approach of methanol to the bottom face of 31 has an energy barrier of approximately 5.9 kcal/ mol, some 3-4 kcal/mol higher than that for top-face attack (2.1 kcal/mol). The transition states for the additions of methanol to the top and bottom faces of **31** retain the ^{2,5}B boat conformation of 31 (see Figure 1).

Conclusion

On the basis of the calculated barriers for **TS2–TS4**, the most favorable mechanism for the glycosylation of the model thioglycoside involves addition to the oxocarbenium ion **31** (**TS3**). Attack on the acyloxonium ion **32** (**TS2**) is about 1 kcal/mol higher in energy. The calculations correctly predict that the 1,2*trans* glycoside would be the favored product, but they overestimate the level of selectivity. In our experiments with thioglycosides **10**, **17**, and **19** (Table 1), anomeric mixtures with α/β ratios in the range 1:1–3:1 were obtained under most conditions, whereas the estimated barrier for **TS4** would predict much higher ratios. It is possible that the exact α/β ratio of glycoside formed in any given reaction is influenced by factors not included in our model, such as ion-pairing related phenomena and cage effects; these would vary with the reaction conditions and are more difficult to quantify by computational means. Previous theoretical work on glucose-related systems showed that solvent has an influence on the conformation of the ring, which in turn controls the stereoselectivity of the reaction.^[31] The effect of coordination of the counterion to the oxocarbenium ion has also been investigated.[32] Another factor to consider is the effect of substituents at C3 and C4, omitted in our model for simplicity, which could affect the stability of the cationic intermediates. What is clear, from both our experiments and our calculations, is that contrary to the commonly invoked mechanistic argument, the glycosylations of L-idose and L-idoA donors do not exclusively entail stereospecific attack by the acceptor on an acyloxonium intermediate. Non-stereospecific addition to the oxocarbenium ion is predicted to be a competitive, even dominant, pathway. We are currently studying the mechanisms of these glycosylation reactions in further detail, including the role of the configuration at C5, and will report our findings in due course.

Experimental Section

General Methods: General experimental details have been given previously.^[33] DCM and BF₃·OEt₂ were distilled from CaH₂ and freshly used for glycosylation reactions. Methanol for glycosylation reactions was distilled from magnesium turnings and stored over 3 Å molecular sieves. *n*-Butanol and 2-propanol were dried with molecular sieves.

1,2,4,6-O-Tetra-O-acetyl-3-O-benzyl-L-idopyranose (2): To a stirred solution of 1,6-anhydrosugar **1** (2.0 g, 8.0 mmol) in acetic anhydride (30 mL) under nitrogen at 0 °C was added TFA (1 mL). The mixture was then stirred at room temp. for 24 h, quenched with MeOH (10 mL) and concentrated under reduced pressure. Flash chromatography (hexane/EtOAc, 1:1) of the crude material af-



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forded tetraacetate **2** (3.4 g, 98 %, 1.6:1 α/β) as a colourless oil. The ¹H NMR spectroscopic data for the α -anomer were in agreement with the literature.^[11] 2α : ¹H NMR (500 MHz, CDCl₃): δ = 6.05 (br. s, 1 H, H-1), 4.94-4.92 (m, 1 H, H-2), 4.91-4.90 (m, 1 H, H-4), 4.71, 4.69 (ABq, J = 11.8 Hz, 2 H, CH₂Ph), 4.51 (ddd, J_{5,6b} = 6.4, J_{4,5} = 1.8 Hz, 1 H, H-5), 4.24–4.17 (m, 2 H, H-6a, H-6b), 3.76 (ddd, J_{2.3} = 2.9, J_{3.4} = 1.2 Hz, H-3) ppm. $^{13}{\rm C}$ NMR (125 MHz, CDCl_3): δ = 91.4 (C-1), 71.8 (C-3), 66.7 (C-4), 66.1 (C-2), 65.8 (C-5), 62.3 (C-6) ppm. The ¹H and ¹³C NMR spectroscopic data for the β -anomer were in agreement with the literature.^[11] $\mathbf{2\beta}$: ¹H NMR (500 MHz, CDCl₃): δ = 6.07 (d, $J_{1,2} = 1.8$ Hz, 1 H, H-1), 5.03–5.02 (m, 1 H, H-2), 4.86–4.83 (m, 1 H, H-4), 4.72, 4.67 (ABq, J = 11.7 Hz, 2 H, CH₂Ph), 4.37 (ddd, J_{5.6a} = 7.4, J_{5,6b} = 5.8, J_{4,5} = 2.1 Hz, 1 H, H-5), 4.18–4.12 (m, 2 H, H-6a, H-6b), 3.87 (t, J_{2,3} = J_{3,4} = 3.2 Hz, 1 H, H-3) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 90.3 (C-1), 73.2 (C-3), 71.8 (C-5), 66.9 (C-2), 66.4 (C-4), 62.4 (C-6) ppm. ESMS: m/z 461.2 [M + Na]+.

2,4,6-Tri-O-acetyl-3-O-benzyl-L-idopyranose (4): Compound 2 (0.3 g, 0.7 mmol) was dissolved in anhydrous DCM and activated 4 Å molecular sieves were added and the mixture kept under nitrogen for 15 min. A solution of 30 % HBr in acetic acid (0.5 mL) was then added, and the mixture was stirred at room temp. for 2 h. The reaction was then guenched with cold sat. NaHCO₃ (5 mL) and extracted with DCM (3×5 mL). The organic layer was then washed with water, dried (MgSO₄) and concentrated under reduced pressure. Flash chromatography (hexane/EtOAc, 1:1) of the crude mixture afforded hemiacetal **4** (0.2 g, 74 %, 1.7:1 α/β) as colourless oil. **4**α: ¹H NMR (500 MHz, CDCl₃): δ = 5.18 (d, $J_{1,2}$ = 1.8 Hz, 1 H, H-1), 4.90-4.95 (m, 1 H, H-4), 4.81-4.83 (m, 1 H, H-2), 4.71-4.76 (m, 2 H, CH₂Ph), 4.54 (dd, J_{5,6} = 6.4, J_{4,5} = 1.7 Hz, 1 H, H-5), 4.29-4.16 (m, 2 H, H-6a, H-6b), 3.89-3.91 (m, 1 H, H-3) ppm. ¹³C NMR (100 MHz, $CDCl_3$): $\delta = 91.7$ (C-1), 68.6 (C-4), 66.3 (C-2), 73.8 (CH₂Ph), 62.8 (C-5), 72.1 (C-3), 62.7 (C-6) ppm. **4** β : δ = 5.16 (br. s, 1 H, H-1), 4.90–4.92 (m, 1 H, H-4), 4.71–4.76 (m, 2 H, CH₂Ph), 4.31 (d, J_{1,2} = 1.4 Hz, H-2), 4.29–4.16 (m, 3 H, H-5, H-6a, H-6b), 3.93 (dd, 1 H, J_{2,3} = J_{3,4} = 3.0 Hz, H-3), 3.40 (d, 1 H, J_{1.0H} = 9.3 Hz, OH) ppm. ¹³C NMR (100 MHz, $CDCl_3$): $\delta = 92.8$ (C-1), 66.0 (C-4), 73.2 (CH₂Ph), 73.1 (C-3), 72.0 (C-5), 62.7 (C-6) ppm. ESMS: m/z 419.2 [M + Na]+.

2,4,6-Tri-O-acetyl-3-O-benzyl-L-idopyranosyl Chloride (5): To a stirred solution of the acetate 2 (1.8 g, 4.1 mmol) in anhydrous DCM (50 mL), thionyl chloride (0.6 mL, 8.4 mmol) and stannic chloride (0.5 mL, 9.6 mmol) were added. The reaction mixture was then stirred at room temp. for 90 min, neutralized with cold sat. NaHCO₃ and extracted with DCM (2×10 mL). The combined organic layer was then dried (MgSO₄) and concentrated under reduced pressure to obtain the crude glycosyl chloride **5** (1.5 g, 88 %, 10:1 α/β) as colourless oil, used directly in the next step without further purification. **5** α : ¹H NMR (500 MHz. CDCl₃): δ = 7.39–7.26 (m, 5 H, Ph), 6.01 (br. s, 1 H, H-1), 5.13-5.12 (m, 1 H, H-2), 4.92-4.90 (m, 1 H, H-4), 4.81, 4.65 (ABq, J = 11.8 Hz, 2 H, CH₂Ph), 4.72–4.68 (m, 1 H, H-5), 4.19 (d, J_{5,6} = 6.5 Hz, 2 H, H-6), 3.76–3.74 (m, 1 H, H-3), 2.08 (s, 3 H, CH₃), 2.06 (s, 3 H, CH₃), 2.05 (s, 3 H, CH₃) ppm. ¹³C NMR (125 MHz. CDCl₃): δ = 170.5, 169.9, 169.2 (3 × CO₂CH₃), 137.0, 128.6, 128.0, 127.6 (Ph), 88.5 (C-1), 72.2 (CH2Ph), 71.7 (C-3), 68.6 (C-2), 66.5 (C-4), 66.0 (C-5), 62.1 (C-6), 20.8 (\times 2), 20.7 (3 \times CH_3) ppm.

Glycosylation with Glycosyl Chloride 5: To the glycosyl chloride 5 (0.3 g, 0.7 mmol) in anhydrous toluene (10 mL) containing 3 Å molecular sieves, anhydrous methanol (0.7 mL) was added and the mixture heated to 70 °C. Ag₂CO₃ (260 mg, 0.94 mmol) was then added to the reaction mixture in 3 portions over 3 h and the reaction was maintained at 70 °C for 24 h. The reaction mixture was then filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (hexane/EtOAc, 2:1)

to give the orthoester 7 (0.1 g, 34 %) as colourless oil, $R_{\rm f}$ = 0.7. The ¹H NMR spectrum was in accord with the literature.^[8c] ¹H NMR (500 MHz. CDCl₃): δ = 7.38–7.37 (m, 5 H, Ph), 5.52 (d, $J_{1,2}$ = 2.7 Hz, 1 H, H-1), 4.80–4.77 (m, 1 H, H-4), 4.74, 4.64 (ABq, J = 11.8 Hz, 2 H, CH₂Ph), 4.15-4.10 (m, 3 H, H-5, H-6a, H-6b), 4.07-4.03 (m, 2 H, H-3, H-2), 3.22 (s, 3 H, OCH₃), 2.05 (s, 3 H, CH₃), 2.04 (s, 3 H, CH₃), 1.66 (s, 3 H, CH₃) ppm. ¹³C NMR (125 MHz. CDCl₃): δ = 170.6, 170.4 (2 × CO₂CH₃), 137.0, 128.6, 128.2, 127.9, 127.8, 123.8 [Ph, C(CH₃)(OCH₃)], 96.4 (C-1), 76.3 (C-3), 72.8 (CH2Ph), 71.6 (C-2), 67.8 (C-5), 65.8 (C-4), 62.9 (C-6), 49.1 (OCH₃), 25.0, 20.8, 20.7 (3 × CH₃) ppm. ESMS: m/z 433.0 [M + Na]⁺. Further elution gave methyl 2,4,6-tri-O-acetyl-3-Obenzyl- α -L-idopyranoside **6** α (50 mg, 17 %) as a colourless oil, $R_{\rm f}$ = 0.5. ¹H NMR (500 MHz. CDCl₃): δ = 7.39–7.25 (m, 5 H, Ph), 4.89–4.87 (m, 1 H, H-2), 4.85–4.83 (m, 1 H, H-4), 4.74, 4.65 (ABq, J = 11.8 Hz, 2 H, CH₂Ph), 4.71–4.69 (m 1 H, H-1), 4.43 (ddd, J_{4.5} = 1.5, J_{5.6b} = 5.2, J_{5.6a} = 7.2 Hz, 1 H, H-5), 4.24–4.18 (m, 1 H, H-6a), 4.14 (dd, J_{6a.6b} = 11.4 Hz, 1 H, B part of ABX, H-6b), 3.64 (dd, J = 1.0, J = 2.7 Hz, 1 H, H-3) ppm. ¹³C NMR (125 MHz. CDCl₃): δ = 170.5, 170.0, 169.5 (3 ×

CO₂CH₃), 137.4, 128.4, 127.9 (Ph), 99.2 (C-1), 72.3 (C-3), 72.1 (CH₂Ph), 67.3 (C-2), 67.1 (C-4), 63.5 (C-5), 60.4 (C-6), 55.5 (OCH₃), 20.9, 20.8, 20.7 (3 \times CH₃) ppm. HRMS (ESI); m/z [M + Na]⁺ calcd. for C₂₀H₂₆O₉Na: 433.1469, found 433.1469. 2,4,6-Tri-O-Acetyl-3-O-benzyl-α-L-idopyranosyl Trichloroacetimidate (8): To a mixture of hemiacetal 4 (0.2 g, 0.5 mmol) in anhy-

drous DCM (20 mL), under a nitrogen atmosphere at 0 °C was added DBU (0.1 mL, 0.8 mmol) and trichloroacetonitrile (0.1 mL, 1.0 mmol). This mixture was then stirred at this temperature for 1 h and quenched with water (20 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure. The crude material obtained was purified by flash chromatography (hexane/EtOAc, 2:1) to give the imidate **8** (0.13 g, 48 %, 2:1 α/β) as colourless oil. **8** α : ¹H NMR (500 MHz. CDCl₃): δ = 8.66 (s, 1 H, NH), 7.30–7.24 (m, 5 H, Ph), 6.26 (s, 1 H, H-1), 5.13-5.11 (m, 1 H, H-2), 4.94-4.91 (m, 1 H, H-4), 4.77, 4.67 (ABg, J = 11.8 Hz, 2 H, CH_2Ph), 4.68–4.63 (m, 1 H, H-5), 4.20 (dd, J_{5,6a} = 5.5, J_{6a,6b} = 11.7 Hz, 1 H, A part of ABX, H-6a), 4.15 (dd, J_{5.6b} = 7.3 Hz, 1 H, B part of ABX, H-6b), 3.81–3.78 (m, 1 H, H-3), 2.09 (s, 6 H, CH₃), 1.99 (s, 3 H, CH₃) ppm. ¹³C NMR (125 MHz. $CDCI_3$): $\delta = 170.5$, 170.0, 169.3 (3 × C=O), 160.4 (C=NH), 137.2, 128.3, 127.8, 127.6, 94.7 (C-1), 72.3 (CH₂Ph), 71.5 (C-3), 66.5 (C-2), 66.1 (C-4), 65.4 (C-5), 62.4 (C-6), 20.8, 20.7, 20.6 (3 × CH₃) ppm.

Ethyl 2,4,6-Tri-O-acetyl-3-O-benzyl-1-thio-L-idopyranoside (9): To a mixture of peracetate 2 (0.2 g, 0.4 mmol) in anhydrous DCM (10 mL) at 0 °C was added BF₃•Et₂O (0.18 mL, 6.4 mmol) and ethanthiol (40 $\mu\text{L},$ 0.5 mmol). The reaction mixture was then stirred at this temperature for 2.5 h, washed with sat. NaHCO₃, dried (MgSO₄) and concentrated under reduced pressure. The crude material obtained was purified by flash chromatography (hexane/EtOAc, 2:1) to give the thioglycoside **9** (86 mg, 49 %, 2:1 α/β) as colourless oil. There are some differences compared with the ¹H NMR spectroscopic data reported in the literature;^{[9c] 13}C NMR have not previously been reported. ¹H NMR (500 MHz. CDCl₃): δ = 7.34–7.21 (m, 7 H, Ph), 5.26 (br. s, 1 H, H-1 α), 4.99 (d, $J_{1,2}$ = 1.7 Hz, 0.5 H, H-1 β), 4.97–4.96 (m, 1 H, H-2 α), 4.96–4.94 (m, 0.5 H, H-2 β), 4.83–4.78 (m, 2.5 H, H-4 α , H-4 β , H-5 α), 4.73, 4.61 (ABq, J = 11.8 Hz, 2 H, CH₂Ph), 4.22–4.11 (m, 3.5 H, H-5 β , H-6a β , H-6b β , H-6a α , H-6b α), 3.79 (dd, $J_{2,3} = J_{3,4} = 2.7$ Hz, 0.5 H, H-3 β), 3.69–3.66 (m, 1 H, H-3 α), 2.76–2.54 (m, 3 H, CH_2CH_3), 2.06, 2.05, 2.04, 2.03, 2.01, 2.00 (6 × s, 6 × 3 H, COCH₃), 1.28 (t, J = 7.6 Hz, 4 H, 4.7 H, CH₂CH₃) ppm. ¹³C NMR (125 MHz. CDCl₃): δ = 170.5, 170.4, 170.0, 169.9, 169.5 (6 × C=O), 137.1, 128.5, 128.3, 127.7, 127.6, 82.3 (C-1α), 81.1 (C-1β), 72.8 (C-5β), 72.3 (CH₂Ph, C-3β), 71.6 (C-3α), 69.1 (C-2β), 68.8 (C-2α), 67.2 (C-5α), 65.9 (C-4 β), 64.0 (C-4 α), 62.6 (C-6), 28.5, 25.8, 20.9, 20.7, 20.6 (6 \times





CH₃), 15.0 (CH₂CH₃), 14.8 (CH₂CH₃) ppm. HRMS (ESI); m/z [M + Na]⁺ calcd. for C₂₁H₂₈O₈NaS: 463.1397, found 463.1392.

Phenyl 2,4,6-Tri-O-acetyl-3-O-benzyl-1-thio-L-idopyranoside (10): Thiophenol (1.1 mL, 10.6 mmol) was added at 0 °C to a solution of 2 (4.2 g, 9.6 mmol) and freshly distilled BF₃·Et₂O (3.6 mL, 28.8 mmol), in anhydrous DCM. After stirring for 5 h at 0 °C the reaction mixture was guenched with sat. NaHCO₃. The organic layer was then separated, dried (MgSO₄) and concentrated under reduced pressure. The crude material obtained was purified by flash chromatography (hexane/EtOAc, 1:1) to give thioglycoside 10 (3.7 g, 79 %, 10:1 α/β) as a colourless oil. The NMR spectroscopic data were in accord with the literature.^[9d] **10** α : ¹H NMR (500 MHz, CDCl₃): δ = 7.54-7.22 (m, 10 H, Ph), 5.48 (br. s, 1 H, H-1), 5.16-5.14 (m, 1 H, H-2), 4.99 (ddd, J_{4,5} = 1.5, J_{5,6b} = 4.9 Hz, 1 H, H-5), 4.88–4.86 (m, 1 H, H-4), 4.82, 4.68 (ABq, J = 11.8 Hz, 2 H, CH₂Ph), 4.25 (dd, J_{5.6a} = 8.0, J_{6a.6b} = 11.5 Hz, 1 H, A part of ABX, H-6a), 4.17 (dd, 1 H, B part of ABX, H-6b), 3.78-3.76 (m, 1 H, H-3), 2.07, 2.05, 2.00 (3 × s, 3 × 3 H, CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 170.6, 170.0, 169.5 (3 × C=O), 137.0, 135.8, 128.9, 128.5, 128.0, 127.7, 85.8 (C-1), 72.6 (CH2Ph), 71.4 9 (C-3), 68.7 (C-2), 67.1 (C-4), 64.6 (C-5), 62.8 (C-6), 20.9, 20.8, 20.7 (3 × CH₃) ppm. HRMS (ESI); m/z [M + Na]⁺ calcd. for C25H28O8NaS: 511.1397, found 511.1392.

Methyl 2,4,6-Tri-O-acetyl-3-O-benzyl-L-idopyranoside (6): To the glycosyl donor **10** (1.8 g, 3.7 mmol) and methanol (0.5 mL) in anhydrous DCM (180 mL) at room temp., NIS (2.0 g, 8.8 mmol) followed by TMSOTf (0.7 mL of 1 M TMSOTf in DCM, 0.7 mmol) were added and stirred at this temperature for 2 h. The reaction mixture was then quenched with sat. Na₂S₂O₃ (50 mL) and the organic layer was washed with sat. NaHCO₃, dried (MgSO₄) and concentrated under reduced pressure. The crude material obtained was dissolved in pyridine (10 mL) and acetic anhydride (2 mL) and stirred at room temp. for 18 h. The reaction mixture was then concentrated under reduced pressure (x 2 toluene). The crude material was then dissolved in DCM and washed with sat. NaHCO₃, dried (MgSO₄) and concentrated under reduced pressure. The crude material was then dissolved in DCM and washed with sat. NaHCO₃, dried (MgSO₄) and concentrated under reduced pressure. The crude material was then dissolved in DCM and washed with sat. NaHCO₃, dried (MgSO₄) and concentrated under reduced pressure. The crude material was purified by flash chromatography (hexane/EtOAc, 3:1) to give the glycoside **6** (1.2 g, 79 %, 3.3:1 α/β) as a colourless oil.

1,6-Anhydro-2-O-benzoyl-3-O-benzyl-β-L-idopyranose (11): To a solution of 1^[10] (4.5 g, 17.8 mmol) in anhydrous DCM (20 mL) at 0 °C, were added anhydrous pyridine (5 mL) and benzoyl chloride (2.8 mL) and the mixture was stirred at this temperature for 2 h and then quenched with water (5 mL). The organic layer was then washed with 1 M HCl (2 × 10 mL), sat. NaHCO₃, dried (MgSO₄), and concentrated under reduced pressure. The crude material was then purified by flash chromatography (hexane/EtOAc, 1:1) to give the anhydrosugar 11 (4.2 g, 66 %) as white solid. m.p. 140-141 °C (hexane/EtOAc, lit.^[14] 142–143 °C). $[\alpha]_D = +120.5$ (c = 0.7, CHCl₃; lit.^[14] + 127.5). The NMR spectroscopic data were in accord with the literature.^[14,34] ¹H NMR (500 MHz, CDCl₃): δ = 8.07–8.03, 7.59–7.54, 7.46– 7.41, 7.27–7.19 (m, 10 H, Ph), 5.51 (d, J_{1,2} = 1.8 Hz, 1 H, H-1), 5.05 (dd, J_{2.3} = 8.1 Hz, 1 H, H-2), 4.77, 4.65 (ABq, J = 11.8 Hz, 2 H, CH₂Ph), 4.44 (dd, J_{4,5} = J_{5,6a} = 4.5 Hz, 1 H, H-5), 4.13 (d, J_{6a,6b} = 7.7 Hz, 1 H, H-6a), 3.97 (dd, J_{3,4} = 8.2 Hz, 1 H, H-4), 3.85 (dd, 1 H, H-3), 3.72 (dd, $J_{5,6b}$ = 5.1 Hz, 1 H, H-6b) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 165.8 (C=O), 137.9, 133.4, 129.8, 129.4, 128.5, 128.4, 128.0, 127.8, 99.4 (C-1), 80.2 (C-3), 76.7 (C-2), 75.1 (C-5), 74.6 (CH₂Ph), 71.3 (C-4), 65.3 (C-6) ppm. ESMS: m/z 379.1 [M + Na]+.

Phenyl 2-O-Benzoyl-3-O-benzyl-1-thio-α-L-idopyranoside (12): To a solution of **11** (0.3 g, 0.8 mmol) in anhydrous DCM (30 mL) were added trimethyl(phenylthio)silane (0.6 mL, 1.8 mmol) and Znl₂ (0.7 g, 3.0 mmol). The mixture was stirred at room temperature overnight and filtered through a pad of Celite. The filtrate was di-



luted with DCM (50 mL), after which a solution of 1 м HCl in dioxane (5 mL) and water (10 mL) were added. The mixture was stirred at room temp. for 10 min, the organic layer was washed with 2 M HCl, sat. NaHCO₃, dried (MgSO₄) and concentrated under reduced pressure. The crude residue was purified by flash chromatography (hexane/EtOAc, 3:1) on silica gel to afford the thioglycoside 12 (0.3 g, 81 %) as colourless oil. $[\alpha]_D = +5.9$ (c = 0.3, CHCl₃; lit.^[25] +8.8) There are some differences compared with the reported ¹H NMR spectroscopic data but the ¹³C NMR spectroscopic data was in accord with the literature.^[25] ¹H NMR (500 MHz, CDCl₃): $\delta = 8.09-8.04$, 7.59-7.51, 7.46-7.34, 7.33-7.22 (4 × m, 15 H, Ph), 5.65 (br. s, 1 H, H-1), 5.43–5.41 (m, 1 H, H-2), 4.93, 4.63 (ABq, J = 11.8 Hz, 2 H, CH₂Ph), 4.76 (ddd, $J_{4,5} = 1.7$, $J_{5,6a} = 4.1$, $J_{5,6b} = 7.3$ Hz, 1 H, H-5), 3.91 (dd, J_{6a,6b} = 11.7 Hz, 1 H, A part of ABX, H-6a), 3.73–3.71 (m, 1 H, H-4), 3.70 (dd, 1 H, B part of ABX, H-6b), 3.66 (ddd, J = 1.1, J = 4.2, J = 3.1 Hz, H-3) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 165.6 (C=O), 137.7, 136.4 133.2, 131.5, 130.0, 128.8, 128.5, 128.2, 128.0, 127.9, 127.1, 86.0 (C-1), 73.9 (C-3), 72.2 (CH2Ph), 69.2 (C-2), 68.8 (C-4), 68.3 (C-5), 62.9 (C-6) ppm. ESMS: m/z 489.1 [M + Na]+.

1,6-Anhydro-2-O-benzoyl-3,4-di-O-benzyl-β-L-idopyranose (13): To a mixture of the alcohol 11 (0.9 g, 2.5 mmol) and Ag₂O (1.2 g, 5.2 mmol) in anhydrous DCM containing 4 Å molecular sieves at 0 °C under nitrogen was added benzyl bromide (0.4 mL, 3.1 mmol). The reaction temperature was then gradually warmed up to room temp., and the solution was kept stirring for 2 d. The resulting mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography (hexane/EtOAc, 3:1) to provide the dibenzyl ether 13 [0.57 g, 51 % (80 % based on starting material recovered)] as white solid, m.p. 83–85 °C (hexane/EtOAc). $[\alpha]_{D} = +38.9$ (c = 1.1, CHCl₃). The NMR spectroscopic data were in accord with the literature.^[24] ¹H NMR (500 MHz, CDCl₃): δ = 8.03–8.00, 7.59–7.53, 7.44– 7.39, 7.38–7.14 (m, 15 H, Ph), 5.49 (d, J_{1,2} = 1.8 Hz, 1 H, H-1), 5.01 (dd, J_{2,3} = 8.4 Hz, 1 H, H-2), 4.76, 4.75, 4.72, 4.65 (2 × ABq, J = 11.8 Hz, 4 H, 2 \times CH_2Ph), 4.47 (dd, $J_{4,5}$ = $J_{5,6b}$ = 4.5, $J_{5,6a}$ = 0 Hz, 1 H, H-5), 4.17 (d, $J_{6a,6b} = 7.6$ Hz, 1 H, H-6a), 3.96 (app t, $J_{2,3} \approx J_{3,4} =$ 8.0 Hz, 1 H, H-3), 3.86–3.82 (ddd, J_{4,6b} = 1.1 Hz, 1 H, H-4), 3.73–3.68 (m, 1 H, H-6b) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 165.6 (C=O), 137.9, 137.8, 133.1, 129.7, 129.4, 128.4, 128.2, 128.1, 127.8, 127.7, 127.5, 127.4, 99.1 (C-1), 79.2 (C-4), 79.1 (C-3), 76.6 (C-2), 74.6 (PhCH₂), 73.1 (PhCH₂), 73.0 (C-5), 65.3 (C-6) ppm. ESMS: m/z 469.0 [M + Na]⁺.

Phenyl 2-O-Benzoyl-3,4-di-O-benzyl-1-thio-α-L-idopyranoside (14): To a solution of 13 (0.6 g, 1.4 mmol) in anhydrous DCM (20 mL) were added trimethyl(phenylthio)silane (1.0 mL, 5 mmol) and Znl₂ (0.9 g, 2.8 mmol). The mixture was stirred at room temp. for 18 h and filtered through a pad of Celite. The filtrate was diluted with DCM (20 mL), after which a solution of 1 m HCl in dioxane (5 mL) and water (10 mL) were added. The mixture was stirred at room temp. for 10 min, the organic layer was washed with 2 $\ensuremath{\mathsf{m}}$ HCl, sat. NaHCO₃, dried (MgSO₄) and concentrated under reduced pressure. The crude residue was purified by flash chromatography (hexane/EtOAc, 6:1) to give the thioglycoside 14 (0.6 g, 77 %) as a colourless oil. $[\alpha]_D = -110$ (c = 0.5, CHCl₃; lit.^[22] -98). The NMR spectroscopic data were in accord with the literature.^[22] ¹H NMR (500 MHz, CDCl₃): δ = 8.00–7.95, 7.55–7.19, 7.14–7.09 (m, 20 H, Ph), 5.64 (br. s, 1 H, H-1), 5.48-5.46 (m, 1 H, H-2), 4.92, 4.63 (ABq, J = 11.8 Hz, 2 H, CH₂Ph), 4.71 (ddd, J_{4,5} = 2.0 Hz, 1 H, H-5), 4.48, 4.30 (ABq, J = 11.8 Hz, 2 H, CH₂Ph), 4.00 (dd, J_{5,6a} = 6.6, J_{6a,6b} = 11.7 Hz, 1 H, A part of ABX, H-6a), 3.97 (dd, J_{2.3} = 3.1, J_{3.4} = 1.1 Hz, 1 H, H-3), 3.78 (dd, J_{5,6b} = 4.4 Hz, 1 H, B part of ABX, H-6b), 3.57–3.53 (m, 1 H, H-4) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ = 165.6 (C=O), 137.3, 137.2, 135.6, 133.3, 131.7, 130.0, 129.5, 129.0, 128.5, 128.4, 128.3, 128.0 (× 2), 127.9, 127.4, 85.9 (C-1), 74.5 (C-4), 72.4, 72.1 (2 × CH₂Ph),

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70.5 (C-3), 69.2 (C-2), 68.3 (C-5), 62.9 (C-6) ppm. HRMS (ESI); m/z [M + Na]⁺ calcd. for C₃₃H₃₂O₆NaS: 579.1812, found 579.1795.

Methyl (Phenyl 2-O-benzoyl-3,4-di-O-benzyl-1-thio-α-L-idopyranosid) Uronate (15): To a biphasic mixture of alcohol 14 (0.32 g, 0.6 mmol) in DCM/H₂O (3:1, 18 mL) at room temp., TEMPO (16 mg, 0.1 mmol) and BAIB (0.16 g, 0.5 mmol) were added and stirred vigorously for 2 h. 2M Na₂S₂O₃ (10 mL) was then added to the reaction mixture and the organic layer was separated. The aqueous layer was then extracted with DCM (5 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. The crude syrup obtained was dissolved in anhydrous DMF (5 mL) and MeI (0.1 mL, 1.5 mmol) and KHCO₃ (0.2 g, 1.6 mmol) was added and stirred at room temp. for 4 h. The mixture was then concentrated under reduced pressure and the crude material was dissolved in DCM, filtered and concentrated under reduced pressure. The crude residue was then purified by flash chromatography (hexane/EtOAc, 4:1) to give the methyl ester 15 (0.24 g, 68 %) as colourless oil, $[\alpha]_{D} = -76.6$ (c = 1.5, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ = 7.96–7.91, 7.54–7.08 (m, 20 H, Ph), 5.76 (br. s, 1 H, H-1), 5.44–5.41 (m, 1 H, H-2), 5.31 (d, J_{4,5} = 2.4 Hz, 1 H, H-5), 4.88, 4.64 (ABq, J = 11.8 Hz, 2 H, CH₂Ph), 4.46, 4.40 (ABq, J = 11.8 Hz, 2 H, CH₂Ph), 3.97–3.93 (m, 2 H, H-3, H-4), 3.76 (s, 3 H, CO₂CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 169.7, 165.6 (2 × C=O), 137.3, 137.1, 135.6, 133.2, 131.0, 130.0, 129.3, 128.8, 128.5, 128.2, 128.0, 127.9, 127.7, 127.3, 85.9 (C-1), 74.5 (C-3), 72.5 (2 × CH₂Ph), 71.1 (C-4), 68.9 (C-2), 68.7 (C-5), 52.5 (OCH₃) ppm. HRMS (ESI); m/z [M + Na]⁺ calcd. for C33H32O6NaS: 607.1761, found 607.1768.

Methyl (Methyl 2-O-benzoyl-3,4-di-O-benzyl-α-L-idopyranosid) Uronate (16): To a solution of thioglycoside 15 (100 mg, 0.2 mmol), Ph₂SO (340 mg, 0.5 mmol) and TTBP (130 mg, 0.5 mmol) in anhydrous DCM (5 mL) at -60 °C under an argon atmosphere, was added trifluromethanesulfonic anhydride (40 µL, 0.2 mmol). The reaction mixture was then stirred at this temperature for 5 min, after which a solution of methanol (0.1 mL) in anhydrous DCM (2 mL) was added. The mixture was stirred at -60 °C for 30 min, after which it was guenched with sat. NaHCO₃ (5 mL) and slowly warmed up to room temp. The organic layer was washed with brine, dried (MgSO₄), and concentrated under reduced pressure. The crude residue was purified by flash chromatography (hexane/EtOAc, 3:1) to give the glycoside 16 (10 mg, 10 %) as a colourless oil: ¹H NMR (500 MHz, CDCl₃): δ = 7.99–7.95, 7.52–7.46, 7.35–7.07 (m, 15 H, Ph), 5.17–5.14 (m, 1 H, H-5), 5.04–5.02 (m, 1 H, H-1), 4.82 (d, J_{2.3} = 1.9 Hz, 1 H, H-2), 4.82, 4.63 (ABq, J = 11.8 Hz, 2 H, CH₂Ph), 4.42, 4.33 (ABq, J = 11.8 Hz, 2 H, CH₂Ph), 3.89–3.86 (m, 2 H, H-3, H-4), 3.74 (s, 3 H, CO₂CH₃), 3.47 (s, 3 H, OCH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 170.0 (C=O), 165.6 (C=O), 137.5, 137.4, 133.2, 130.0, 128.6, 128.4, 128.2 (× 2), 127.9, 127.8, 127.7, 99.7 (C-1), 74.3 (C-3), 72.4 (CH₂Ph), 72.2 (CH₂Ph), 71.9 (C-4), 68.1 (C-2), 67.8 (C-5) ppm. HRMS (ESI); m/z $[M + Na]^+$ calcd. for $C_{34}H_{32}O_7Na$: 607.1761, found 607.1768.

Phenyl 2-O-Benzoyl-3,4-di-O-benzyl-6-O-tert-butyldimethylsilyl-1-thio-α-L-idopyranoside (17): To a solution of compound **14** (0.6 g, 1.1 mmol) in anhydrous pyridine (10 mL), TBDMSCI (0.3 g, 2.0 mmol) and a catalytic amount of DMAP (10 mg) were added and the mixture stirred at room temp. for 24 h. The reaction mixture was then concentrated under reduced pressure (× 2 toluene). The crude mixture was then left on the high vacuum for 24 h to give the silyl ether **17** (0.7 g, 97 %) as a colourless oil. The crude material obtained was used without further purification. ¹H NMR (500 MHz, CDCl₃): δ = 7.96–7.91, 7.55–7.13 (m, 20 H, Ph), 5.60 (d, *J*_{1,2} = 2.0 Hz, 1 H, H-1), 5.42 (ddd, *J*_{2,4} = 0.9, *J*_{2,3} = 3.4 Hz, H-2), 4.89, 4.63 (ABq, *J* = 12.0 Hz, 2 H, CH₂Ph), 4.63–4.59 (m, 1 H, H-5), 4.48, 4.41 (ABq, *J* = 11.5 Hz, 2 H, CH₂Ph), 3.98 (dd, *J*_{3,4} = 3.6 Hz, 1 H, H-3), 3.91 (dd,



General Procedure for NIS-TMSOTf-Promoted Glycosylation: To the glycosyl donor (1 equiv.) and acceptor (5 equiv.) in anhydrous DCM (10 mL) at the required temperature, NIS (2 equiv.) followed by cat. TMSOTf (0.1 equiv.) were added and the mixture was stirred until the reaction was complete. The reaction mixture was then quenched with sat. $Na_2S_2O_3$ (10 mL) and the organic layer was washed with sat. $NaHCO_3$, dried (MgSO₄) and concentrated under reduced pressure. The crude material was purified by flash chromatography (hexane/EtOAc, 3:1) to obtain the glycoside.

Methyl 2-O-Benzoyl-3,4-di-O-benzyl-L-idopyranoside (18): Glycosylation with methanol of glycosyl donor 17 via the general procedure for NIS-TMSOTf gave **18** (room temp.: 90 %, 1:1 α/β ; 0 °C: 88 %, 1.3:1 α/β; 35 °C: 78 %, 1.2:1 α/β; 65 °C: 72 %, 1.2:1 α/β) as a colourless oil. ¹H NMR (500 MHz, CDCl₃): δ = 8.06–7.99 (m, 4 H), 7.56-7.51 (m, 2 H), 7.39-7.27 (m, 14 H), 7.27-7.21 (m, 7 H), 7.19-7.15 (m, 2 H), 7.15–7.11 (m, 2 H) ppm. **18** α : δ = 5.23–5.21 (m, 1 H, H-2), 4.89-4.88 (br. s, 1 H, H-1), 4.86, 4.65 (ABq, 2 H, J = 11.8 Hz, CH₂Ph), 4.49, 4.27 (ABq, 2 H, J = 11.8 Hz, CH₂Ph), 4.26–4.22 (m, 1 H, H-5), 4.03–3.98 (m, 1 H, H-6a), 3.91 (dd, 1 H, $J_{23} = J_{34} = 3.1$ Hz, H-3), 3.74 (dd 1 H, B part of ABX, $J_{5,6b} = 4.4$, $J_{6a,6b} = 11.8$ Hz, H-6b), 3.53–3.51 (m, 1 H, H-4), 3.46 (s, 3 H, OCH₃) ppm. **18** β : δ = 5.21 (dd, 1 H, J_{1,2} = 2.5, J_{2,3} = 5.7 Hz, H-2), 4.92 (d, 1 H, H-1), 4.81, 4.72 (ABq, 2 H, J = 11.8 Hz, CH₂Ph), 4.58, 4.39 (ABq, 2 H, J 11.8 Hz, CH₂Ph), 4.16 (dd, 1 H, J_{3.4} = 5.5 Hz, H-3), 4.09–4.05 (m, 1 H, H-5), 4.03–4.05 (m, 1 H, H-6a), 3.86 (dd, B part of ABX, 1 H, $J_{5.6b} = 4.5$, $J_{6a.6b} =$ 11.8 Hz, H-6b), 3.59 (dd, 1 H, J_{4.5} = 3.7 Hz, H-4), 3.52 [s, 3 H, (OCH₃)] ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 166.2, 165.6, 137.6, 137.4, 137.3, 133.2, 130.0, 129.9, 128.5 (× 2), 128.4 (× 2), 128.3, 128.0 (× 2), 127.9 (× 2); **18** α : δ = 99.5 (C-1), 74.4 (C-4), 72.1 (2 × CH₂Ph), 71.7 (C-3), 68.4 (C-4), 67.2 (C-5), 62.9 (C-6), 55.6 (OCH₃) ppm. **18** β : δ = 98.9 (C-1), 75.6 (C-4), 75.0 (C-5), 73.7 (C-3), 72.9, 72.2 (2 × CH₂Ph), 69.8 (C-2), 62.8 (C-6), 57.2 (OCH₃) ppm. HRMS (ESI); m/z [M + Na]⁺ calcd. for C₂₈H₃₀O₇Na: 501.1884, found 501.1899.

4'-Methyphenyl 2-O-Benzoyl-3-O-benzyl-4,6-O-isopropylidene-1-thio-α-L-idopyranoside (19):^[28] White solid; m.p. 119.6–120.7 °C. $[\alpha]_{\rm D} = -88.7 \ (c = 1.0, \ {\rm CHCl}_3).$ ¹H NMR (500 MHz, ${\rm CDCl}_3): \delta = 8.1 \ (dd,$ J = 1.3, 8.2 Hz, 2 H, H-Ar), 7.54 (tt, J = 1.3, 7.4 Hz, 1 H, H-Ar), 7.46-7.30 (m, 9 H, H-Ar), 7.08 (d, J = 8.2 Hz, 2 H, H-Ar), 5.70 (s, 1 H, H-1), 5.49 (dd, J_{1,2} = 1.1, J_{2,3} = 2.4 Hz, 1 H, H-2), 4.97, 4.66 (ABq, J_{A,B} = 11.7 Hz, 2 H, CH_2Ph), 4.37 (ddd, $J_{4,5} = J_{5,6b} = 1.7$, $J_{5,6a} = 2.3$ Hz, 1 H, H-5), 4.18 (dd, J_{5,6a} = 2.3, J_{6a,6b} = 12.9 Hz, 1 H, H-6a), 4.02 (dd, J_{4,5} = 2.3, $J_{3,4} = 0.8$ Hz, 1 H, H-4), 3.97 (dd, $J_{5,6b} = 1.7$, $J_{6a,6b} = 12.9$ Hz, 1 H, H-6b), 3.76 (dt, $J_{2,3} = 2.4$, $J_{3,4} = 0.8$ Hz, 1 H, H-3), 2.31 (s, 3 H, SPhCH₃), 1.46 (s, 3 H, CH₃), 1.45 (s, 3 H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 165.5 (C=O), 137.4, 137.0, 133.2, 132.7, 130.8, 130.0, 129.7, 129.6, 128.6, 128.4, 128.2, 127.9, 127.8 (C-Ar), 98.5 [C(CH₃)₂], 86.2 (C-1), 73.7 (C-3), 72.4 (CH₂Ph), 68.1 (C-2), 66.7 (C-4), 63.1 (C-6), 60.4 (C-5), 29.3 (SPhCH₃), 21.0 (CH₃), 18.4 (CH₃) ppm. LRMS: $m/z = 538.1 [M + NH_4]^+$, 543.1 [M + Na]⁺, 559.1 [M + K]⁺.

Methyl 2-O-Benzoyl-3-O-benzyl-L-idopyranoside (20): Glycosylation with methanol of glycosyl donor **19** via the general procedure for NIS-TMSOTf gave **20** (80 %, 1.7:1 α/β) as a colourless oil. ¹H NMR (500 MHz, CDCl₃): δ = 8.02–7.97, 7.60–7.54, 7.46–7.41, 7.35–7.25 (m, Ph), 5.31 (ddd, *J* = 1.0, *J*_{1,2} = 2.1, *J*_{2,3} = 4.3 Hz, 0.6 H, H-2β), 5.22– 5.26 (m, 1 H, H-2α), 4.89 (d, 0.6 H, H-1β), 4.86 (br. s, 1 H, H-2α), 4.82, 4.63 (ABq, *J* = 12.1 Hz, 2 H, α-CH₂Ph), 4.75, 4.66 (ABq, *J* = 11.9 Hz, 1.2 H, β-CH₂Ph), 4.27 (ddd, *J* = 1.0, *J*_{4α,5α} = 4.2, *J* = 5.7 Hz, 1 H, H-5α), 4.07 (ddd, *J* = 2.2, *J* = 6.7 Hz, 0.6 H, H-5β), 4.62–3.82 (m, 3.8 H, H-6α, H-6β, H-3β), 3.79–3.74 (m, 2.6 H, H-3α, H-4α, H-4β), 3.53 (s,

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1.8 H, OCH₃β), 3.46 (s, 3 H, OCH₃α) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 165.5 (2 × C=O), 137.6, 137.3, 133.6, 133.4, 129.8, 129.7, 129.2, 128.6, 128.5, 128.5, 128.1, 127.9,127.8, 127.7, 99.8 (C-1α), 99.3 (C-1β), 76.3, 75.1, 74.9, 72.9, 69.3, 68.2, 68.1, 68.0, 66.8, 57.2 (OCH₃), 55.7 (OCH₃) ppm. HRMS (ESI); m/z [M + Na]⁺ calcd. for C₂₁H₂₄O₇Na: 411.1414, found 411.1423.

n-Butvl 2-O-Benzovl-3-O-benzvl-L-idopvranoside (21): Thioalvcoside 19 (1.0 g, 1.92 mmol), anhydrous nBuOH (0.88 mL, 9.61 mmol) and activated 4 Å molecular sieves (500 mg) were suspended in anhydrous DCM (30 mL), and stirred at room temperature for 30 min under argon. The reaction mixture was cooled to 0 °C and NIS (648 mg, 2.88 mmol) and TMSOTf (0.52 µL, 2.88 mmol) were added. The reaction mixture was stirred at 0 °C for 2 h and quenched with sat. ag. Na₂S₂O₃ solution. The mixture was then filtered through celite with DCM, and the filtrate was washed with H_2O , sat. aq. NaHCO₃ solution, brine, dried (MgSO₄), filtered and concentrated. The residue was purified by flash chromatography (EtOAc/hexane, 3: 7) to give the glycoside 21 as a colorless oil (420 mg, 51 %, 2:1 α/β); **21** β : $R_f = 0.48$ (EtOAc/hexane, 1: 1). $[\alpha]_D =$ +167.1 (c = 0.4, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ = 8.01 (dd, J = 1.3, 8.2 Hz, 2 H, H-Ar), 7.58 (tt, J = 1.3, 7.4 Hz, 1 H, H-Ar), 7.45 (t, J = 7.4 Hz, 2 H, H-Ar), 7.36–7.28 (m, 5 H, H-Ar), 5.29 (dd, J_{1,2} = 2.1, J_{2,3} = 4.3 Hz, 1 H, H-2), 4.99 (d, J_{1,2} = 2.1 Hz, 1 H, H-1), 4.78, 4.70 (ABq, $J_{A,B} = 11.7$ Hz, 2 H, CH₂Ph), 4.09 (ddd, $J_{4,5} = 2.6$, $J_{5,6a} = 4.6$, $J_{5,6b} = 4.6$ 6.5 Hz, 1 H, H-5), 4.0-3.97 (m, 2 H, H-3, H-6a), 3.91-3.86 (m, 2 H, H-6b, OCH₂-a), 3.78 (t, J_{3.4} = J_{4.5} = 2.6 Hz, 1 H, H-4), 3.53 (dt, J = 6.8, 9.5 Hz, 1 H, OCH2-b), 1.56-1.50 (m, 2 H, CH2), 1.32-1.27 (m, 2 H, CH₂), 0.84 (t, J = 7.4 Hz, 3 H, CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 165.5 (C=O), 137.4, 133.3, 129.7, 129.5, 128.6, 128.5, 128.0, 127.7, 123.4, 121.2 (Ar), 97.9 [C-1, J(C,H) = 160.2 Hz], 76.5 (C-3), 75.0 (C-5), 72.9 (CH₂Ph), 69.9 (C-2), 69.7 (OCH₂), 68.2 (C-4), 62.9 (C-6), 31.5 (CH₂), 19.0 (CH₂), 13.7 (CH₃) ppm. **21** α : $R_{\rm f}$ = 0.4 (EtOAc/hexane, 1:1). [α]_D = $-30.9 (c = 0.6, CHCl_3)$. ¹H NMR (500 MHz, CDCl_3): $\delta = 8.01 (dd, J =$ 1.3, 8.3 Hz, 2 H, H-Ar), 7.59 (tt, J = 1.3, 7.5 Hz, 1 H, H-Ar), 7.46 (t, J = 7.5 Hz, 2 H, H-Ar), 7.38–7.28 (m, 5 H, H-Ar), 5.26 (dd, J_{1.2} = 1.3, J_{2.3} = 3.6 Hz, 1 H, H-2), 4.98 (s, 1 H, H-1), 4.86, 4.61 (ABq, J = 11.6 Hz, 2 H, CH₂Ph), 4.33 (ddd, J_{4,5} = 1.0, J_{5,6a} = 6.2, J_{5,6b} = 4.2 Hz, 1 H, H-5), 3.97 (dd, $J_{5,6a} = 6.2$, $J_{6a,6b} = 11.9$ Hz, 1 H, H-6a), 3.85 (dd, $J_{5,6b} = 4.2$, J_{6a.6b} = 11.9 Hz, 1 H, H-6b), 3.82–3.77 (m, 3 H, H-3, H-4, OCH₂-a), 3.48 (dt, J = 6.2, 9.5 Hz, 1 H, OCH₂-b), 1.65–1.59 (m, 2 H, CH₂), 1.44– 1.38 (m, 2 H, CH₂), 0.92 (t, J = 7.4 Hz, 3 H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 165.1 (C=O), 137.7, 133.5, 129.7, 129.3, 128.6, 128.3, 127.7, 127.6 (Ar), 98.5 (C-1, J_{C,H} = 166.7 Hz), 75.1 (C-3), 71.8 (CH2Ph), 68.4 (C-4), 68.0 (OCH2, C-2), 66.8 (C-5), 63.4 (C-6), 31.5 (CH2), 19.3 (CH₂), 13.8 (CH₃) ppm. LRMS: m/z = 453.1 [M + Na]⁺, 469.1 [M + K]⁺. HRMS: *m/z* calcd. for C₂₄H₃₀O₇Na [M + Na]⁺: 453.2000, found 453.1879

Methyl 2-Azido-3-O-benzyl-6-O-benzoyl-2-deoxy-α-D-gluco**pyranoside** (22):^[28] White solid; m.p.: 55.3–57.9 °C. $[\alpha]_{D} = +78.3$ $(c = 3.65, CHCl_3)$. ¹H NMR (500 MHz, CDCl₃): $\delta = 8.04$ (dd, J = 1.1, 8.3 Hz, 2 H, H-Ar), 7.57 (tt, J = 1.4, 7.3 Hz, 1 H, H-Ar), 7.46-7.30 (m, 7 H, H-Ar), 4.93, 4.83 (ABq, J_{A,B} = 11.1 Hz, 2 H, CH₂Ph), 4.81 (d, J_{1,2} = 3.6 Hz, 1 H, H-1), 4.74 (dd, $J_{5,6a}$ = 4.2, $J_{6a,6b}$ = 12.2 Hz, 1 H, H-6a), 4.47 (dd, J_{5,6b} = 2.2, J_{6a,6b} = 12.2 Hz, 1 H, H-6b), 3.87 (ddd, J_{4,5} = 9.1, J_{5.6b} = 2.2, J_{5.6a} = 4.2 Hz, 1 H, H-5), 3.85 (dd, J_{3.4} = 9.1, J_{2.3} = 10.1 Hz, 1 H, H-3), 3.57 (t, J_{3,4} = J_{4,5} = 9.1 Hz, 1 H, H-4), 3.45 (s, 3 H, OCH₃), 3.38 (dd, J_{1,2} = 3.6, J_{2,3} = 10.1 Hz, 1 H, H-2), 2.79 (br. s, 1 H, OH-4) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 167.1 (C=O), 137.8, 133.3, 129.7, 129.4, 128.6, 128.4, 128.2, 128.1 (C-Ar), 98.8 (C-1), 79.7 (C-3), 75.3 (OCH2), 70.6 (C-4), 70.0 (C-5), 63.3 (C-6), 63.1 (C-2), 55.3 (OMe) ppm. LRMS: *m*/*z* = 436.1 [M + Na]⁺, 849.2 [2M + Na]⁺.

Disaccharide 23: Glycosylation of acceptor 22 with glycosyl donor 19 via the general procedure for NIS-TMSOTf gave the disaccharide



23 (75 %) as a colourless oil. ¹H NMR (500 MHz, CDCl₃): δ = 8.00 (dd, J = 1.2, 8.3 Hz, 2 H, Ph), 7.94 (dd, J = 1.2, 8.3 Hz, 2 H, Ph), 7.56-7.50 (m, 2 H, Ph), 7.44-7.35 (m, 10 H, Ph), 7.32-7.25 (m, 4 H, Ph), 5.22 (dd, J_{1',2'} = 1.2, J_{2',3'} = 2.7 Hz, 1 H, H-2'), 5.14 (s, 1 H, H-1'), 4.84-4.79 (m, 1 H, H-6a), 4.82 (d, J_{1,2} = 3.6 Hz, 1 H, H-1), 4.83, 4.67 (ABq, J_{AB} = 11.2 Hz, 2 H, CH₂Ph), 4.79, 4.66 (ABq, J_{AB} = 10.5 Hz, 2 H, CH_2Ph), 4.49 (dd, $J_{5,6b}$ = 3.8, $J_{6a,6b}$ = 12.3 Hz, 1 H, H-6b), 4.28 (ddd, $J_{4',5'} =$ 1.5, $J_{5',6a'} =$ 6.1, $J_{5',6b'} =$ 4.7 Hz, 1 H, H-5'), 4.05–4.03 (m, 2 H, H-5, H-4), 3.89 (dd, J_{2,3} = 10.1, J_{3,4} = 8.8 Hz, 1 H, H-3), 3.83 (dd, $J_{2',3'} = 2.7, J_{3',4'} = 1.0$ Hz, 1 H, H-3'), 3.68 (dd, $J_{4',5'} = 1.5, J_{3',4'} = 1.0$ Hz, 1 H, H-4'), 3.50 (dd, J_{1,2} = 3.6, J_{2,3} = 10.1 Hz, 1 H, H-2), 3.47 (s, 3 H, OMe), 3.36 (dd, $J_{5',6a'} = 6.1$, $J_{6a',6b'} = 11.9$ Hz, 1 H, H-6a'), 3.24 (dd, $J_{5',6b'} = 4.7$, $J_{6a',6b'} = 11.9$ Hz, 1 H, H-6b') ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 165.9, 165.3 (C=O × 2), 137.5, 137.4, 133.5, 133.1, 129.8, 129.7, 129.6, 129.0, 128.7, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8 (C-Ar), 98.4 (C-1'), 97.8 (C-1), 79.1 (C-3), 75.5 (C-3'), 75.4 (CH₂Ph), 73.8 (C-4), 72.4 (CH₂Ph), 69.4 (C-5), 68.1 (C-2'), 67.8 (C-4'), 67.1 (C-5'), 64.2 (C-2), 62.8 (C-6), 62.6 (C-6'), 55.4 (OMe) ppm.

4'-Methyphenyl 3-O-Benzyl-4,6-O-isopropylidene-2-O-pivaloyl-1-thio-α-L-idoside (24): Pivaloyl chloride (0.74 mL, 6.0 mmol) was added to a solution of 4'-methyphenyl 3-O-benzyl-4,6-O-isopropylidene-1-thio- α -L-idoside^[28] (1.0 g, 2.4 mmol), anhydrous pyridine (0.4 mL, 4.8 mmol), Et₃N (0.7 mL, 4.8 mmol) and DMAP (60 mg) in anhydrous DCM (25 mL). The solution was stirred at 60 °C for 24 h and then washed with 2 M HCl (2 \times 25 mL), sat. aq. NaHCO₃ (2 \times 25 mL), dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (EtOAc/n-hexane, 1:4) to give the pivaloate **24** as pale yellow oil (762 mg, 64 %); $R_f = 0.6$ (EtOAc/nhexane, 1:4). ¹H NMR (500 MHz, CDCl₃): δ = 7.45–7.29 (m, 7 H, Ar), 7.09 (d, J = 8.0 Hz, 2 H, Ar), 5.55 (s, 1 H, H-1), 5.20 (dd, $J_{1,2} = 0.7$, J_{2.3} = 1.6 Hz, 1 H, H-2), 4.93, 4.62 (ABq, J_{A,B} = 11.7 Hz, 2 H, PhCH₂), 4.31 (d, $J_{5.6a} = J_{5.6b} = J_{4.5} = 1.8$ Hz, 1 H, H-5), 4.13 (dd, $J_{5.6}a = 1.8$, $J_{6a,6b}$ = 13.0 Hz, 1 H, H-6a), 3.96 (d, $J_{4,5}$ = $J_{3,4}$ = 1.8 Hz, 1 H, H-4), 3.95 (dd, $J_{6a,6b}$ = 13.0 Hz, 1 H, H-6b), 3.58 (dd, 1 H, H-3), 2.32 (s, 3 H, CH₃), 1.44 (s, 3 H, CH₃), 1.43 (s, 3 H, CH₃), 1.23 (s, 9 H, 3 × CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 177.7 (C=O), 137.6, 136.9, 132.8, 130.8, 129.6, 128.3, 127.8, 127.7 (Ar), 98.6 [C(CH₃)₂], 86.3 (C-1), 73.9 (C-3), 72.3 (PhCH₂), 67.7 (C-2), 66.8 (C-4), 62.9 (C-6), 60.3 (C-5), 38.8 [C(CH₃)₃], 29.4 (CH₃), 27.0 (3 × CH₃), 21.0 (CH₃), 18.4 (CH₃) ppm. LRMS: $m/z = 523.21 [M + Na]^+$. HRMS: m/z calcd. for C₂₈H₃₆O₆SNa [M + Na]⁺: 523.2200, found 523.2102.

General Procedure for NIS-TfOH-Promoted Glycosylation: A mixture of the glycosyl donor (1 equiv.) and anhydrous acceptor (5 equiv.) with freshly dried AW300 mol sieves in anhydrous DCM (\approx 10 mm) was stirred at room temperature for 30 min under N_2. The mixture was cooled to -78 °C and then NIS (1.2 equiv.) was added and stirring continued at -78 °C for 10 min; TfOH (0.2 equiv.) was then added at -78 °C. The solution was stirred at -78 °C and slowly warmed up to -10 to 0 °C over 3–7 h under N₂ until the reaction was complete (TLC). The reaction was then quenched by addition of Et_3N , sat. aq. NaHCO₃, and 10 % aq. Na₂S₂O₃ to pH 8. The resulting solution was filtered through celite and the filter cake was washed with DCM. The combined filtrate was washed 10 % aq. $Na_2S_2O_3$ (10 mL), dried (MgSO_4), filtered and concentrated to dryness. The residue was then purified by flash chromatography (EtOAc/hexane, 1:9) to give the glycoside.

Methyl 2-O-Benzoyl-3-O-benzyl-4,6-O-isopropylidene-L-idoside (25): Reaction of MeOH with thioglycoside 19 following the general procedure for NIS-TfOH-promoted glycosylation gave the glycoside **25** (68 %, 2:1 α/β) as a colourless oil. The isopropylidene groups on the α and β -anomers were unstable and easily cleaved, even inside the NMR tube in CDCl₃. β -25: $R_f = 0.15$ (EtOAc/hexane, 1: 4); LRMS:



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 $m/z = 451.1 [M + Na]^+$, 467.1 [M + K]⁺. ¹H NMR (500 MHz, CDCl₃): δ = 8.01–7.27 (m, 10 H, H-Ar), 5.24 (dd, $J_{1,2}$ = 1.5, $J_{2,3}$ = 2.6 Hz, 1 H, H-2), 4.81, 4.65 (ABq, $J_{A,B}$ = 11.7 Hz, 2 H, CH_2Ph), 4.79 (d, $J_{1,2}$ = 1.5 Hz, 1 H, H-1), 4.11 (dd, $J_{5,6a}$ = 2.4, $J_{6a,6b}$ = 12.9 Hz, 1 H, H-6a), 4.09–4.05 (m, 1 H, H-6b), 3.86 (t, J_{3,4} = J_{4,5} = 2.6 Hz, 1 H, H-4), 3.84 (t, $J_{2,3} = J_{3,4} = 2.6$ Hz, 1 H, H-3), 3.66–3.64 (m, 1 H, H-5), 3.53 (s, 3 H, OCH₃), 1.39 (s, 3 H, CH₃), 1.39 (s, 3 H, CH₃) ppm. ¹³C NMR (125 MHz, $CDCI_3$): δ = 166.2 (C=O), 137.4, 133.4, 130.1, 129.8, 128.5, 128.1, 128.0, 127.7 (C-Ar), 98.9 [CH(CH₃)₂], 98.4 (C-1), 76.1 (C-3), 72.7 (CH₂Ph), 66.8 (C-5), 66.7 (C-2), 66.0 (C-4), 62.9 (C-6), 57.1 (OCH₃), 29.2 (CH₃), 18.2 (CH₃). α -25: $R_f = 0.22$ (EtOAc/hexane, 1: 4); LRMS: m/z =451.1 [M + Na]⁺, 467.1 [M + K]⁺. ¹H NMR (500 MHz, CDCl₃): δ = 8.08 (dd, J = 1.3, 8.5 Hz, 2 H, H-Ar), 7.53 (tt, J = 1.3, 7.5 Hz, 1 H, H-Ar), 7.40 (t, J = 7.5 Hz, 2 H, H-Ar), 7.32-7.24 (m, 5 H, H-Ar), 5.22 (dd, $J_{1,2} = 2.1, J_{2,3} = 4.1$ Hz, 1 H, H-2), 4.89 (d, $J_{1,2} = 2.1$ Hz, 1 H, H-1), 4.81, 4.63 (ABq, J_{AB} = 12.0 Hz, 2 H, CH_2Ph), 4.08 (dd, $J_{5,6a}$ = 2.2, $J_{6a,6b} = 12.2$ Hz, 1 H, H-6a), 3.96 (dd, $J_{3,4} = 1.8$, $J_{4,5} = 2.5$ Hz, 1 H, H-4), 3.91 (dd, $J_{5,6b} = 2.4$, $J_{6a,6b} = 12.2$ Hz, 1 H, H-6b), 3.90–3.89 (m, 1 H, H-5), 3.67 (dt, J_{2,3} = 4.1, J_{3,4} = 1.8 Hz, 1 H, H-3), 3.42 (s, 3 H, OCH₃), 1.44 (s, 3 H, CH₃), 1.40 (s, 3 H, CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 165.5 (C=O), 137.8, 133.1, 129.9, 129.8, 128.3, 128.2, 127.8, 127.7 (C-Ar), 99.9 (C-1), 98.6 [CH(CH₃)₂], 75.1 (C-3), 72.1 (CH₂Ph), 67.7 (C-2), 67.5 (C-4), 62.6 (C-6), 60.2 (C-5), 55.6 (OCH₃), 28.8 (CH₃), 18.9 (CH₃) ppm. The NMR and MS data of α -25 was in accord with the literature data.[35]

n-Butyl 2-O-Benzoyl-3-O-benzyl-4,6-O-isopropylidene-L-idoside (26): Reaction of nBuOH with thioglycoside 19 following the general procedure for NIS-TfOH-promoted glycosylation gave the glycoside **26** as a colourless oil (82 %, 3.2:1 α/β). α -**26**: $R_f = 0.46$ (EtOAc-petroleum spirit, 1:4). ¹H NMR (500 MHz, CDCl₃): δ = 8.11 (dd, J = 1.3, 8.3 Hz, 2 H, Ar), 7.55 (tt, J = 1.4, 7.5 Hz, 1 H, Ar), 7.42 (t, J = 7.5 Hz, 2 H, Ar), 7.35–7.27 (m, 5 H, Ar), 5.26 (dd, $J_{1,2} = 2.0$, $J_{2,3} = 3.8$ Hz, 1 H, H-2), 5.02 (d, 1 H, H-1), 4.85, 4.63 (ABq, $J_{A,B} =$ 11.7 Hz, 2 H, CH_2Ph), 4.10 (dd, $J_{5,6a}$ = 2.3, $J_{6a,6b}$ = 12.2 Hz, 1 H, H-6a), 4.02 (dd, J_{3,4} = J_{4,5} = 2.4 Hz, 1 H, H-4), 3.94–3.90 (m, 2 H, H-5, H-6b), 3.75 (dt, J = 6.6, 9.7 Hz, 1 H, OCH₂-a), 3.71 (dd, $J_{2,3} = 3.8$, J_{3,4} = 2.4 Hz, 1 H, H-3), 3.47 (dt, J = 6.4, 9.7 Hz, 1 H, OCH₂-b), 1.62-1.57 (m, 2 H, CH₂), 1.47 (s, 3 H, CH₃), 1.45 (s, 3 H, CH₃), 1.41-1.36 (m, 2 H, CH₂), 0.90 (t, J = 7.4 Hz, 3 H, CH₃) ppm. ¹³C NMR (125 MHz, $CDCl_3$): $\delta = 165.6$ (C=O), 137.9, 133.1, 129.9, 128.3, 128.2, 127.7, 127.6 (Ar), 98.7 [C(CH₃)₂], 98.6 (C-1), 75.1 (C-3), 71.9 (CH₂Ph), 67.9 (C-4), 67.8 (OCH₂), 67.2 (C-2), 62.7 (C-6), 60.2 (C-5), 31.6 (CH₂), 28.9 (CH₃), 19.3 (CH₂), 18.9 (CH₃), 13.8 (CH₃) ppm. β-26: R_f = 0.43 (EtOAcpetroleum spirit, 1:4). ¹H NMR (500 MHz, CDCl₃): δ = 8.17 (dd, J = 1.4, 8.4 Hz, 2 H, Ar), 7.52 (tt, J = 1.4, 7.4 Hz, 1 H, Ar), 7.43-7.30 (m, 7 H, Ar), 5.22 (dd, J_{1,2} = 1.4, J_{2,3} = 2.4 Hz, 1 H, H-2), 4.88 (d, 1 H, H-1), 4.83, 4.67 (ABq, J_{A,B} = 11.7 Hz, 2 H, CH₂Ph), 4.11 (dd, J_{5,6a} = 2.4, J_{6a,6b} = 12.9 Hz, 1 H, H-6a), 4.06 (dd, J_{5,6b} = 1.6 Hz, 1 H, H-6b), 3.95 (dt, J = 7.0, 9.4 Hz, 1 H, OCH₂-a), 3.87 (dd, J_{3,4} = 2.6, J_{4,5} = 1.5 Hz, 1 H, H-4), 3.85 (dd, $J_{2,3} = 2.4$, $J_{3,4} = 2.6$ Hz, 1 H, H-3), 3.65 (ddd, $J_{4,5} =$ 1.5, J_{5,6a} = 2.4, J_{5,6b} = 1.6 Hz, 1 H, H-5), 3.47 (dt, J = 7.0, 9.4 Hz, 1 H, OCH2-b), 1.56-1.51 (m, 2 H, CH2), 1.40 (s, 3 H, CH3), 1.39 (s, 3 H, CH₃), 1.33–1.28 (m, 2 H, CH₂), 0.86 (t, J = 7.4 Hz, 3 H, CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 166.3 (C=O), 137.6, 132.9, 130.3, 130.1, 128.5, 128.1, 128.0, 127.7 (Ar), 98.4 [C(CH₃)₂], 97.7 (C-1), 76.2 (C-3), 72.7 (CH2Ph), 69.4 (OCH2), 67.1 (C-5), 66.7 (C-2), 66.0 (C-4), 62.9 (C-6), 31.5 (CH₂), 29.2 (CH₃), 19.1 (CH₂), 18.3 (CH₃), 13.9 (CH₃) ppm. LRMS: $m/z = 493.22 \text{ [M + Na]}^+$. HRMS: m/z calcd. for $C_{27}H_{34}O_7Na$ [M + Na]+: 493.2300, found 493.2175.

Isopropyl 2-O-Benzoyl-3-O-benzyl-4,6-O-isopropylidene-L-idoside (27): Reaction of *i*PrOH with thioglycoside **19** following the general procedure for NIS-TfOH-promoted glycosylation gave the glycoside **27** as a colourless oil (77 %, 2.8:1 α/β). LRMS: m/z = 479.20

 $[M + Na]^+$. HRMS: *m/z* calcd. for C₂₆H₃₂O₇Na $[M + Na]^+$: 479.2100, found 479.2018; α -27: $R_{\rm f}$ = 0.43 (EtOAc-petroleum spirit, 1.5:8.5). ¹H NMR (500 MHz, CDCl₃): δ = 8.12 (dd, J = 1.4, 8.4 Hz, 2 H, H-Ar), 7.56 (tt, J = 1.7, 7.4 Hz, 1 H, H-Ar), 7.44-7.26 (m, 7 H, H-Ar), 5.23 (dd, $J_{1,2} = 2.0, J_{2,3} = 3.3$ Hz, 1 H, H-2), 5.14 (d, $J_{1,2} = 2.0$ Hz, 1 H, H-1), 4.87, 4.62 (ABq, J_{A,B} = 11.7 Hz, 2 H, CH₂Ph), 4.10 (dd, J_{5.6a} = 2.7, J_{6a,6b} = 12.6 Hz, 1 H, H-6a), 4.03 (dd, J_{3,4} = 3.3, J_{4,5} = 2.4 Hz, 1 H, H-4), 3.99 (ddd, $J_{4,5}$ = 2.4, $J_{5,6a}$ = 2.7, $J_{5,6b}$ = 2.4 Hz, 1 H, H-5), 3.96 (septet, J = 6.1, 6.2 Hz, 1 H, CH), 3.90 (dd, J_{5,6b} = 2.4, J_{6a,6b} = 12.6 Hz, 1 H, H-6b), 3.71 (t, J_{3,4} = J_{2,3} = 3.3 Hz, 1 H, H-3), 1.48 (s, 3 H, CH₃), 1.45 (s, 3 H, CH₃), 1.24 (d, J = 6.2 Hz, 3 H, CH₃), 1.17 (d, J = 6.1 Hz, 3 H, CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 165.6 (C=O), 138.1, 133.1, 129.9, 128.2, 127.6, 127.5 (C-Ar), 98.6 [C(CH₃)₂], 96.8 (C-1), 75.2 (C-3), 71.7 (CH₂Ph), 69.7 (CH), 68.1 (C-4), 67.6 (C-2), 62.7 (C-6), 60.3 (C-5), 28.9 (CH₃), 23.3 (CH₃), 21.4 (CH₃), 18.9 (CH₃) ppm. 1D NOESY (500 MHz, CDCl₃): H-1 is not coupled to H-5; β -27: R_f = 0.24 (EtOAcpetroleum spirit, 1.5:8.5). ¹H NMR (500 MHz, CDCl₃): δ = 8.18 (dd, J = 2.2, 8.4 Hz, 2 H, H-Ar), 7.53 (tt, J = 1.4, 7.4 Hz, 1 H, H-Ar), 7.42-7.30 (m, 7 H, H-Ar), 5.16 (dd, J_{1,2} = 1.4, J_{2,3} = 2.4 Hz, 1 H, H-2), 4.97 (d, J_{1,2} = 1.4 Hz, 1 H, H-1), 4.83, 4.68 (ABq, J_{A,B} = 11.7 Hz, 2 H, CH₂Ph), 4.10 (dd, J_{5,6a} = 2.5, J_{6a,6b} = 12.8 Hz, 1 H, H-6a), 4.05 (septet, J = 6.1, 6.2 Hz, 1 H, CH), 4.03 (dd, J_{5,6b} = 1.7, J_{6a,6b} = 12.8 Hz, 1 H, H-6b), 3.84 (d, J_{2,3} = J_{3,4} = J_{4,5} = 2.4 Hz, 2 H, H-3, H-4), 3.64 (ddd, J_{4,5} = 2.4, J_{5.6a} = 2.5, J_{5.6b} = 1.7 Hz, 1 H, H-5), 1.39 (s, 3 H, CH₃), 1.38 (s, 3 H, CH₃), 1.20 (d, J = 6.2 Hz, 3 H, CH₃), 1.14 (d, J = 6.1 Hz, 3 H, CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 166.4 (C=O), 137.6, 132.8, 130.4, 130.1, 128.5, 128.1, 128.0, 127.7 (C-Ar), 98.3 [C(CH₃)₂], 95.2 (C-1), 76.3 (C-3), 72.7 (CH₂Ph), 70.3 (CH), 67.7 (C-2), 66.7 (C-5), 66.0 (C-4), 63.0 (C-6), 29.1 (CH₃), 23.1 (CH₃), 21.4 (CH₃), 18.3 (CH₃) ppm.

n-Butyl 3-O-Benzyl-2-O-pivaloyl-4,6-O-isopropylidene-L-idoside (28): Reaction of nBuOH with thioglycoside 24 following the general procedure for NIS-TfOH-promoted glycosylation gave the glycoside **28** as a colourless oil (85 %, 3.8:1 α/β). LRMS: m/z = 473.25 $[M + Na]^+$. HRMS: *m/z* calcd. for C₂₅H₃₈O₇Na $[M + Na]^+$: 473.2500, found 473.2488; α -28: $R_{\rm f} = 0.33$ (EtOAc-petroleum spirit, 1:9). ¹H NMR (500 MHz, CDCl₃): δ = 7.36–7.27 (m, 5 H, H-Ar), 4.97 (dd, $J_{1,2}$ = 2.1, J_{2.3} = 3.7 Hz, 1 H, H-2), 4.87 (d, 1 H, H-1), 4.82, 4.60 (ABq, J_{A.B} = 11.6 Hz, 2 H, CH_2Ph), 4.06 (dd, $J_{5,6a}$ = 2.5, $J_{6a,6b}$ = 12.5 Hz, 1 H, H-6a), 3.95 (dd, $J_{3,4}$ = 2.8, $J_{4,5}$ = 2.4 Hz, 1 H, H-4), 3.90–3.86 (m, 2 H, H-5, H-6b), 3.72 (dt, J = 6.6, 9.7 Hz, 1 H, OCH₂-a), 3.53 (dd, 1 H, H-3), 3.43 (dt, J = 6.4, 9.7 Hz, 1 H, OCH₂-b), 1.60–1.54 (m, 2 H, CH₂), 1.42 (s, 6 H, CH₃ × 2), 1.40–1.34 (m, 2 H, CH₂), 1.22 (s, 9 H, CH₃ × 3), 0.90 (t, J = 7.4 Hz, CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): $\delta = 177.7$ (C=O), 138.2, 128.2, 127.6, 127.5 (C-Ar), 98.8 [C(CH₃)₂], 98.6 (C-1), 75.3 (C-3), 71.8 (CH2Ph), 67.9 (OCH2), 67.7 (C-4), 66.8 (C-2), 62.7 (C-6), 60.2 (C-5), 38.7 [C(CH₃)₃], 31.6 (CH₂), 29.0 (CH₃), 27.0 (CH₃ × 3), 19.3 (CH₂), 18.9 (CH₃), 13.8 (CH₃) ppm. β -28: R_f = 0.28 (EtOAc-petroleum spirit, 1:9). $^1\mathrm{H}$ NMR (500 MHz, CDCl_3): δ = 7.37–7.30 (m, 5 H, H-Ar), 4.98 (dd, J_{1,2} = 1.4, J_{2,3} = 2.6 Hz, 1 H, H-2), 4.79, 4.63 (ABq, $J_{A,B} = 11.7$ Hz, 2 H, CH_2Ph), 4.75 (d, 1 H, H-1), 4.07 (dd, $J_{5,6a} = 2.4$, $J_{6a,6b} = 12.8$ Hz, 1 H, H-6a), 4.01 (dd, $J_{5,6b} = 1.7$ Hz, 1 H, H-6b), 3.93 (dt, J = 6.7, 9.3 Hz, 1 H, OCH₂-a), 3.83 (dd, J_{3,4} = 2.6, J_{4,5} = 1.6 Hz, 1 H, H-4), 3.64 (dd, J_{2,3} = J_{3,4} = 2.6 Hz, 1 H, H-3), 3.57 (ddd, 1 H, H-5), 3.46 (dt, J = 6.9, 9.3 Hz, 1 H, OCH₂-b), 1.56–1.53 (m, 2 H, CH₂), 1.42 (s, 3 H, CH₃), 1.41 (s, 3 H, CH₃), 1.33–1.29 (m, 2 H, CH₂), 1.25 (s, 9 H, $CH_3 \times 3$), 0.89 (t, J = 7.4 Hz, 3 H, CH_3) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 181.7 (C=O), 137.7, 128.5, 127.9, 127.6 (C-Ar), 98.5 [C(CH₃)₂], 97.8 (C-1), 77.6 (C-3), 72.6 (CH₂Ph), 69.2 (OCH₂), 66.6 (C-5), 66.3 (C-2), 66.1 (C-4), 62.9 (C-6), 39.0 [C(CH₃)₃], 31.6 (CH₂), 29.7 (CH₃), 27.1 (CH₃ × 3), 19.1 (CH₂), 18.4 (CH₃), 13.9 (CH₃) ppm.

Isopropyl 3-O-Benzyl-2-O-pivaloyl-4,6-O-isopropylidene-L-idoside (29): Reaction of *i*PrOH with thioglycoside **24** following the general procedure for NIS-TfOH-promoted glycosylation gave the

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glycoside **29** as a colourless oil (78 %, 5.6:1 α/β). LRMS: m/z = 459.23[M + Na]⁺. HRMS: *m/z* calcd. for C₂₄H₃₆O₇Na [M + Na]⁺: 459.2500, found 459.2336; α -29: $R_{\rm f}$ = 0.25 (EtOAc-petroleum spirit, 1:9). ¹H NMR (500 MHz, CDCl₃): δ = 7.37–7.26 (m, 5 H, H-Ar), 4.98 (d, $J_{1,2}$ = 2.4 Hz, 1 H, H-1), 4.95 (dd, J_{1,2} = 2.4, J_{2,3} = 4.1 Hz, 1 H, H-2), 4.82, 4.60 (ABq, J_{A,B} = 11.7 Hz, 2 H, CH₂Ph), 4.05 (dd, J_{5.6a} = 2.8, J_{6a.6b} = 12.7 Hz, 1 H, H-6a), 3.97 (dd, J_{3,4} = 3.1, J_{4,5} = 2.3 Hz, 1 H, H-4), 3.95-3.90 (m, 2 H, H-5, CH), 3.86 (dd, J_{5,6b} = 2.6 Hz, 1 H, H-6b), 3.54 (dd, 1 H, H-3), 1.42 (s, 6 H, CH₃ × 2), 1.22 (s, 9 H, CH₃ × 3), 1.21 (d, J = 6.2 Hz, 3 H, CH₃), 1.16 (d, J = 6.1 Hz, 3 H, CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 177.7 (C=O), 138.3, 128.2, 127.6, 127.5 (C-Ar), 98.6 [C(CH3)2], 97.1 (C-1), 75.6 (C-3), 71.7 (CH2Ph), 69.6 (CH), 68.3 (C-4), 67.4 (C-2), 62.6 (C-6), 60.5 (C-5), 38.7 [C(CH₃)₃], 28.9 (CH₃), 27.1 (CH₃ × 3), 23.3 (CH₃), 21.4 (CH₃), 19.0 (CH₃); β -29: R_{f} = 0.20 (EtOAcpetroleum spirit, 1:9). ¹H NMR (500 MHz, CDCl₃): δ = 7.38–7.30 (m, 5 H, H-Ar), 4.92 (dd, J_{1,2} = 1.6, J_{2,3} = 2.5 Hz, 1 H, H-2), 4.84 (d, 1 H, H-1), 4.78, 4.63 (ABq, $J_{A,B}$ = 11.7 Hz, 2 H, CH_2Ph), 4.06 (dd, $J_{5.6a}$ = 2.5, J_{6a,6b} = 12.8 Hz, 1 H, H-6a), 4.01 (septet, J = 6.2, 6.1 Hz, 1 H, CH), 3.98 (dd, $J_{5.6b}$ = 1.8 Hz, 1 H, H-6b), 3.82 (dd, $J_{4.5}$ = 1.5, $J_{3.4}$ = 2.5 Hz, 1 H, H-4), 3.64 (dd, J_{2,3} = J_{3,4} = 2.5 Hz, 1 H, H-3), 3.56 (ddd, H-5), 1.42 (s, 3 H, CH₃), 1.41 (s, 3 H, CH₃), 1.25 (s, 9 H, CH₃ × 3), 1.19 (d, J = 6.2 Hz, 3 H, CH₃), 1.11 (d, J = 6.2 Hz, 3 H, CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 178.6 (C=O), 137.8, 128.5, 127.9, 127.6 (C-Ar), 98.4 [C(CH₃)₂], 95.0 (C-1), 77.0 (C-3, under CDCl₃ peak), 72.6 (CH₂Ph), 69.7 (CH), 66.8 (C-2), 66.5 (C-5), 66.1 (C-4), 62.9 (C-6), 39.0 [C(CH₃)₃], 29.3 (CH₃), 27.1 (CH₃ × 3), 23.1 (CH₃), 21.2 (CH₃), 18.4 (CH₃) ppm.

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