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Single-step glycosylations with ^{13}C-labelled sulfoxide donors: a low-temperature NMR cartography of the distinguishing mechanistic intermediates

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Abstract: Glycosyl sulfoxides have gained recognition in the total synthesis of complex oligosaccharides and as model substrates for dissecting the mechanisms involved. While these donors are usually reacted under pre-activation conditions, an experimentally more convenient single-step protocol has also been reported, whereby the activation is performed in the presence of the acceptor alcohol; yet, the nature and prevalence of the reaction intermediates formed in this more complex scenario have comparatively received minimal attention. Herein, we report a systematic NMR-based study employing both ^{13}C-labelled and unlabelled glycosyl sulfoxide donors for the detection and monitorization of marginally populated intermediates. Our results conclusively show that glycosyl triflates play a key role in these glycosylations despite the presence of the acceptor alcohol. Importantly, the formation of covalent donor/acceptor sulfonium adducts has been identified as the main competing reaction, thus defining a non-productive consumption of the acceptor that could limit the reaction yield.

Introduction

The realization of the key role played by oligosaccharides in biological processes has undoubtedly sparked the search for more efficient stereoselective glycosylation methods.[1-4] These reactions involve the coupling of a glycosyl donor and an acceptor, and are the central transformation in saccharide synthesis. More recently, it has also become clear that a better understanding of the mechanistic aspects of the glycosylation process can contribute to its optimization in terms of yield and stereoselectivity.[5-11] A case in point in this regard has been Crich's β-mannosylation reaction, one of the best-studied glycosylations to date.[12,13] These investigations, which started

back in the mid-1990s with 4,6-O-benzylidene D-mannopyranosyl sulfoxide donors, paved the way for the stereoselective construction of 1,2-cis β-D-mannopyranosides, one of the most challenging glycosidic linkages to synthetically attain until then. Thus, a first protocol based on the pre-activation[14] of mannopyranosyl sulfoxides with triflic anhydride was shown to take place through putative sulfonium triflate species ultimately leading to α-glycosyl triflates, which produced the final β-mannopyranosides through an S_N2-like displacement by the incoming nucleophile (Scheme 1a).[15,16] Low-temperature NMR analysis of the reaction mixture after pre-activation and before addition of the acceptor provided the required evidence for the α-glycosyl triflate existence and its role as the key intermediate in the process. Opposite to that, a close ion pair (CIP) intermediate was proposed to account for the different stereoselective outcome of the *in situ* activation variant of the same reaction performed in Et_2O, although the β-stereoselective trend was restored in DCM, thus signalling a more complex scenario (Scheme 1b).[7,17]

It is now well-accepted that glycosylation reactions can occur within a mechanistic continuum spanning the gap between S_N1 and S_N2 archetypes, and that the identification and characterization of the reactive species, e.g. oxocarbenium-like or other neutral or cationic covalent intermediates, can help understand the reaction pathway and eventually allow to control its outcome.[18,19] In this context, kinetic isotope effects,[20] cation clock methodologies[21] and more recently NMR[22] have been used to study these chemical processes. Interestingly, in many occasions triflate anions have been shown to facilitate the reaction course, probably by promoting the formation of reactive glycosyl triflate species through nucleophilic catalysis.[23] For sulfoxide-promoted glycosylations, numerous activated entities have been postulated to coexist upon pre-activation of the donor, above which glycosyl triflates seem to occupy a hierarchical posi-

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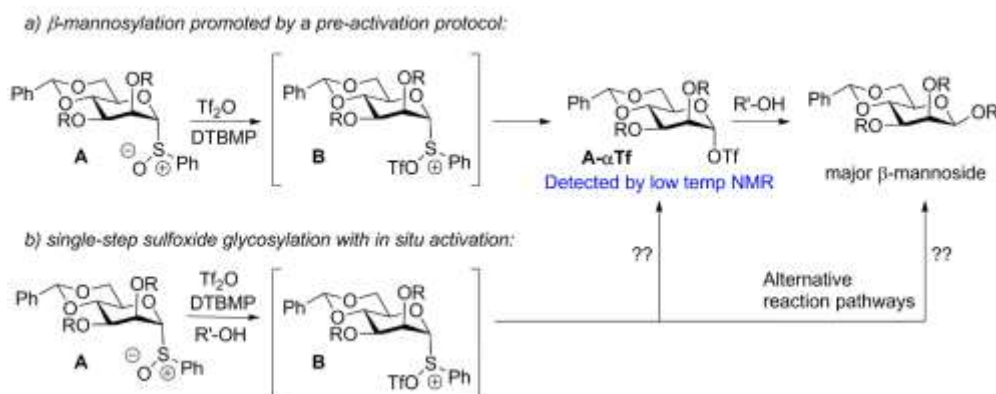
Scheme 1. a) Proposed reaction mechanism and intermediates involved in glycosylations with sulfoxide donors under pre-activation conditions. b) The role played by glycosyl triflates along with other alternative intermediates under single-step conditions is presently unknown and represents the central topic of our study.

tion, both mechanistically and concentration-wise, acting as either true glycosylating species against the acceptor or as reservoirs of even more reactive cationic intermediates.[24] However, this scenario might not hold when the acceptor alcohol is present in the reaction mixture from the beginning. Specifically, the critical role of glycosyl triflates in the presence of other competing nucleophiles has not been proven to date, and this assumption is therefore questionable. Moreover, the occurrence of previously undetected reaction intermediates involving donor and/or acceptor could also be viable under these experimental conditions. From all of the above, it became evident to us that the study of reaction intermediates in single-step glycosylations with *in situ* activation, as well as their intertwined reactivity dynamics, is pertinent to clarify the main reaction pathways governing glycoside formation, ultimately eliciting the development of more efficient and stereoselective saccharide synthesis. It should be noted that dissecting glycosylation mechanisms has proven a challenging task given the high reactivity and marginal concentration of many of the key reacting intermediates involved, often present within complex mixtures. Indeed, the ability to monitor the reaction progress with sufficient sensitivity and time resolution is key to fulfil this purpose. Herein, we would like to disclose our studies on the single-step variant of the glycosyl sulfoxide glycosylation reaction triggered by triflic anhydride. The employment of both ^{13}C-labelled and unlabelled glycosyl sulfoxide donors will enable, for the first time, the monitorization of *in situ* promoted glycosylations by low-temperature NMR experiments. The scope and limitations of this methodology have been determined as a function of various structural and experimental parameters, thus helping compose a detailed picture of the ongoing mechanistic landscape.

Results and Discussion

To have a first indication of the reactive species involved in the one-step process scenario, unlabelled D-manno-donor **1** was activated in the presence of diacetone-D-galactose (acceptor **a**, 2.2 equiv) and DTBMP (3 equiv) at -60 °C and the reaction progress was followed by 1D-NMR experiments (Figures 1a,b and S1). It can be observed that immediately after donor activation two new signals appear in the anomeric region of the spectrum (6.05 and 5.25 ppm, respectively). Interestingly, they

display identical intensities throughout the reaction, pointing to the accumulation of a single intermediate species (**I-1a**). To increase the reaction rate, the temperature was raised to -45 °C till this latter species reached an adequate population for 2D-NMR analysis (40%).[25] At this point, we cooled the sample back to -65 °C and acquired 2D-NOESY and TOCSY experiments. The obtained data sets allowed assigning NMR peaks at 6.05 and 5.25 ppm to mannose and galactose anomeric protons, respectively. More importantly, both scaffolds belong to a discrete structure, which also integrates the -SO-Ph fragment, as revealed by the presence of weak NOEs connecting both anomeric signals with the sulfoxide phenyl ring (Figure 1c).[26] At higher temperatures (ca. -20 °C), the detected intermediate evolves to produce a mixture of α/β (1:5) glycosylation products (**1a-α/β**) with an excellent yield (90%). Significantly, glycosylations carried out with a pre-activation protocol furnished an identical stereochemical outcome, indicating that the α-mannosyl triflate must still be playing an important role in both glycosylation processes.

This point was further confirmed with ^{13}C-labelling of the anomeric carbon of the mannopyranosyl sulfoxide **1**. Thus, reaction courses monitored through sequential 2D-HSQC experiments revealed the presence of a minor transient concentration of the α-mannosyl triflate (6.18 and 97.4 ppm, respectively for anomeric ^{1}H and ^{13}C chemical shifts; indicated also in Figure 1d), together with a small amount of the reduced thioglycoside (4.90 ppm and 88.7 ppm) and the previously described intermediate (6.05 and 95.8 ppm; $^1J_{HC}$ = 168 MHz) which is now detected along with a minor isomer (6.31 and 97.4 ppm) as judged by the similar ^{1}H and ^{13}C chemical shifts and identical $^1J_{HC}$ anomeric coupling (168 MHz). Based on the obtained spectroscopic data, these two latter species were assigned as the sulfonium salts **I-1a** (two stereomers), presumably formed from the triflate-activated sulfonium (**B**, Scheme 1).[27] According to our data such intermediate undergoes a triflate substitution by the acceptor alcohol at the sulfur atom, to yield a more stable sulfonium intermediate (**I-1a**) which, even in the presence of additional alcohol in the reaction mixture, evolves to produce the key glycosyl triflate (**1-αTf**), perhaps by releasing a neutral phenyl-sulfenate. It is worth mentioning that the corresponding acceptor-sulfenate has been neither isolated nor detected by us. Instead a sulfinate, as those reported by Seeberger's group[28] has been identified by HRMS directly from the glycosidation crude. We hypothesised that the relative population of the detected reaction intermediates (**I-1a** and **1-αTf**) along with their intrinsic reactivities should be strongly dependent
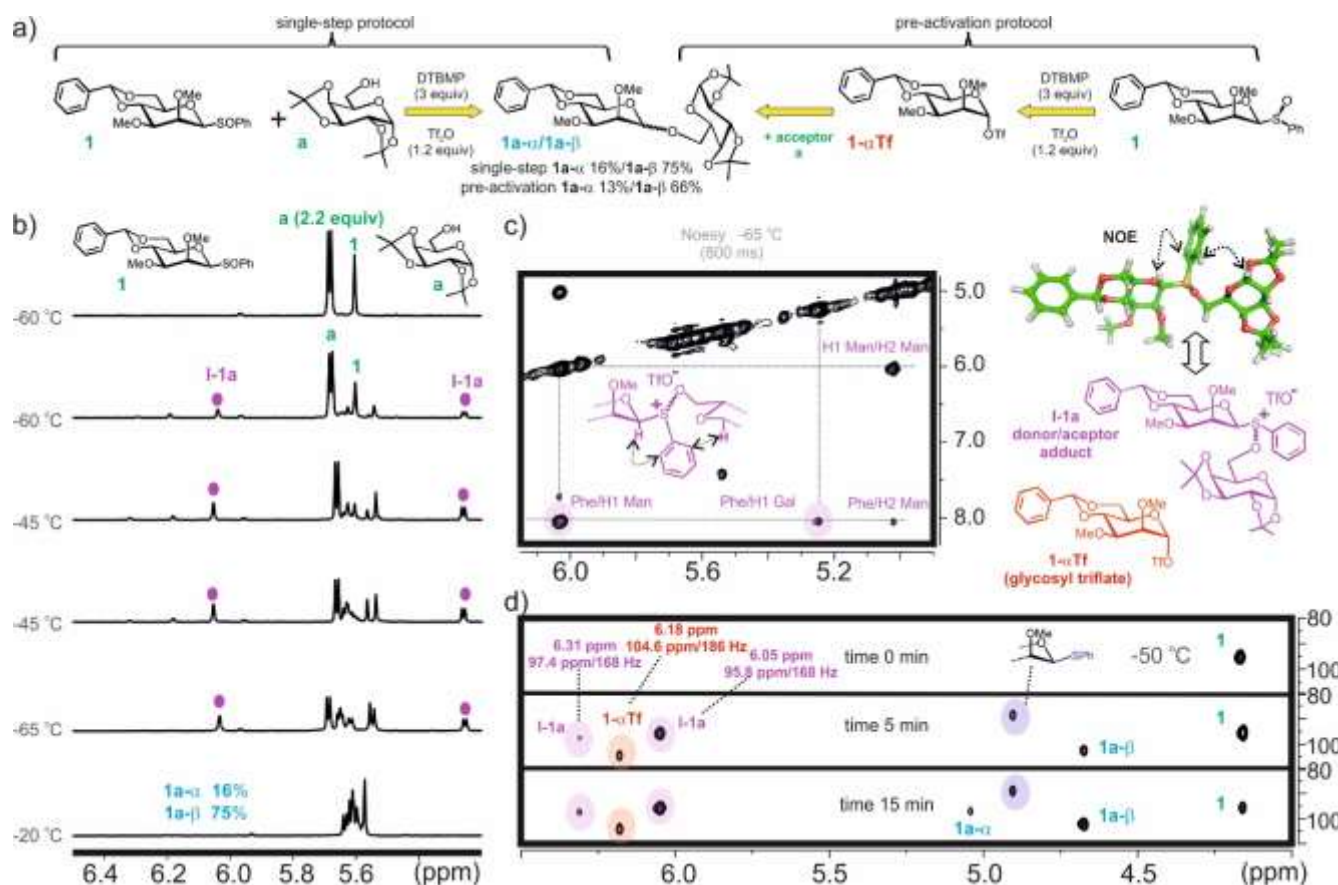
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Figure 1. a) Schematic representation of glycosylation reactions involving donor **1** and acceptor **a** with a single-step (left) or a pre-activation (right) protocol. Obtained yields for α and β products are indicated. b) Time evolution of a donor **1**/acceptor **a** mixture upon activation with Tf₂O in CDCl₃ at -60 °C. NMR anomeric signals for intermediate **I-1a** are indicated with a mauve circle. c) Through-space connections revealed by NOESY experiments (left) allowed the structural assignment of intermediate **I-1a** to the represented donor/acceptor sulfonium adduct (right). d) Reactions carried out with ¹³C-labelled **1** and monitored by means of HSQC spectra confirmed the coexistence of donor/acceptor sulfonium adducts (**I-1a**) and α-glycosyl triflates (**1-αTf**) as the only detectable reaction intermediates. ¹H and ¹³C chemical shifts for the detected intermediates are also shown.

on both the donor and acceptor chemical properties. With this idea in mind, we set out to investigate the structural and electronic requirements governing the stability and reactivity of these sulfonium adducts. As a first step, we focused our attention on the influence exerted by the anomeric configuration. For this purpose, parallel single-step glycosylations of β-manno (**1**) and α-manno (**2**) sulfoxide donors with acceptor **a** were monitored by low-temperature NMR under otherwise identical conditions. Fittingly, significant differences between these two anomers were immediately apparent, since β-donor **1** exhibited the formation of multiple activated species, as previously mentioned, while α-donor **2** exclusively provided the corresponding α-mannosyl triflate (**1-αTf**) as the only detectable intermediate. As a result, this second glycosylation finished in a shorter reaction time and with a considerable better yield than the one employing donor **1** as starting material (Figure 2). Indeed, this experimental evidence suggests a non-productive consumption of the acceptor alcohol in the formation of the epimeric sulfonium species that cannot be recovered later, and therefore presents a significant limitation of the reaction's overall performance. Consequently, this finding clearly highlights the importance of the donor anomeric configuration in the reaction evolution under one-step activation conditions, and points toward much favourable sulfonium formation with a beta anomeric configuration, either because of grave steric hindrance of the sulfonium adduct with an α-axial

configuration, or because of a stabilization of the cationic aglycon in the β configuration by reverse anomeric effect.[29] However, along this line, an alternative rationale based on the easiness of the expelling of the leaving group in the axial alfa anomer, compared to the conformationally locked beta isomer, could not be excluded.

Encouraged by these results, we tested this point further to generalise the scope of our conclusions by carrying out additional glycosylation reactions employing ¹³C-labelled donors[30] with β-manno (**1**), α-manno (**2**) and β-gluco (**3**) configurations and alcohols spanning a range of nucleophilicities (trifluoroethanol, **b**; monofluoroethanol, **c**; and isopropanol, **d**). In all cases, acceptors were employed in a significant excess (4 equiv) to ensure that this reagent was not limiting, except for those glycosylations involving diacetone-D-galactose as the acceptor counterpart, that were carried out under more realistic conditions using only a slight excess (1.3 equiv) of the alcohol (Figure 3). In Figure 3a, three sets of HSQC experiments acquired 5-10 min after activation with Tf₂O are shown, one for each glycosyl donor. The obtained yields for α and β products depicted correspond to a reaction time of 1 hour at the indicated temperature (time evolutions for some of the analysed reaction mixtures are fully displayed in Figures 2 and S2-S8). Anomeric ¹H and ¹³C chemical shifts and ¹J_{HC} heteronuclear coupling constants for some selected sulfonium intermediates are also represented below (Figure 3b). According
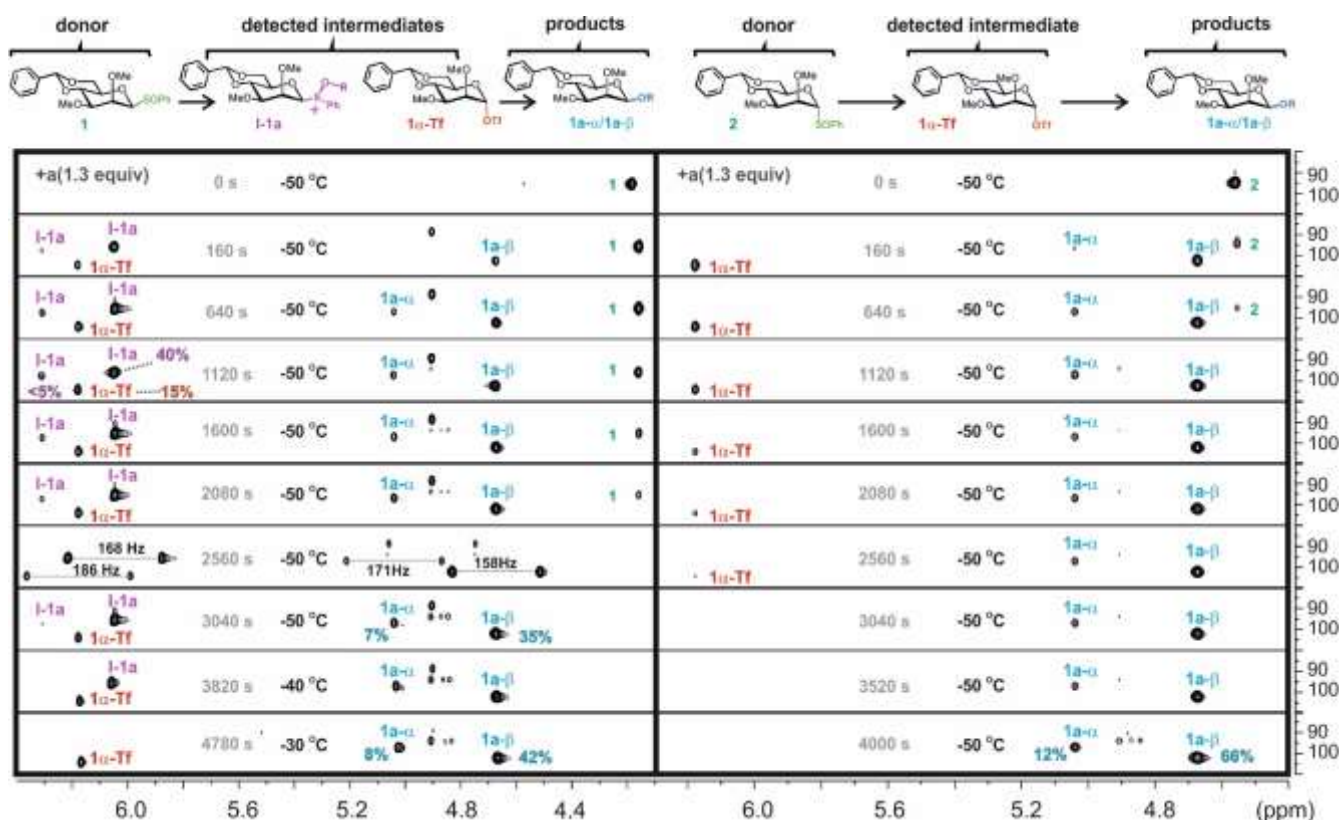
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Figure 2. Influence of the anomeric configuration in the reaction intermediate profile: comparative reaction evolution of β-manno- (**1**) and α-manno-donors (**2**) with acceptor **a**. Time-evolution of ^{13}C-labelled **1** (10 mM; right) and **2** (10 mM; left) in the presence of the galactose acceptor **a** (1.3 equiv) and DTBMP (3 equiv) after addition of Tf$_2$O (2 equiv) at the indicated temperature, monitored by 2D-HSQC NMR experiments. Assignments for key anomeric signals for the starting materials, intermediates and products, together with their $^1J_{HC}$ coupling constants are shown. Final yields are indicated in cyan at the bottom of each panel.

to these data, it quickly became evident that the evolution path for each glycosylation reaction is highly dependent on the structural and electronic properties of both donor and acceptor species. Thus, the impact of the electronic nature of the acceptor on sulfonium adduct formation was apparent when more nucleophilic alcohols (such as 2-fluoroethanol, MFE) were employed, which translates into a paradoxically slower progression of the reaction with richer rather than with weakly nucleophilic alcohols. Thus, the balance between glycosyl-triflate and sulfonium transient concentrations is highly dependent on the nucleophilic character of the acceptor alcohol: while triflates are dominant with poor nucleophiles (like TFE), these species progressively disappear in favour of the sulfonium adducts with increasingly better nucleophiles, till they become virtually undetectable (Figure 3, from top to bottom within each panel). It is worth mentioning that a set of reactions involving the same donors and acceptors were performed under the pre-activation protocol, which provided a mixture of the expected glycosylation products (Figure 3c; see the supp. info. for experimental details). Interestingly, the observed stereoselectivities seem relatively insensitive to the activation protocol employed, showing only minor variations for single-step vs pre-activation reactions with identical triflic anhydride concentrations (this experimental parameter has been shown to have an influence on the α/β ratios, increasing α-product population at larger concentrations of the activating agent).[19] This remark points toward a convergent reaction pathway and underlines the relevance of glycosyl triflates as the key common reaction intermediate, whether detectable or not.

Regarding the donor structural features, the anomeric configuration is shown to have a major influence on the steady concentrations of reactive intermediates. Thus, while stereoselectivity trends for both α- and β-mannose donors are similar, the former exhibits a markedly reduced tendency to form sulfonium intermediates (vide supra). Accordingly, the β-mannose donor reacts with a higher accumulation of sulfonium species and a concomitant decrease in the obtained yields with respect to its α-epimer is observed. This effect is particularly clear with the employed galactose acceptor, which, as previously mentioned, produces significant transient concentrations of sulfonium adducts only with the β-mannose donor. On the contrary, for the α-sulfoxide the reaction seems to proceed cleanly through the glycosyl triflate with an excellent yield. Hence, the different propensity to form covalent donor/acceptor adducts renders α- and β-donors not equivalent, being the former recommended based on its improved yields. Furthermore, the axial/equatorial configuration of position 2, neighbouring to the acetalic centre, also exerts a strong influence on the formation of sulfonium species. In fact, this process seems greatly facilitated for D-gluco- with respect to D-manno-donors (Figure 3a). Thus, for donor **3**, exhibiting equatorial orientations for both C-1 and C-2 substituents, donor/acceptor adducts are detectable even with weakly nucleophilic acceptors such as TFE. This observation agrees with the overall poor performance exhibited by the β-glucosyl sulfoxide donor in all the glycosylations tested.

Overall, increased accumulation of transient donor/acceptor sulfonium adducts directly correlates with decreased yields. This
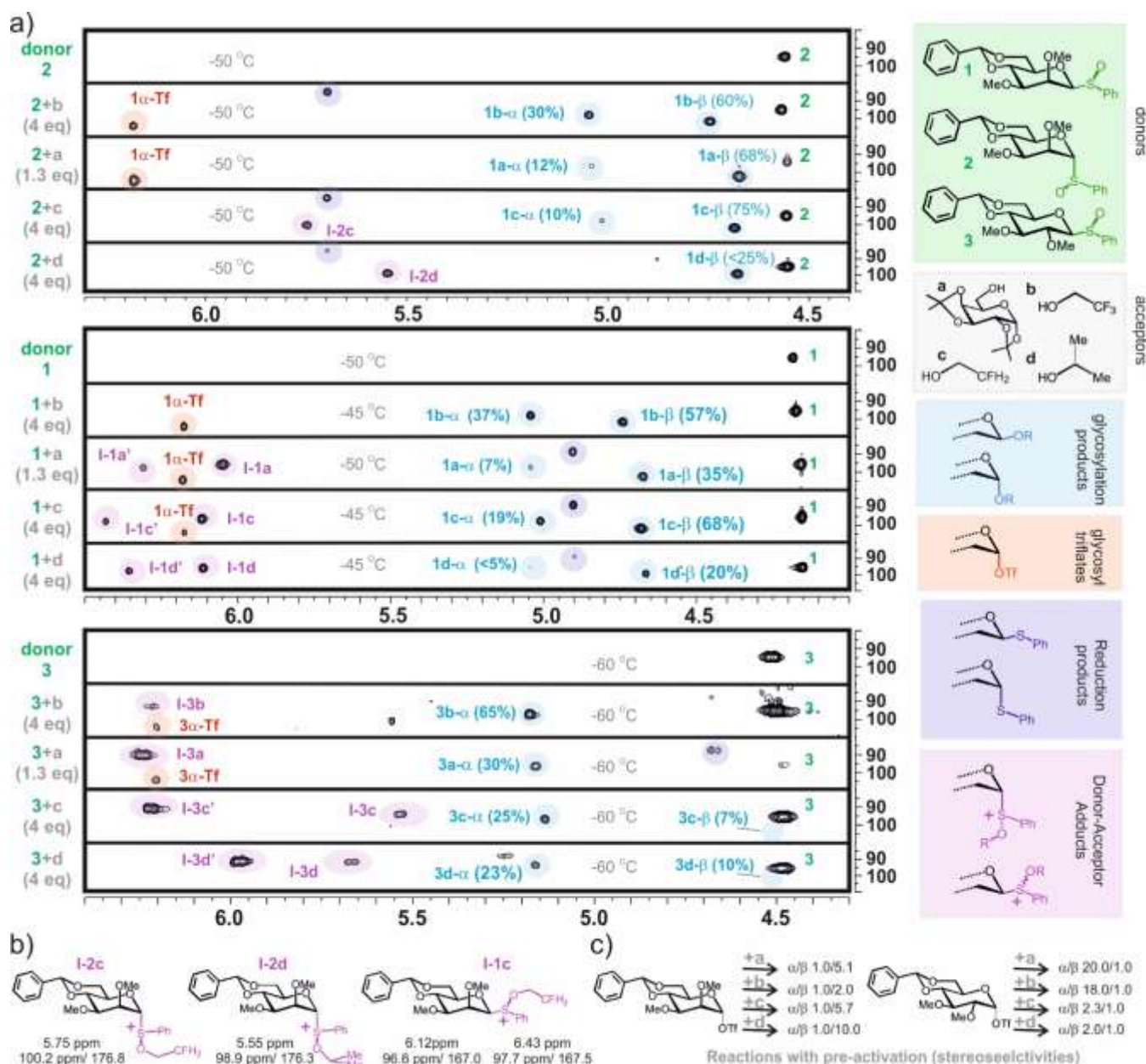
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Figure 3. a) NMR detection of key intermediates in glycosylations carried out with ^{13}C-labelled donors **1-3** and acceptors **a-d** (structures shown on the right). HSQC spectra (anomeric region) acquired with the unmodified donors and 5-10 min after activation of the different reaction mixtures are shown. Key signals are coloured according to the code shown on the right for intermediates and products. Conversions for α- and β-glycosylation products, after 60 min of evolution are indicated. b) Representative examples of the detected donor/acceptor sulfonium adducts, together with their anomeric ^{1}H and ^{13}C chemical shifts and $^1J_{HC}$ values. c) Stereoselectivities obtained with acceptors **a-d** employing a pre-activation protocol are represented for comparison.

negative influence on the glycosylation process results from a combination of two effects: first, stable sulfonium formation implies a non-productive consumption of the acceptor, which might be limiting when used in stoichiometric or sub-stoichiometric amounts (e.g. acceptor **a** cases). This further aggravates the problems derived from direct triflation of the acceptor with triflic anhydride, especially relevant for more nucleophilic alcohols (e.g. acceptor **d**). Secondly, good nucleophiles lead to exceedingly stable adducts (*e.g.* **I-3d**) whose evolution require temperatures at which parasitic reactions might be operative, perhaps involving the own sulfonium adduct, the glycosyl triflate or even more reactive glycosyl oxocarbenium-like

species. According to this view, sulfonium adducts would be acting as a kinetic trap for a successful glycosylation process. On the other hand, taking into account that some literature precedents had already shown that the absolute configuration at sulfur, in anomeric sulfoxides, has some effect in the outcome of their glycosylation reactions, we have designed some experiments to test if that would be the case in our systems.[31–33] Thus, glycosylations carried out employing both glucose donors **3** with opposite stereochemistry at the sulfur atom confirmed that identical sulfonium adducts, with the same stereomeric ratio, are formed in both cases (Figure S9). On the contrary, β-mannose donors (strongly affected by the modulatory influence of the axial
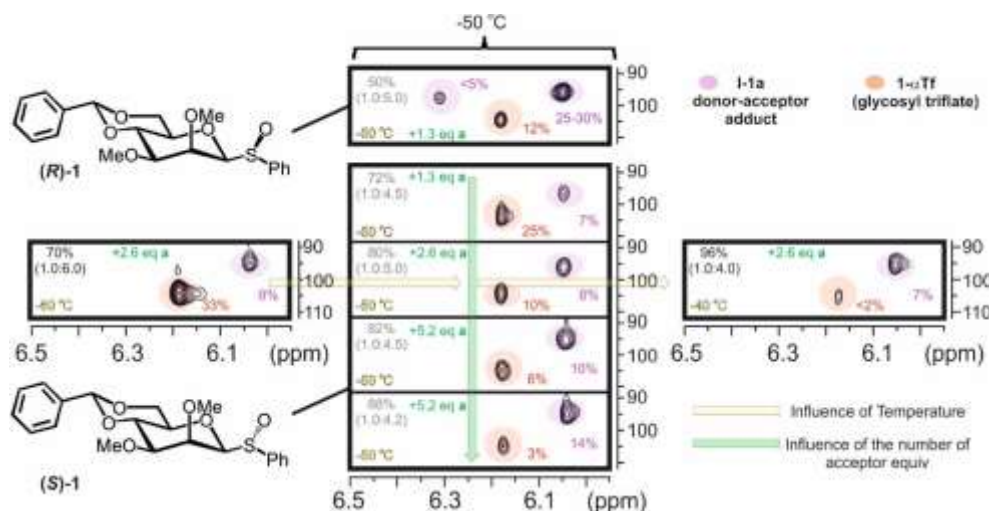
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Figure 4. NMR detection of key intermediates in glycosylations with ^{13}C-labelled donors. Reactions carried out with acceptor **a** and diastereomeric sulfoxides *(R)*-**1** (up) and *(S)*-**1** (down). In the latter case, the influence of the temperature and the number of acceptor equivalents was also tested (yellow and green arrows, respectively). HSQC spectra (anomeric region) acquired 5-10 min after activation of the different reaction mixtures are shown. Conversions for α- and β-glycosylation products after 60 min of evolution are indicated.

substituent at position C-2) lead to rather different ratios of the same activated sulfur species, being one of them barely detectable in one of the cases (compound *(S)*-**1**, Figure 4).[34] Moreover, glycosylations performed with either of the sulfoxide stereomers separately showed that the formation of donor/acceptor sulfonium adducts is greatly facilitated from one of the isomers with respect to the other (Figure 4). Indeed, reactions with donor *(R)*-**1** proceed with significantly larger transient concentrations of the sulfonium intermediates, ultimately leading to somewhat decreased reaction yields when a moderate excess of acceptor alcohol is employed.

Next, the influence of other experimental parameters, such as the donor/acceptor ratio or the temperature, on the extent by which reactive intermediates are formed throughout the reaction course and the resulting outcome, was also evaluated (Figure 4). As expected, increased fractions of acceptor alcohol translate into a slightly larger accumulated concentration of the sulfonium intermediates, with a concomitant reduction in that of the corresponding glycosyl triflate. However, under these circumstances the acceptor is not limiting, and consequently, the reactions afford somewhat improved yields in the end. Interestingly, the observed α/β stereoselectivities are, in all cases, in the 1:4-1:5 range, almost identical to those obtained with a pre-activation protocol (Figure 3c). As a result, the direct nucleophilic attack of the acceptor to the reactive sulfonium species to furnish the α-glycosylation product is not operative even in the presence of a 7-fold excess of the alcohol. Instead, reactive donor/acceptor sulfonium adducts seem to preferentially react with the more nucleophilic triflate anions[23] to yield the corresponding α-glycosyl triflates. The dominance of this process is probably facilitated by the reduced reactivity and more discriminative character of the detected sulfonium species, and by the fact that a cationic anomeric leaving group will favourably interact with the negatively charged triflate acting as counterion, whereas such coulombic attraction cannot occur with the neutral acceptor. Intriguingly, the addition of exogenous tetra-butylammonium triflate (TBAOTf) to the activated reaction mixture does not perturb the sulfonium adduct/glycosyl triflate ratio in favour of the second, possibly signalling the preferential attack of the endogenous triflate

counterion already positioned within the coordination sphere of the anomeric centre (Fig. S10) Finally, regarding the influence of temperature on the reaction outcome, the obtained data show that detected steady glycosyl triflate concentrations gradually decrease in the -60 to -40 °C range, consistent with the more limited stability of these intermediates. On the contrary, covalent donor/acceptor sulfonium adducts remain relatively minor (<10%), yet constant.

The experimental reaction parameters tested, such as the initial acceptor/donor ratio or the temperature at which the reaction is performed, both seem to have a minor influence on the steady concentrations of sulfonium species: while more acceptor translates into a higher build-up of the donor/acceptor adducts, these eventually react to yield the desired glycosylation products thanks to the excess of alcohol employed. Similarly, higher reaction temperatures have almost no effect on the concentration of sulfonium adducts, but translate into lower steady concentrations of the corresponding glycosyl triflates. Finally, the chirality of the sulfur atom at the initial sulfoxide can pose a different reactivity profile for each epimer, as in manno-derivative **1**, or have no impact at all, as in gluco-donor **3**.

Based on these results, we wondered whether the identified reactivity trends were maintained for more reactive glycosyl donors. To complete the scope of this study, the *in situ* activation methodology was also applied to 2-deoxy-β-D-glucosyl sulfoxide (**4**), which due to the lack of an electron-withdrawing substituent at the neighbouring C-2 position, generally exhibits a more reactive profile than the corresponding oxygenated counterparts (Figure 5). In a first instance, the reaction mixtures of donor **4** against the four different acceptors contemplated in this study (**a-d**) were monitored upon activation with triflic anhydride. To our surprise, no significant build-up of any of the reaction intermediates already seen for donors **1**-**3** (sulfonium salts or glycosyl triflates) was apparent regardless of the alcohol employed. Instead, a new set of intermediates was instantly detected and identified, according to their spectroscopic features, as the corresponding α- and β-phenyl sulfenates, **4α-Sf/4β-Sf**, which somehow did not seem to hamper the formation of glycosylation products over time, thus probably acting as glycosyl
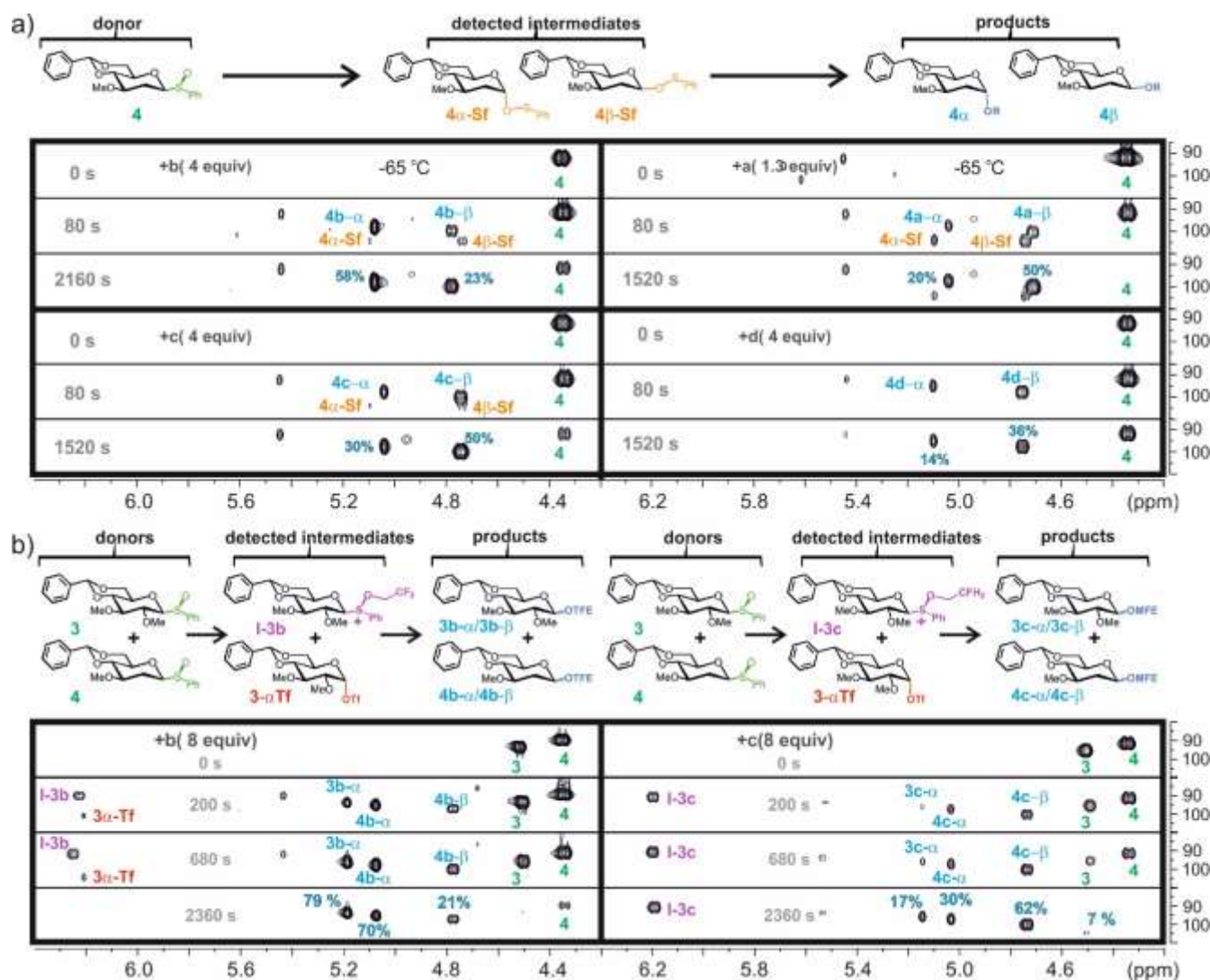
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Figure 5. a) Glycosylations carried out with 2-deoxy-β-D-glucosyl donor (**4**, 10 mM) and acceptors **a** (1.3 equiv) or **b-d** (4 equivalents) at -65 ºC monitored by HSQC experiments. Three snapshots for each reaction are shown. Assignments for key anomeric signals (starting material, intermediates and products) are displayed. Final yields are indicated in cyan. b) Time evolution of an equimolecular **3/4** mixture (10 mM each) in the presence of TFE (left) or MFE (right) upon activation with triflic anhydride at -65 ºC. Four equivalents of alcohol and three equivalents of DTBMP per donor were employed. Assignments for key anomeric signals (starting material, intermediates and products) and final yields are indicated.

triflate reservoirs or as true glycosyl donors by their own merit (Figures 5a and S11-S15). Formation of anomeric phenylsulfenates has previously been reported in the course of the glycosylation of activated sulfoxide donors by Khane and col., which showed that these intermediates, being stable at low temperatures, could be further activated and coupled with acceptors at warmer temperatures.[18] Of note, identical mixtures of activated species, with similar α/β ratios, also formed under pre-activation conditions (data not shown). To check the relative glycosylation rate of 2-deoxy-glucosyl sulfoxide in comparison with its 2-oxygenated analogue, competition experiments were designed whereby donors **2** and **4** were simultaneously reacted against TFE or MFE (acceptors **b** and **c**, respectively) (Figure 5b and S16). By doing so, we were able to observe that indeed the 2-deoxy donor reacts with no apparent accumulation of any reaction intermediates, unlike glucose donor **2**, which ultimately translated into a shorter reaction time and a better yield for the former donor species, a trend that is further accentuated for more nucleophilic alcohols, such as MFE. Overall, glycosylations

involving highly reactive donors, such as 2-deoxy-glycosyl sulfoxides, seem to evolve through a differing reaction pathway that entails glycosyl sulfenates as the only detectable intermediates. However, it should be pointed out that this observation does not rule out the participation of glycosly triflates, or the derived close-ion-pairs, as key reactive species. As expected, the glycosylations performed with donor **4** in this study maintained neither the β-stereoselectivity typical of manno-donor **1** nor the α-selectivity of glucose donor **3**, regardless of the alcohol employed, which were generally able to sway the α/β stereoselectivity from 2.5:1 with TFE to its opposite, 1:2.5 with 2-propanol.[10a]

In summary, the one-step glycosylation protocol works best for reactions involving weak acceptors, or donors less prone to form and stabilise sulfonium adducts, such as α-sulfoxides or 2- deoxy-derivatives. The opposite scenario is presented by donors with β-D-gluco configuration, whose performance is poor even with moderate nucleophiles, despite forming more reactive glycosyl triflates. This counterintuitive observation is due to the effective-
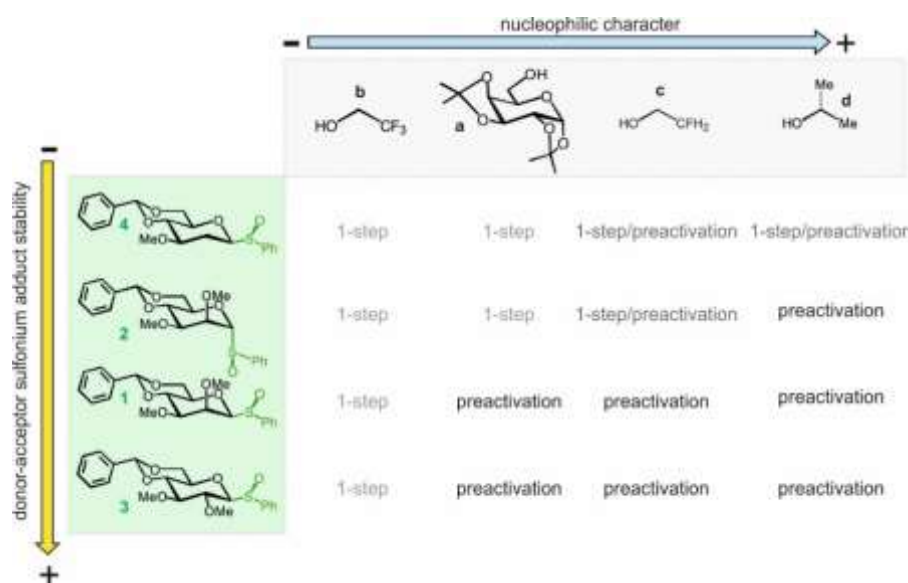
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Figure 6. Summarized conclusions indicating the recommended glycosylation protocol for each model donor/acceptor pair.

ness of the mechanistic kinetic trap herein identified for this particular example. In these cases, the alternative two-step pre-activation protocol provides a much better alternative. To sum up, all the experimental findings previously commented about have been gathered in the following chart that is aimed at managing a better informed choice of glycosylation protocol depending on the structural and electronic nature of both donor and acceptor (Figure 6).

As a corollary, it should be noted that most disaccharide-forming reactions will fall within the acceptor range loosely illustrated by the left half of the table (Figure 6), defined by moderately poor and/or relatively hindered acceptors. Thus, according to our collective data, the single-step activation variant of the sulfoxide glycosylation presents significant experimental advantages over the more widely spread pre-activation protocol for particular donor/acceptor combinations. In this regard, the employment of the *in situ* activation protocol herein studied should be definitively considered a robust, yet simpler method for the efficient construction of glycosidic linkages for 2-deoxy-glycosyl sulfoxide donors.

Conclusion

In conclusion, our results show that glycosyl triflate intermediates remain the key players in glycosylations involving glycosyl sulfoxides, even when donor activation is performed in the presence of the acceptor alcohol. Despite the fact that the observed steady concentration for this intermediate can be influenced by a variety of structural and experimental factors, the similar stereoselectivity obtained for the same donor/acceptor pairs regardless of the protocol employed rules out the participation of other activated species downstream the reaction pathway (particularly at the critical stereoselectivity-determining step) and consolidates the role of glycosyl triflates as ubiquitous true donors whenever triflate anions partake in the reaction mixture. This is due to the fact that almost any other preceding or by-standing glycosyl-intermediate must eventually transform, even if transiently, into the corresponding glycosyl-triflate for the glycosylation to come to fruition. Certainly, the formation of covalent donor/acceptor sulfonium adducts has been identified as the main competing reaction, which determines an irreversible non-productive consumption of the alcohol and consequently has the potential to curtail the reaction yield. The prevalence of such species, which can pose a kinetic trap for the glycosylation to proceed, seems to mainly depend on the structure of the donor and the electronic nature of the acceptor, although other experimental factors have been shown to have a minor influence, too; to circumvent this issue, single-step glycosylations should be given enough time and, whenever possible, higher reaction temperatures. Moreover, the use of super-stoichiometric amounts of acceptor alcohol, while economically inconvenient, can also help alleviate this problem. The extent of this detrimental pathway and its progression as a function of different experimental and structural parameters has provided valuable guidelines for the selection of an optimal glycosylation protocol for each donor/acceptor dyad.

Experimental Section

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to residual protium in the NMR solvent (CHCl₃: δ 7.26 ppm). High Resolution Mass spectra were recorded by direct injection with an Accurate Mass Q-TOF LC/MS spectrometer equipped with an electrospray ion source in positive mode.

For the preparation of donors **1-4** and their ^{13}C-labelled versions see Supporting Information.

General Procedures:

Procedure I. General method for the glycosylation experiments with sulfoxide donors **1-4** and acceptor **a**: To an oven-dried 50 mL round-bottomed flask containing the corresponding glycosyl sulfoxide (1.0 mmol), equipped with a stirring bar, was added 4 Å m.s. (100% w/w), DTBMP (3 mmol), and 1,2:3,4-di-O-isopropylidene-□-D-galactose (1.3 mmol), and then, the flask was purged three times with vacuum/Ar. Next, the mixture was dissolved in dry DCM (25 mL) under Ar atmosphere and cooled down to the designated temperature with an acetone/dry ice bath. The triflic anhydride (1.2 mmol) was injected into the solution and the resulting mixture was stirred during 1 h, at which point TEA (0.1 mL) was added, and the quenched reaction mixture was allowed to warm up to room temperature, filtered and evaporated under vacuum. The resulting crude material was purified through a silica gel column chromatography.

Procedure II. General method for the glycosylation experiments with sulfoxide donors **1-4** and acceptors **b-d**: To an oven-dried 50 mL round-bottomed flask containing the corresponding glycosyl sulfoxide (1.0 mmol), equipped with a stirring bar, was added 4 Å m.s. (100% w/w) and DTBMP (3 mmol), and then the flask was purged three times with vacuum/Ar. Next, the mixture was dissolved in dry DCM (25 mL) under Ar atmosphere and cooled down to the designated temperature with an acetone/dry ice bath. The acceptor (4 mmol) was injected into the mixture, followed by a dropwise addition of triflic anhydride (1.2 mmol). The resulting mixture was stirred during 1 h, at which point TEA (0.1 mL) was added, and the quenched reaction mixture was allowed to warm up to room temperature, filtered and evaporated under vacuum. The resulting crude material was purified through a silica gel column chromatography.

Synthesis of 4,6-O-benzylidene-2,3-di-O-methyl-α/β-D-mannopyranosyl-(1 → 6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (1a-α/β): Glycosyl sulfoxide **1** (153 mg, 0.38 mmol) and 1,2:3,4-di-O-isopropylidene-α-D-galactose (138 mg, 0.49 mmol) were coupled following the general procedure I (-50 ºC, 1 h). After work up, the residue was purified by flash silica gel chromatography (hexane/ethyl acetate 8:2 to 7:3) to give glycoside **1a-α** (12 mg, 6 %) along with glycoside **1a-β** (79 mg, 39 %).

Similarly, glycosyl sulfoxide **2** (140 mg, 0.34 mmol) and 1,2:3,4-di-O-isopropylidene-D-galactose (126 mg, 0.45 mmol) were also coupled following the general procedure I (-50 ºC, 1 h). After work up, the residue was purified by flash silica gel chromatography (hexane/ethyl acetate 8:2 to 7:3) to give glycoside **1a-α** (17 mg, 9 %) along with glycoside **1a-β** (108 mg, 59 %). For **1a-α** : ^{1}H-NMR (500 MHz, CDCl₃) δ 7.51-7.44 (m, 2H, Ar), 7.38-7.30 (m, 3H, Ar), 5.58 (s, 1H, O-CH-O), 5.54 (d, J = 5.0 Hz, 1H, H-1), 4.97 (d, J = 1.6 Hz, 1H, H-1´), 4.64 (dd, J = 7.9, 2.4 Hz, 1H, H-3), 4.34 (dd, J = 5.0, 2.4 Hz, 1H, H-2), 4.26-4.23 (m, 2H, H-4, H-6a´), 4.06 (t, J = 9.2 Hz, 1H, H-4´), 4.03-3.99 (m, 1H, H-5), 3.84-3.79 (m, 3H, H-6b´, H-5´, H-6a), 3.77-3.71 (m, 2H, H-6b, H-3´), 3.68 (dd, J = 3.3, 1.6 Hz, 1H, H-2´), 3.55 (s, 3H, OCH₃), 3.54 (s, 3H, OCH₃), 1.55 (s, 3H, CH₃), 1.46 (s, 3H, CH₃), 1.35 (s, 3H, CH₃), 1.34 (s, 3H, CH₃); ^{13}C-NMR (126 MHz, CDCl₃) δ 137.8 (C, Ar), 129.0 (CH, Ar), 128.3 (2 CH, Ar), 126.3 (2 CH, Ar), 109.6 (O-C-O), 108.8 (O-C-O), 101.8 (O-CH-O), 98.2 (CH-1´), 96.5 (CH-1), 79.3 (CH-4´), 79.0 (CH-2´), 77.7 (CH-3´), 71.2 (CH-4), 70.9 (CH-3), 70.8 (CH-2), 68.9 (CH₂-6´), 66.2 (CH₂-6), 65.7 (CH-5), 64.3 (CH-5´), 59.8 (OCH₃), 59.2 (OCH₃), 26.3 (CH₃), 26.1 (CH₃), 25.1 (CH₃), 24.7 (CH₃). HRMS (ESI) m/z calcd for C₂₇H₃₉O₁₁ [M+H]⁺: 539.24869, found: 539.25069. For **1a-β** : ^{1}H-NMR (300 MHz, CDCl₃) δ 7.50-7.41 (m, 2H, Ar), 7.39-7.29 (m, 3H, Ar), 5.54 (s, 1H, O-CH-O), 5.50 (d, J = 5.0 Hz, 1H, H-1), 4.62-4.58 (m, 2H, H-1´, H-3), 4.33-4.30 (m, 1H, H-2), 4.29 (dd, J = 10.5, 4.9 Hz, 1H, H-6eq´), 4.19 (dd, J = 7.9, 1.8 Hz, 1H, H-4), 4.14 (dd, J = 11.1, 2.3 Hz, 1H, H-6a), 4.03 (t, J = 9.4 Hz, 1H, H-4´), 4.08-3.94 (m, 1H, H-5), 3.94-3.81 (m, 2H, H-3´ H-6ax´), 3.73-3.61 (m, 1H, H-6b), 3.68 (s, 3H, OCH₃), 3.54 (s, 3H, OCH₃), 3.41 (dd, J = 9.9, 3.2 Hz, 1H, H-2´), 3.32 (td, J = 9.7, 4.9 Hz, 1H,

H-5´), 1.51 (s, 3H, CH₃), 1.45 (s, 3H, CH₃), 1.33 (s, 3H, CH₃), 1.32 (s, 3H, CH₃); ^{13}C-NMR (126 MHz, CDCl₃) δ 137.6 (C, Ar), 129.0 (CH, Ar), 128.3 (2 CH, Ar), 126.2 (2 CH, Ar) 109.6 (O-C-O), 108.8 (O-C-O), 102.7 (CH-1´), 101.7 (O-CH-O), 96.4 (CH-1), 79.9 (CH-2´), 78.7 (CH-3´), 78.7 (CH-4´), 71.7 (CH-4), 70.8 (CH-3), 70.6 (CH-2), 70.2 (CH₂-6), 68.6 (CH₂-6´), 68.3 (CH-5), 67.3 (CH-5´), 62.2 (OCH₃), 58.8 (OCH₃), 26.1 (CH₃), 26.0 (CH₃), 25.1 (CH₃), 24.5 (CH₃). HRMS (ESI) m/z calcd for C₂₇H₃₈NaO₁₁ [M+Na]⁺: 561.23063, found: 561.23013.

Synthesis of 2,2,2-trifluoroethyl 4,6-O-benzylidene-2,3-di-O-methyl-α/β-D-mannopyranoside (1b-α/β and 2b-α/β): Glycosyl sulfoxide **1** (205 mg, 0.51 mmol) and 2,2,2-trifluoroethanol (0.15 mL, 2.03 mmol) were coupled following the general procedure II (-45 ºC, 1 h). After work up, the residue was purified by flash silica gel chromatography (hexane/ethyl acetate 9:1 to 7:3) to give glycoside **1b-α** (59 mg, 31 %) along with glycoside **1b-β** (94 mg, 49 %).

Similarly, glycosyl sulfoxide **2** (167 mg, 0.41 mmol) and and 2,2,2-trifluoroethanol (0.12 mL, 1.65 mmol) were also coupled following the general procedure II (-50 ºC, 1 h). After work up, the residue was purified by flash silica gel chromatography (hexane/ethyl acetate 9:1 to 7:3) to give glycoside **1b-α** (42 mg, 27 %) along with glycoside **1b-β** (82 mg, 53 %). For **1b-α** : ^{1}H-NMR (400 MHz, CDCl₃) δ 7.68-7.62 (m, 3H, Ar), 7.50-7.42 (m, 2H, Ar), 5.59 (s, 1H, O-CH-O), 4.97 (d, J = 1.5 Hz, 1H, H-1), 4.24 (dd, J = 9.9, 4.1 Hz, 1H, H-6eq), 4.09 (t, J = 9.5 Hz, 1H, H-4), 4.00-3.92 (m, 2H, CH₂-CF₃), 3.84 (t, J = 9.9 Hz, 1H, H-6ax), 3.81-3.76 (m, 1H, H-5), 3.73 (m, 2H, H-2, H-3), 3.57 (s, 3H, OCH₃), 3.56 (s, 3H, OCH₃); ^{13}C-NMR (101 MHz, CDCl₃) δ 145.7 (C, Ar), 131.2 (CH, Ar), 130.0 (q, J = 280 Hz, CH₂-CF₃), 129.4 (2 CH, Ar), 124.9 (2 CH, Ar), 101.8 (O-CH-O), 99.1 (CH-1), 78.9 (CH-4), 78.3 (CH-2), 77.4 (CH-3), 68.6 (CH₂-6), 64.8 (CH-5), 64.4 (q, J = 64.0 Hz, CH₂-CF₃), 60.1 (OCH₃), 59.4 (OCH₃). HRMS (ESI) m/z calcd for C₁₇H₂₁F₃NaO₆ [M+Na]⁺: 401.11824, found: 401.1189. For **1b-β**: ^{1}H-NMR (500 MHz, CDCl₃) δ 7.52-7.42 (m, 2H, Ar), 7.42-7.29 (m, 3H, Ar), 5.57 (s, 1H, O-CH-O), 4.64 (br.s, 1H, H-1), 4.32 (dd, J = 10.3, 4.9 Hz, 1H, H-6eq), 4.20 (dq, J = 12.6, 8.8 Hz, 1H, CH₂-CF₃), 4.05 (t, J = 9.9 Hz, 1H, H-4), 4.02-3.94 (m, 1H, CH₂-CF₃), 3.91 (t, J = 10.3 Hz, 1H, H-6ax), 3.82 (dd, J = 3.1, 1.0 Hz, 1H, H-2), 3.67 (s, 3H, OCH₃), 3.57 (s, 3H, OCH3), 3.43 (dd, J = 9.9, 3.1 Hz, 1H, H-3), 3.35 (ddd, J = 10.3, 9.9, 4.9 Hz, 1H, H-5); ^{13}C-NMR (126 MHz, CDCl₃) δ 137.4 (C, Ar), 129.1 (CH, Ar), 128.3 (2 CH, Ar), 126.2 (2 CH, Ar), 123.8 (q, J = 280.5 Hz, CF₃), 101.80 (CH-1), 101.78 (O-CH-O), 79.9 (CH-3), 78.5 (CH-2), 78.4 (CH-4), 68.4 (CH₂-6), 67.7 (CH-5), 66.1 (q, J = 34.8 Hz, CH₂-CF₃), 62.3 (OCH₃), 59.1 (OCH₃). HRMS (ESI) m/z calcd for C₁₇H₂₁F₃NaO₆ [M+Na]⁺: 401.11824, found: 401.11834.

Synthesis of 2-fluoroethyl 4,6-O-benzylidene-2,3-di-O-methyl-α/β-D-mannopyranoside (1c-α/β): Glycosyl sulfoxide **1** (182 mg, 0.45 mmol) and 2-fluoroethanol (0.10 mL, 1.80 mmol) were coupled following the general procedure II (-45 ºC, 1 h). After work up, the residue was purified by flash silica gel chromatography (hexane/ethyl acetate 9:1 to 7:3) to give glycoside **1c-α** (23 mg, 15 %) along with glycoside **1c-β** (94 mg, 61 %).

Similarly, glycosyl sulfoxide **2** (174 mg, 0.43 mmol) and 2-fluoroethanol (0.10 mL, 1.72 mmol) were also coupled following the general procedure II (-50 ºC, 1 h). After work up, the residue was purified by flash silica gel chromatography (hexane/ethyl acetate 9:1 to 7:3) to give glycoside **1c-α** (10 mg, 7 %) along with glycoside **1c-β** (100 mg, 68 %). For **1c-α**: ^{1}H-NMR (500 MHz, CDCl₃) δ 7.51-7.46 (m, 2H, Ar), 7.38-7.30 (m, 3H, Ar), 5.59 (s, 1H, O-CH-O), 4.94 (d, J = 1.6 Hz, 1H, H-1), 4.67-4.52 (m, 2H, CH₂-F), 4.27-4.20 (m, 1H, H-6a), 4.08 (t, J = 10.1 Hz, 1H, H-4), 3.96– 3.81 (m, 1H, CH₂-CH₂-F), 3.85-3.82 (m, 2H, H-6b, H-5), 3.79-3.71 (m, 1H, CH₂-CH₂-F), 3.76 (dd, J = 10.1, 3.4 Hz, 1H, H-3), 3.71 (dd, J = 3.4, 1.6 Hz, 1H, H-2), 3.57 (s, 3H, OCH3), 3.56 (s, 3H, OCH3); ^{13}C-NMR (126 MHz, CDCl₃) δ 137.7 (C, Ar), 129.0 (CH, Ar), 128.3 (2 CH, Ar), 126.2 (2 CH, Ar), 101.8 (O-CH-O), 98.8 (CH-1), 82.6 (d, J = 170.1 Hz, CH₂-F), 79.2 (CH-4), 78.7 (CH-2), 77.7 (CH-3), 68.9 (CH₂-6), 66.9 (d, J = 19.7 Hz, CH₂-CH₂-F), 64.3 (CH-5), 60.0 (OCH₃), 59.3 (OCH₃). HRMS (ESI) m/z calcd for C₁₇H₂₄FO₆ [M+H]⁺: 343.15514, found: 343.15288. For **1c-β**: ^{1}H-NMR (500 MHz, CDCl₃) δ 7.52-7.43 (m, 2H, Ar), 7.40-7.30 (m, 3H, Ar), 5.56 (s, 1H, O-CH-O), 4.71-4.50 (m, 2H, CH₂-F), 4.59 (br.s, 1H, H-1), 4.30 (dd, J = 10.3, 4.9 Hz, 1H, H-6eq), 4.13-4.02 (m, 2H, CH₂-CH₂-F), 4.04 (t, J = 10.3 Hz, 1H, H-4), 3.89 (t, J = 10.3 Hz, 1H, H-6ax), 3.82 (d, J = 3.1 Hz, 1H, H-2), 3.68 (s, 3H, OCH₃), 3.56 (m, 3H, OCH₃), 3.43 (dd, J = 10.3, 3.1 Hz, 1H, H-3),

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3.35 (td, J = 10.3, 4.9 Hz, 1H, H-5); ^{13}C-NMR (126 MHz, CDCl$_3$) δ 137.5 (C, Ar), 129.0 (CH, Ar), 128.3 (2 CH, Ar), 126.2 (2 CH, Ar), 102.2 (CH-1), 101.7 (O-CH-O), 82.9 (d, J = 169.7 Hz, CH$_2$-F), 80.1 (CH-3), 78.8 (CH-2), 78.7 (CH-4), 68.9 (d, J = 19.7 Hz, CH$_2$-CH$_2$-F), 68.6 (CH$_2$-6), 67.49 (CH-5), 62.3 (OCH$_3$), 59.0 (OCH$_3$). HRMS (ESI) m/z calcd for C$_{17}$H$_{23}$FNaO$_6$ [M+Na]$^+$: 365.13709, found: 365.13753.

Synthesis of 2-propyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α/β-D-mannopyranoside (1d-α/β): Glycosyl sulfoxide **1** (158 mg, 0.39 mmol) and 2-propanol (0.12 mL, 1.56 mmol) were coupled following the general procedure II (-45 ºC, 1 h). After work up, the residue was purified by flash silica gel chromatography (hexane/ethyl acetate 9:1 to 8:2) to give glycoside **1d-α** (5 mg, 4 %), along with glycoside **1d-β** (20 mg, 15 %). Similarly, glycosyl sulfoxide **2** (123 mg, 0.30 mmol) and 2-propanol (0.09 mL, 1.22 mmol) were also coupled following the general procedure II (-50 ºC, 1 h). After work up, the residue was purified by flash silica gel chromatography (hexane/ethyl acetate 9:1 to 8:2) to give exclusively glycoside **1d-β** (21 mg, 20 %). For **1d-α**: ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.54-7.44 (m, 2H, Ar), 7.41-7.29 (m, 3H, Ar), 5.59 (s, 1H, O-CH-O), 4.98 (d, J = 1.7 Hz, 1H, H-1), 4.27-4.17 (m, 1H, H-6a), 4.06 (t, J = 9.0 Hz, 1H, H-4), 3.93 (hept, J = 6.2 Hz, 1H, CH$_3$-CH-CH$_3$), 3.86-3.80 (m, 2H, H-5, H-6b), 3.74 (dd, J = 9.9, 3.3 Hz, 1H, H-3), 3.59 (dd, J = 3.3, 1.7 Hz, 1H, H-2), 3.57 (s, 3H, OCH$_3$), 3.55 (s, 3H, OCH$_3$), 1.23 (d, J = 6.2 Hz, 3H, CH$_3$-CH-CH$_3$), 1.17 (d, J = 6.1 Hz, 3H, CH$_3$-CH-CH$_3$); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 137.7 (C, Ar), 128.9 (CH, Ar), 128.3 (2 CH, Ar), 126.2 (2 CH, Ar), 101.6 (O-CH-O), 96.5 (CH-1), 79.53 (CH-2), 79.50 (CH-4), 77.8 (CH-3), 69.6 (CH$_3$-CH-CH$_3$), 69.0 (CH$_2$-6), 64.1 (CH-5), 59.9 (OCH$_3$), 59.2 (OCH$_3$), 23.4 (CH$_3$-CH-CH$_3$), 21.4 (CH$_3$-CH-CH$_3$). HRMS (ESI) m/z calcd for C$_{18}$H$_{26}$NaO$_6$ [M+Na]$^+$: 361.16092, found: 361.16216. For **1d-β**: ^{1}H-NMR (400 MHz,CDCl$_3$) δ 7.56-7.38 (m, 3H, Ar), 7.37 (s, 2H, Ar), 5.55 (s, 1H, O-CH-O), 4.59 (d, J = 1.0 Hz, 1H, H-1), 4.29 (dd, J = 10.5, 4.9 Hz, 1H, H-6eq), 4.04 (t, J = 9.6 Hz, 1H, H-4), 4.01 (hept, J = 6.3 Hz, 1H, CH$_3$-CH-CH$_3$), 3.90 (t, J = 10.3 Hz, 1H, H-6ax), 3.69 (dd, J = 3.2, 1.0 Hz, 1H, H-2), 3.67 (s, 3H, OCH$_3$), 3.55 (s, 3H, OCH$_3$), 3.42 (dd, J = 9.9, 3.2 Hz, 1H, H-3), 3.33 (ddd, J = 10.0, 9.2, 4.9 Hz, 1H, H-5), 1.26 (d, J = 6.2 Hz, 3H, CH$_3$-CH-CH$_3$), 1.19 (d, J = 6.1 Hz, 3H, CH$_3$-CH-CH$_3$); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 137.6 (C, Ar), 128.9 (CH, Ar), 128.3 (2 CH, Ar), 126.2 (2 CH, Ar), 101.7 (O-CH-O), 100.1 (CH-1), 80.3 (CH-3), 79.7 (CH-2), 78.8 (CH-4), 71.4 (CH$_3$-CH-CH$_3$), 68.7 (CH$_2$-6), 67.4 (CH-5), 62.2 (OCH$_3$), 58.9 (OCH$_3$), 23.6 (CH$_3$-CH-CH$_3$), 21.7 (CH$_3$-CH-CH$_3$). HRMS (ESI) m/z calcd for C$_{18}$H$_{26}$NaO$_6$ [M+Na]$^+$: 361.16092, found: 361.16164.

Synthesis of 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranosyl-(1 → 6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (3a-α): Glycosyl sulfoxide **3** (142 mg, 0.35 mmol) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactose (128 mg, 0.46 mmol) were coupled following the general procedure I (-60 ºC, 1 h). After work up, the residue was purified by flash silica gel chromatography (hexane/ethyl acetate 8:2 to 7:3) to give exclusively glycoside **3a-α** (53 mg, 28 %). ^{1}H-NMR (500 MHz, CDCl$_3$) δ 7.54-7.46 (m, 2H, Ar), 7.39-7.30 (m, 3H, Ar), 5.54 (s, 1H, O-CH-O), 5.52 (d, J = 5.0 Hz, 1H, H-1), 5.05 (d, J = 3.7 Hz, 1H, H-1´), 4.62 (dd, J = 8.0, 2.4 Hz, 1H, H-3), 4.33 (dd, J = 8.0, 1.9 Hz, 1H, H-4), 4.31 (dd, J = 5.0, 2.4 Hz, 1H, H-2), 4.28 (dd, J = 10.3, 5.1 Hz, 1H, H-6eq´), 4.05 (td, J = 6.7, 1.9 Hz, 1H, H-5), 3.89 (td, J = 9.9, 4.9 Hz, 1H, H-5), 3.82 (dd, J = 10.5, 1.9 Hz, 1H, H-6a), 3.74 (dd, J = 10.4, 7.1 Hz, 1H, H-6b), 3.70 (t, J = 10.3,1H, H-6ax´), 3.68 (t, J = 9.3 Hz, 1H, H-3´) 3.63 (s, 3H, OCH$_3$), 3.53 (t, J = 9.3 Hz, 1H, H-4´) 3.51 (s, 3H, OCH$_3$), 3.29 (dd, J = 9.3, 3.7 Hz, 1H, H-2´), 1.54 (s, 3H, CH$_3$), 1.44 (s, 3H, CH$_3$), 1.33 (s, 6H, 2 CH$_3$); ^{13}C-NMR (126 MHz, CDCl$_3$) δ 137.6 (C, Ar), 129.0 (CH, Ar), 128.3 (2 CH, Ar), 126.2 (2 CH, Ar), 109.3 (O-C-O), 108.7 (O-C-O), 101.4 (O-CH-O), 97.6 (CH-1´), 96.4 (CH-1), 82.3 (CH-4´), 81.3 (CH-2´), 79.4 (CH-3´), 70.9 (CH-2), 70.8 (CH-3), 70.7 (CH-4), 69.1 (CH$_2$-6´), 67.0 (CH$_2$-6), 65.9 (CH-5), 62.4 (CH-5´), 61.1 (OCH$_3$), 58.4 (OCH$_3$), 26.2 (CH$_3$), 26.1 (CH$_3$), 25.0 (CH$_3$), 24.5 (CH$_3$). HRMS (ESI) m/z calcd for C$_{27}$H$_{42}$NO$_{11}$ [M+NH$_4$]$^+$: 556.27524, found: 556.27532.

Synthesis of 2,2,2-trifluoroethyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside (3b-α): Glycosyl sulfoxide **3** (202 mg, 0.50 mmol) and 2,2,2-trifluoroethanol (0.14 mL, 1.99 mmol) were coupled following the general procedure II (-60 ºC, 1 h). After work up, the residue was purified

by flash silica gel chromatography (hexane/ethyl acetate 9:1 to 7:3) to give exclusively glycoside **3b-α** (110 mg, 58 %). ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.53-7.42 (m, 3H, Ar), 7.41-7.30 (m, 2H, Ar), 5.54 (s, 1H, O-CH-O), 5.05 (d, J = 3.8 Hz, 1H, H-1), 4.27 (dd, J = 9.8, 4.6 Hz, 1H, H-6eq), 4.06-3.95 (m, 2H, CH$_2$-CF$_3$), 3.89-3.81 (m, 1H, H-5), 3.72 (t, J = 9.8 Hz, 1H, H-6ax), 3.71 (t, J = 9.2, 1H, H-3) 3.65 (s, 3H, OCH$_3$), 3.54 (s, 3H, OCH$_3$), 3.33 (t, J = 9.2 Hz, 1H, H-4), 3.33 (dd, J = 9.2, 3.8, Hz, 1H, H-2); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 145.4 (C, Ar), 131.2 (CH, Ar), 129.5 (2 CH, Ar), 123.8 (q, J = 277.1 Hz, CF$_3$), 124.9 (2 CH, Ar), 101.5 (O-CH-O), 97.2 (CH-1), 81.9 (CH-4), 81.0 (CH-2), 79.3 (CH-3), 68.8 (CH$_2$-6), 64.7 (q, J = 35.0 Hz, CH$_2$-CF$_3$), 63.1 (CH-5), 61.2 (OCH$_3$), 59.1 (OCH$_3$). HRMS (ESI) m/z calcd for C$_{17}$H$_{21}$F$_3$NaO$_6$ [M+Na]$^+$: 401.11879, found: 401.12319.

Synthesis of 2-fluoroethyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α/β-D-glucopyranoside (3c-α/β): Glycosyl sulfoxide **3** (153 mg, 0.38 mmol) and 2-fluoroethanol (0.09 mL, 1.51 mmol) were coupled following the general procedure II (-60 ºC, 1 h). After work up, the residue was purified by flash silica gel chromatography (hexane/ethyl acetate 9:1 to 7:3) to give glycoside **3c-α** (26 mg, 20 %) along with glycoside **3c-β** (6 mg, 5 %). For **3c-α**: ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.54 -7.41 (m, 2H, Ar), 7.39-7.32 (m, 3H, Ar), 5.54 (s, 1H, O-CH-O), 5.03 (d, J = 3.8 Hz, 1H, H-1), 4.62 (dt, J = 47.6, 4.4 Hz, 2H, CH$_2$-F), 4.27 (dd, J = 10.2, 4.8 Hz, 1H, H-6eq), 3.99-3.76 (m, 3H, CH$_2$-CH$_2$-F, H-5), 3.72 (t, J = 9.3 Hz, 1H, H-4), 3.71 (t, J = 10.2 Hz, 1H, H-6ax), 3.65 (s, 3H, OCH$_3$), 3.55 (s, 3H, OCH$_3$), 3.54 (t, J = 9.3 Hz, 1H, H-3), 3.32 (dd, J = 9.3, 3.8 Hz, 1H, H-2); ^{13}C-NMR (101 MHz, CDCl3) δ 137.4 (C, Ar), 129.0 (CH, Ar), 128.3 (2 CH, Ar), 126.2 (2 CH, Ar), 101.4 (O-CH-O), 97.6 (CH-1), 82.5 (d, J = 169.8 Hz, CH$_2$-F), 82.3 (CH-3) 81.3 (CH-2), 79.8 (CH-4), 69.1 (CH$_2$-6), 67.2 (d, J = 20.2 Hz, CH$_2$-CH$_2$-F), 62.5 (CH-5), 61.1 (OCH$_3$), 59.1 (OCH$_3$). HRMS (ESI) m/z calcd for C$_{17}$H$_{23}$FNaO$_6$ [M+Na]$^+$: 365.13709, found: 365.13708. For **3c-β**: ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.50-7.48 (m, 2H, Ar), 7.42-7.29 (m, 3H, Ar), 5.54 (s, 1H, O-CH-O), 4.70-4.49 (m, 2H, CH$_2$-F), 4.45 (d, J = 7.6 Hz, 1H, H-1), 4.32 (dd, J = 10.3, 5.0 Hz, 1H, H-6eq), 4.07 (dddd, J = 31.3, 12.1, 4.6, 3.0 Hz, 1H, CH$_2$-CH$_2$-F), 3.86 (dddd, J = 26.5, 12.2, 5.9, 3.4 Hz, 1H, CH$_2$-CH$_2$-F), 3.76 (t, J = 10.3 Hz, 1H, H-6ax), 3.64 (s, 3H, OCH$_3$), 3.62 (s, 3H, OCH$_3$), 3.57 (t, J = 9.3 Hz, 1H, H-4), 3.39 (t, J = 9.2 Hz, 1H, H-3), 3.42-3.35 (m, 1H, H-5), 3.12 (dd, J = 9.2, 7.6 Hz, 1H, H-2); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 137.4 (C, Ar), 129.1 (CH, Ar), 128.3 (2 CH, Ar), 126.2 (2 CH, Ar), 104.2 (CH-1), 101.3 (O-CH-O), 83.8 (CH-2), 84.3 (d, J = 170.4 Hz, CH$_2$-F), 82.6 (CH-3), 81.3 (CH-4), 69.2 (d, J = 20.1 Hz, CH$_2$-CH$_2$-F), 68.8 (CH$_2$-6), 66.1 (CH-5), 61.1 (OCH$_3$), 61.0 (OCH$_3$). HRMS (ESI) m/z calcd for C$_{17}$H$_{24}$FO$_6$ [M+H]$^+$: 343.15514, found: 343.15362.

Synthesis of 2-propyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α/β-D-glucopyranoside (3d-α/β): Glycosyl sulfoxide **3** (105 mg, 0.26 mmol) and 2-propanol (0.08 mL, 1.04 mmol) were coupled following the general procedure II (-60 ºC, 1 h). After work up, the residue was purified by flash silica gel chromatography (hexane/ethyl acetate 9:1 to 7:3) to give glycoside **3d-α** (17 mg, 19 %) along with glycoside **3d-β** (7 mg, 8 %). For **3d-α**: ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.64-7.44 (m, 2H, Ar), 7.42-7.30 (m, 3H, Ar), 5.55 (s, 1H, O-CH-O), 5.06 (d, J = 3.8 Hz, 1H, H-1), 4.26 (dd, J = 10.3, 4.8 Hz, 1H, H-6eq), 3.93 (hept, J = 6.3 Hz, 1H, CH$_3$-CH-CH$_3$), 3.71 (t, J = 10.3 Hz, 1H, H-6ax), 3.70 (t, J = 9.3 Hz, 1H, H-3), 3.65 (s, 3H, OCH$_3$), 3.60-3.57 (m, 1H, H-5), 3.53 (t, J = 9.3 Hz, 1H, H-4), 3.52 (s, 3H, OCH$_3$), 3.28 (dd, J = 9.3, 3.8 Hz, 1H, H-2), 1.27 (d, J = 6.3 Hz, 3H, CH$_3$-CH-CH$_3$), 1.22 (d, J = 6.3 Hz, 3H, CH$_3$-CH-CH$_3$); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 137.5 (C, Ar), 129.0 (CH, Ar), 128.3 (2 CH, Ar), 126.2 (2 CH, Ar), 101.4 (O-CH-O), 95.3 (CH-1), 82.6 (CH-4), 81.4 (CH-2), 79.6 (CH-3), 69.8 (CH$_3$-CH-CH$_3$), 69.2 (CH$_2$-6), 62.4 (CH-5), 61.1 (OCH$_3$), 58.8 (OCH$_3$), 23.4 (CH$_3$-CH-CH$_3$), 21.4 (CH$_3$-CH-CH$_3$). HRMS (ESI) m/z calcd for C$_{18}$H$_{26}$NaO$_6$ [M+Na]$^+$: 361.16216, found: 361.16278. For **3d-β**: ^{1}H-NMR (400 MHz,CDCl$_3$) δ 7.66-7.42 (m, 2H, Ar), 7.42-7.30 (m, 3H, Ar), 5.53 (s, 1H, O-CH-O), 4.45 (d, J = 7.7 Hz, 1H, H-1), 4.31 (dd, J = 10.3, 5.0 Hz, 1H, H-6eq), 3.98 (hept, J = 6.1 Hz, 1H, CH$_3$-CH-CH$_3$), 3.76 (t, J = 10.3 Hz, 1H, H-6ax), 3.63 (s, 3H, OCH$_3$), 3.61 (s, 3H, OCH$_3$), 3.56 (t, J = 9.3 Hz, 1H, H-4), 3.45-3.28 (m, 2H, H-5, H-3), 3.06 (dd, J = 8.8, 7.7 Hz, 1H, H-2), 1.26 (d, J = 6.1 Hz, 3H, CH$_3$-CH-CH$_3$), 1.23 (d, J = 6.1 Hz, 3H, CH$_3$-CH-CH$_3$); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 137.5 (C, Ar), 129.0 (CH, Ar), 128.3 (2 CH, Ar), 126.2 (2 CH, Ar), 102.7 (CH-1), 101.3 (O-CH-O), 84.0 (CH-2), 82.8 (CH-3), 81.4 (CH-4), 72.8 (CH$_3$-CH-CH$_3$), 67.0 (CH$_2$-6), 66.0 (CH-5), 61.1

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(OCH$_3$), 61.0 (OCH$_3$), 23.7 (CH$_3$-CH-CH$_3$), 22.1 (CH$_3$-CH-CH$_3$). HRMS (ESI) m/z calcd for C$_{18}$H$_{26}$NaO$_6$ [M+Na]+: 361.16216, found: 361.16319.

Synthesis of 4,6-*O*-benzylidene-2-deoxy-3-*O*-methyl-α/β-D-glucopyranosyl-(1 → 6)-1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranose (4a-α/β): Glycosyl sulfoxide **4** (111 mg, 0.297 mmol) and 1,2,3,4-di-*O*-isopropylidene-α-D-galactose (100 mg, 0.386 mmol) were coupled following the general procedure I (-60 ºC, 1 h). After work up, the residue was purified by flash silica gel chromatography (hexane/ethyl acetate 9:1 to 8:2) to give a 1:2 mixture of glycosides **4a-α** and **4a-β** respectively (62 mg, 41 %). For **4a-α**: ^{1}H NMR (400 MHz, CDCl$_3$) (selected signals) δ 7.54 – 7.44 (m, 2H, Ar), 7.40 – 7.30 (m, 3H, Ar), 5.56 (s, 1H, O-CH-O), 5.54 (d, *J* = 5.5 Hz, 1H, H-1), 4.69 (dd, *J* = 9.6, 2.9 Hz, H-1'), 4.60 (dd, *J* = 8.1, 2.7 Hz, H-3), 3.48 (s, 3H, OCH$_3$), 3.37 (td, *J* = 9.0, 4.9 Hz, H-5'), 2.45 (ddd, *J* = 12.4, 4.8, 2.6 Hz, H-2'eq), 1.54 (s, 3H, CH$_3$), 1.45 (s, 3H, CH$_3$), 1.33 (s, 6H, 2 CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 137.4 (C, Ar), 128.9 (CH, Ar), 128.2 (2 CH, Ar), 126.2 (2 CH, Ar), 109.4 (O-C-O), 108.7 (O-C-O), 101.5 (O-CH-O), 101.0 (CH-1'), 96.3 (CH-1), 82.7 (CH-4'), 77.2, 76.6, 71.4, 70.7, 70.4, 69.1, 68.9, 67.8 (CH-5'), 58.0 (OCH$_3$), 36.8 (CH$_2$-2'), 26.0 (CH$_3$), 26.0 (CH$_3$), 25.0 (CH$_3$), 24.4 (CH$_3$). HRMS (ESI) m/z calcd for C$_{26}$H$_{37}$O$_{10}$ [M+H]+: 509.23812, found: 509.23948. For **4a-β**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 – 7.44 (m, 2H, Ar), 7.40 – 7.30 (m, 3H, Ar), 5.58 (s, 1H, O-CH-O), 5.53 (d, *J* = 5.2 Hz, 1H, H-1), 4.97 (d, *J* = 3.7 Hz, 1H, H-1'), 4.63 (dd, *J* = 8.1, 3.2 Hz, 1H, H-3), 4.32 (dd, *J* = 8.1, 5.2 Hz, 1H, H-4), 4.29 – 4.21 (m, 2H, H-2, 6'eq), 4.04 – 3.93 (m, 1H, H-5), 3.90 – 3.73 (m, 4H, H-6a, 6b, 3', 5'), 3.67 (dd, *J* = 10.5, 6.9 Hz, 1H, H-6'ax), 3.59 (t, *J* = 9.5 Hz, 1H, H-4'), 3.50 (s, 3H, OCH$_3$), 2.32 (dd, *J* = 13.4, 5.0 Hz, 1H, H-2'eq), 1.67 (tdd, *J* = 12.0, 3.9, 1.2 Hz, 1H, H-2'ax), 1.55 (s, 3H, CH$_3$), 1.45 (s, 3H, CH$_3$), 1.35 (s, 3H, CH$_3$), 1.34 (s, 3H, CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 137.5 (C, Ar), 128.9 (CH, Ar), 128.2 (2 CH, Ar), 126.2 (2 CH, Ar), 109.3 (O-C-O), 108.6 (O-C-O), 101.5 (O-CH-O), 98.1 (CH-1'), 96.3 (CH-1), 83.6 (CH-4'), 74.3 (CH-3'), 71.0 (CH-2), 70.61 (CH-3), 70.59 (CH-4), 69.0 (CH$_2$-6'), 65.9 (CH$_2$-6), 65.8 (CH-5), 63.0 (CH-5'), 58.4 (OCH$_3$), 35.8 (CH$_2$-2'), 26.1 (CH$_3$), 26.0 (CH$_3$), 24.9 (CH$_3$), 24.5 (CH$_3$). HRMS (ESI) m/z calcd for C$_{26}$H$_{40}$NO$_{10}$ [M+NH$_4$]+: 526.26467, found: 526.26555.

Synthesis of 2,2,2-trifluoroethyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methyl-α/β-D-glucopyranoside (4b-α/β): Glycosyl sulfoxide **4** (78 mg, 0.208 mmol) and 2,2,2-trifluoroethanol (60 μL, 0.834 mmol) were coupled following the general procedure II (-60 ºC, 1 h). After work up, the residue was purified by flash silica gel chromatography (hexane/ethyl acetate 9:1 to 7:3) to give glycosides **4b-β** (17 mg, 23%) and **4b-α** (45 mg, 62%). For **4b-α**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 – 7.46 (m, 2H, Ar), 7.42 – 7.32 (m, 3H, Ar), 5.60 (s, 1H, O-CH-O), 5.01 (d, *J* = 3.7 Hz, 1H, H-1), 4.25 (dd, *J* = 9.7, 4.2 Hz, 1H, H-6eq), 4.03 – 3.78 (m, 5H, H-3, 4, 5, CH$_2$-CF$_3$), 3.76 (t, *J* = 10.0 Hz, 1H, H-6ax), 3.62 (t, *J* = 9.0 Hz, 1H, H-4), 3.52 (s, 3H, OCH$_3$), 2.38 (dd, *J* = 13.4, 5.1 Hz, 1H, H-2eq), 1.73 (ddd, *J* = 13.9, 11.2, 3.9 Hz, 1H, H-2ax); ^{13}C NMR (101 MHz, CDCl$_3$) δ 137.3 (C, Ar), 129.0 (CH, Ar), 128.2 (2 CH, Ar), 127.9 (2 CH, Ar), 123.7 (q, *J* = 277.5 Hz, CF$_3$), 101.6 (O-CH-O), 98.5 (CH-1), 83.2 (CH-4), 73.9 (CH-3), 68.8 (CH$_2$-6), 64.3 (q, *J* = 34.8 Hz, CH$_2$-CF$_3$), 63.5 (CH-5), 58.6 (OCH$_3$), 35.3 (CH$_2$-2). HRMS (ESI) m/z calcd for C$_{16}$H$_{20}$F$_3$O$_5$ [M+H]+: 349.12573, found: 349.12706. For **4b-β**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52 – 7.45 (m, 2H, Ar), 7.40 – 7.32 (m, 3H, Ar), 5.58 (s, 1H, O-CH-O), 4.71 (d, *J* = 9.8, 2.2 Hz, 1H, H-1), 4.32 (dd, *J* = 10.5, 4.9 Hz, 1H, H-6eq), 4.13 (dq, *J* = 12.5, 8.8 Hz, 1H, CH$_2$-CF$_3$), 3.95 (dq, *J* = 12.4, 8.4 Hz, 1H, CH$_2$-CF$_3$), 3.82 (t, *J* = 10.3 Hz, 1H, H-6ax), 3.61 (t, *J* = 8.9 Hz, 1H, H-4), 3.55 (td, *J* = 10.2, 9.4, 5.6 Hz, 1H, H-3), 3.51 (s, 3H, OCH$_3$), 3.38 (ddd, *J* = 9.7, 8.8, 4.9 Hz, 1H, H-5), 2.45 (ddd, *J* = 13.0, 4.8, 2.3 Hz, 1H, H-2eq), 1.65 (dt, *J* = 13.0, 10.2 Hz, 1H, H-2ax); ^{13}C NMR (101 MHz, CDCl$_3$) δ 137.2 (C, Ar), 129.0 (CH, Ar), 128.3 (2 CH, Ar), 127.7 (2 CH, Ar), 123.6 (q, *J* = 280.4 Hz, CF$_3$), 101.6 (O-CH-O), 100.2 (CH-1), 82.4 (CH-4), 76.3 (CH-3), 68.7 (CH$_2$-6), 66.7 (CH-5), 65.6 (q, *J* = 34.8 Hz, CH$_2$-CF$_3$), 58.3 (OCH$_3$), 36.5 (CH$_2$-2). HRMS (ESI) m/z calcd for C$_{16}$H$_{20}$F$_3$O$_5$ [M+H]+: 349.12573, found: 349.12591.

Synthesis of 2-fluoroethyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methyl-α/β-D-glucopyranoside (4c-α/β): Glycosyl sulfoxide **4** (83 mg, 0.222 mmol) and 2-fluoroethanol (51 μL, 0.89 mmol) were coupled following the general procedure II (-60 ºC, 1 h). After work up, the residue was purified by flash silica gel chromatography (hexane/ethyl acetate 9:1 to 7:3) to give

a 1:1.3 mixture of glycosides **4c-α** and **4c-β** respectively (46 mg, 67%). For **4c-α**: ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.54 – 7.46 (m, 2H, Ar), 7.41 – 7.32 (m, 3H, Ar), 5.59 (s, 1H, O-CH-O), 4.97 (d, *J* = 3.7 Hz, 1H, H-1), 4.58 (dt, *J* = 47.6, 4.2 Hz, 2H, CH$_2$F), 4.24 (dd, *J* = 10.0, 4.6 Hz, 1H, H-6eq), 3.93 – 3.78 (m, 3H, H-3, 5; CH$_2$-CH$_2$-F), 3.75 (t, *J* = 10.2 Hz, 1H, H-6ax), 3.72 – 3.64 (m, 1H, CH$_2$-CH$_2$-F), 3.61 (t, *J* = 9.3 Hz, 1H), 3.51 (s, 3H, OCH$_3$), 2.35 (dd, *J* = 13.3, 5.1 Hz, 1H, H-2eq), 1.70 (ddd, *J* = 13.6, 11.2, 3.9 Hz, 1H, H-2ax); ^{13}C NMR (101 MHz, CDCl$_3$) δ 137.5 (C, Ar), 128.9 (CH, Ar), 128.2 (2 CH, Ar), 126.1 (2 CH, Ar), 101.6 (O-CH-O), 98.2 (CH-1), 83.5 (CH-4), 82.6 (d, *J* = 169.8 Hz, CH$_2$F), 74.2 (CH-3), 69.0 (CH$_2$-6), 66.4 (d, *J* = 20.3 Hz, CH$_2$-CH$_2$-F), 63.0 (CH-5), 58.5 (OCH$_3$), 35.7 (CH$_2$-2). HRMS (ESI) m/z calcd for C$_{16}$H$_{21}$FNaO$_5$ [M+Na]+: 335.12652, found: 335.12727. For **4c-β**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 – 7.45 (m, 2H, Ar), 7.40 – 7.32 (m, 3H, Ar), 5.57 (s, 1H, O-CH-O), 4.67 (dd, *J* = 10.1, 2.2 Hz, 1H, H-1), 4.64 (dd, *J* = 6.9, 3.3 Hz, 1H, CH$_2$-CH$_2$-F), 4.56 – 4.48 (m, 1H, CH$_2$-CH$_2$-F), 4.32 (dd, *J* = 10.5, 4.9 Hz, 1H, H-6eq), 4.05 (dddd, *J* = 33.4, 12.3, 4.7, 2.4 Hz, 1H, CH$_2$F), 3.83 (dddd, *J* = 24.8, 12.3, 7.1, 2.4 Hz, 1H, CH$_2$F), 3.82 (t, *J* = 10.5 Hz, 1H, H-6ax), 3.60 (t, *J* = 8.7 Hz, 1H, H-4), 3.55 (td, *J* = 10.1, 8.7, 4.7 Hz, 1H, H-3), 3.50 (s, 3H, OCH$_3$), 3.38 (td, *J* = 9.3, 4.9 Hz, 1H, H-5), 2.43 (ddd, *J* = 12.9, 4.7, 2.2 Hz, 1H, H-2eq), 1.65 (dt, *J* = 12.9, 10.3 Hz, 1H, H-2ax); ^{13}C NMR (101 MHz, CDCl$_3$) δ 137.3 (C, Ar), 129.0 (CH, Ar), 128.2 (2 CH, Ar), 126.1 (2 CH, Ar), 101.5 (O-CH-O), 100.5 (CH-1), 82.71 (d, *J* = 169.5 Hz, CH$_2$F), 82.65 (CH-4), 76.5 (CH-3), 68.8 (CH$_2$-6), 68.3 (d, *J* = 19.8 Hz, CH$_2$-CH$_2$-F), 66.6 (CH-5), 58.2 (OCH$_3$), 36.8 (CH$_2$-2). HRMS (ESI) m/z calcd for C$_{16}$H$_{22}$FO$_5$ [M+H]+: 313.14458, found: 313.14441.

Synthesis of 2-propyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methyl-α/β-D-glucopyranoside (4d-α/β): Glycosyl sulfoxide **4** (95 mg, 0.254 mmol) and 2-propanol (77 μL, 1.016 mmol) were coupled following the general procedure II (-60 ºC, 1 h). After work up, the residue was purified by flash silica gel chromatography (hexane/ethyl acetate 9:1 to 7:3) to give a 1:2.2 mixture of glycosides **4d-α** and **4d-β** respectively (47 mg, 60%). For **4d-α**: ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.54 – 7.47 (m, 2H, Ar), 7.41 – 7.31 (m, 3H, Ar), 5.60 (s, 1H, O-CH-O), 5.03 (d, *J* = 3.7 Hz, 1H, H-1), 4.23 (dd, *J* = 10.2, 4.8 Hz, 1H, H-6eq), 3.93 – 3.78 (m, 2H, H-5, CH$_3$-CH-CH$_3$), 3.74 (t, *J* = 10.3 Hz, 1H, H-6ax), 3.59 (t, *J* = 8.7 Hz, 1H, H-4), 3.52 (s, 3H, OCH$_3$), 2.22 (dd, *J* = 13.2, 5.2 Hz, 1H, H-2eq), 1.69 (ddd, *J* = 13.1, 11.4, 4.0 Hz, 1H, H-2ax), 1.21 (d, *J* = 1.3 Hz, 3H, CH$_3$-CH-CH$_3$), 1.15 (d, *J* = 6.1 Hz, 3H, CH$_3$-CH-CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 137.6 (C, Ar), 128.9 (CH, Ar), 128.2 (2 CH, Ar), 126.1 (2 CH, Ar), 101.4 (O-CH-O), 95.7 (CH-1), 83.9 (CH-4), 74.4 (CH-3), 69.1 (CH$_2$-6), 68.73 (CH$_3$-CH-CH$_3$), 62.9 (CH-5), 58.5 (OCH$_3$), 36.4 (CH$_2$-2), 23.4 (CH$_3$-CH-CH$_3$), 21.3 (CH$_3$-CH-CH$_3$). HRMS (ESI) m/z calcd for C$_{17}$H$_{25}$NaO$_5$ [M+Na]+: 331.15159, found: 331.15347. For **4d-β**: ^{1}H-NMR (400 MHz,CDCl$_3$) δ 7.55 – 7.47 (m, 2H, Ar), 7.40 – 7.33 (m, 3H, Ar), 5.57 (s, 1H, O-CH-O), 4.68 (dd, *J* = 9.8, 1.9 Hz, 1H, H-1), 4.30 (dd, *J* = 10.5, 4.9 Hz, 1H, H-6eq), 4.01 (hept, *J* = 6.2 Hz, 1H, CH$_3$-CH-CH$_3$), 3.82 (t, *J* = 10.3 Hz, 1H, H-6ax), 3.60 (dd, *J* = 9.4, 7.9 Hz, 1H, H-4), 3.57 – 3.52 (m, 1H, H-3), 3.50 (s, 3H, OCH$_3$), 3.37 (ddd, *J* = 10.6, 9.0, 5.2 Hz, 1H, H-5), 2.31 (ddd, *J* = 12.8, 4.7, 2.0 Hz, 1H, H-2eq), 1.62 (td, *J* = 11.0, 1.3 Hz, 1H, H-2ax), 1.24 (d, *J* = 6.4 Hz, 3H, CH$_3$-CH-CH$_3$), 1.18 (d, *J* = 6.1 Hz, 3H, CH$_3$-CH-CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 137.4 (C, Ar), 128.9 (CH, Ar), 128.2 (2 CH, Ar), 126.1 (2 CH, Ar), 101.5 (O-CH-O), 98.4 (CH-1), 82.7 (CH-4), 76.8 (CH-3), 71.1 (CH$_3$-CH-CH$_3$), 68.9 (CH$_2$-6), 66.6 (CH-5), 58.1 (OCH$_3$), 37.5 (CH$_2$-2), 23.5 (CH$_3$-CH-CH$_3$), 21.8 (CH$_3$-CH-CH$_3$). HRMS (ESI) m/z calcd for C$_{17}$H$_{25}$O$_5$ [M+H]+: 309.16965, found: 309.16993.

Pre-activation glycosylations with donors 1-3 and acceptors a-d for qualitative stereoselectivity assessment: The corresponding sulfoxide donor (0.1 mmol) and 2,6-di-tert-butyl-methylpyridine (DTBMP) (0.3 mmol) were co-evaporated twice with dry toluene and dissolved in dry DCM (25 mL/mmol) under Ar. Activated 4 Å molecular sieves were added and the reaction mixture was stirred for 30 min at room temperature under Ar atmosphere. The reaction mixture was cooled down to -78 ºC and then, triflic anhydride (0.13 mmol) was added dropwise. The reaction mixture was allowed to stir at -78 ºC for 20 min before adding the acceptor (0.2-0.3 mmol). The resulting mixture was allowed to stir at the designated temperature for 1 h, at which point TEA (100 μL) was added. The quenched reaction mixture was then filtered, and the filtrate was evaporated under vacuum. The crude material was directly dissolved in

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CDCl₃ and subsequently analyzed by ¹H-NMR to determine the final glycosylation anomeric ratio.

General method for the NMR tube glycosylation experiments with sulfoxide donors: Considering the increased complexity of these muti-component reactions, a minimum of three runs under identical reaction conditions, were completed with each derivative. Additionally, competition experiments were performed for selected equimolecular donor mixtures. Thus, the internal standard 4,4,5,5-tetramethyl-2-(naphthalen-1-yl)-1,3-dioxolane (25.6 mg, 0.1 mmol), DTBMP (61.5 mg, 0.3 mM), the appropriate acceptor alcohol and activated molecular sieves 4 Å (100 mg) were added to a septum-capped oven-dried vial. The vial was twice evacuated and purged with Ar before the addition of CDCl₃ (10 mL). The resulting stock solution (550 μL) was transferred to a 5 mm NMR tube fitted with a septum and purged with Ar. A solution of the adequate donor in CDCl₃ (50 μL, 100 mM) was then added to the tube and shaken to mix. Afterwards, the NMR tubes were cooled down in a liquid nitrogen/acetone bath to the selected reaction temperature before the treatment with triflic anhydride and immediately transferred to the NMR spectrometer, previously equilibrated at the proper working temperature. Glycosylation reactions were followed by low-temperature NMR experiments, employing a Bruker Avance 500 MHz spectrometer. 1D-1H spectra were acquired with 300 excitation pulses and a relaxation delay of 1 s. The extra sensitivity provided by ¹³C-labelled samples allowed us to acquire 2D-HSQC data sets with just 2 scans per increment and 64 increments, limiting the total experimental time to 2-3 minutes. These conditions were found to be adequate to monitor relatively fast glycosylation reactions. Transmitter offsets were set to 5 and 90 ppm, in the proton and carbon dimensions, respectively, which allowed for an optimal excitation of the anomeric CH groups. In addition, a delay corresponding to a J value of 165 Hz (between those values expected for anomeric α- and β-CH fragments) was employed in all cases. Data processing was carried out with MestReNova. The absence of well resolved peaks for some glycosylation products in the 1D data sets led us to mainly rely on 2D-HSQC experiments to derive relative populations at different reaction times. To assess the validity of this approach, control HSQC spectra were measured with increasing relaxation delays (in the 1-10 s range), showing that this parameter had a relatively minor influence (<10%) on the estimated volume ratios. When possible, values derived from 2D data sets were also confirmed by 1D experiments for selected non-overlapped signals. Relative concentrations at short reaction times (<10 min, when <20% evolution had occurred) were taken as indicative of the relative formation rates for the different products. Finally, relative formation rates for the different products were also estimated, without any mechanistic assumptions, from their relative conversions at short reaction times.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: glycosylation • NMR spectroscopy • reaction mechanisms • carbohydrates • glycosyl triflate

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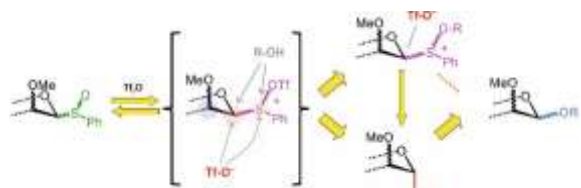
A systematic low-temperature NMR-based study of single-step glycosylations employing ^{13}C-labelled glycosyl sulfoxide donors provides new evidence for the key role of long-postulated glycosylation intermediates, allowing the detection of hitherto unreported reactive species.