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Synthesis of β-glucosides with 3-*O*-picoloyl-protected glycosyl donors in the presence of excess triflic acid: defining the scope

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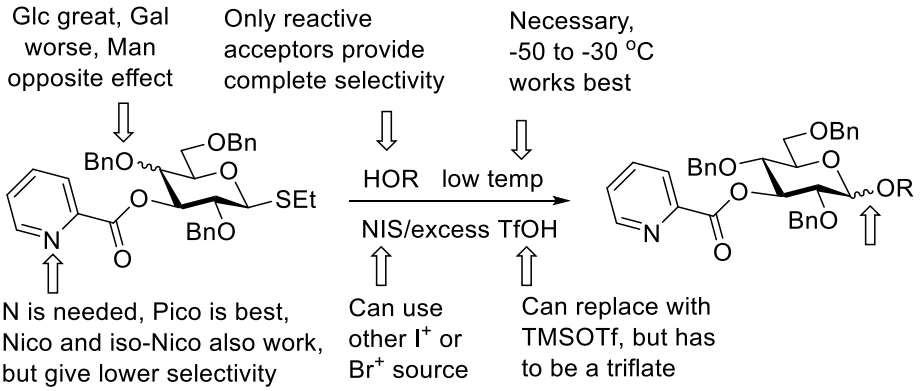
Abstract: Excellent β-stereoselectivity for the glycosylation with 3-Pico glucosyl donors, without the use of participating group, was achieved in the presence of NIS/ excess TfOH promoter system. A complete investigation of the scope of this reaction was performed, revealing all important attributes of successful glycosylation. While altering the halogen source was tolerated, substitution of the triflate anion resulted in complete loss of stereoselectivity. Protonation of the Pico group was determined to be crucial in this reaction. The stability or extent of the protonated pyridine ring was also found to be another important key factor in obtaining high stereoselectivity. The nucleophilicity of the acceptor was found to be proportional to the stereoselectivity obtained, suggesting an S_N2-like mechanism.



Keywords: glycosylation, synthesis, oligosaccharides, stereoselectivity, mechanism

10.1002/chem.201905278

Introduction

Chemical *O*-glycosylation is arguably the most important and challenging reaction in glycochemistry.[1] This reaction connects the hydroxyl group of the glycosyl acceptor to the anomeric carbon of the glycosyl donor through the formation of a glycosidic bond. One of the biggest difficulties this reaction faces is controlling the stereoselectivity of this new bond formation. Many glycosylation reactions have been developed, among which methods and strategies that provide reliable stereocontrol are highly desirable, and have been the focus of many research efforts in the field.[2] One such method is the Hydrogen-bond-mediated Aglycone Delivery (HAD) reaction was introduced by our lab.[3] In accordance with this reaction, the glycosyl donor is functionalized with a hydrogen bond accepting protecting group such as picoloyl ester (Pico) at a remote position of the sugar (C-3, 4 or 6). The Pico group forms a hydrogen bond with the free hydroxyl of the glycosyl acceptor, resulting in the formation of a hydrogen-bonded complex. The orientation of this complex determines the stereoselectivity afforded as the acceptor is "delivered" to the anomeric carbon in a *syn*-fashion with respect to the Pico group. In a majority of applications, the HAD reaction provided excellent stereocontrol and yields.[3]

In the previous article in this issue, we reported excellent β-stereoselectivity obtained without the assistance of a neighboring participating group. Instead, those glycosylations were performed with 3-*O*-picoloyl (Pico) functionalized glucosyl donor. Although the β-stereoselectivity would be expected via the HAD pathway, the reaction conditions that we have developed made us doubt whether the excellent stereoselectivity achieved was actually due to the HAD pathway. In this method, the donors are activated using the *N*-iodosuccinimide (NIS) and triflic acid (TfOH) promoter system. Although typically employed in catalytic amounts, we developed reaction conditions wherein TfOH was used in excess to NIS. The presence of the

excess protic acid suggests that the HAD pathway, by which Pico-protected donors are known to perform,[4] is not active in the presence of excess electrophilic species, as was demonstrated by several labs.[3, 5] A preliminary mechanistic investigation of this reaction by NMR spectroscopy revealed that the 3-Pico group is protonated in the presence of equimolar TfOH, as indicated by a downfield shift in the aromatic Pico protons.[6] This was deemed to be a crucial step in this reaction. Further NMR experiments performed with the entire promoter system consisting of both NIS and TfOH showed the presence of an intermediate derived from the donor substrate with an anomeric signal resonating at 6.9 ppm. The identity of this new species was hypothesized to be the glucosyl triflate, which was the key intermediate *en route* to glycoside products.[6] With the general goal of determining the scope of this new reaction and gaining further mechanistic insights, presented herein is screening of various reaction conditions, studying other promoter systems, protecting groups, and investigating the glycosyl donor and acceptor scope.

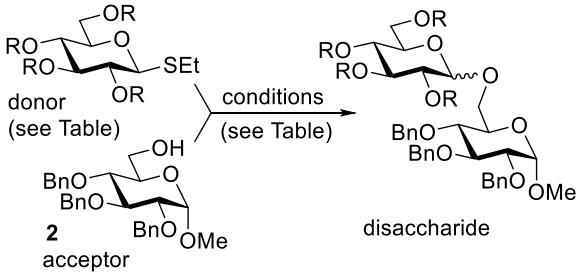
Results and Discussion

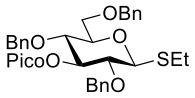
Through our investigation reported in the previous article in this issue,[6] it was discovered that the stereoselective outcome of glycosylations is directly proportional to the amount of TfOH added. Improvements were observed when TfOH was specifically used in excess to NIS. Taking these reaction conditions as the benchmark, herein we present further investigation of this reaction. Typical HAD reaction conditions applied to the glycosidation of donor **1**[6] to acceptor **2**[7] in 1,2-DCE produced disaccharide **3** in an excellent yield of 90% albeit fairy low stereoselectivity α/β = 1/2.6 (Table 1, entry 1). The same glycosylation reaction performed in the presence of NIS (1.2 equiv) and TfOH (2.5 equiv), novel reaction conditions introduced in our previous article,[6] produced disaccharide **3** in a similar yield of 85% but drastically improved stereoselectivity α/β =

10.1002/chem.201905278

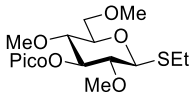
1/23 (entry 2). Our previous mechanistic study employed 3-Pico donor **4** in which all remaining positions were methylated.[6] Glycosidation of donor **4** was performed using the same promoter system, but for the purpose of monitoring by NMR, the reaction was conducted at -50 °C. These conditions were found to be very favorable for glycosylation of acceptor **2** as well, producing the corresponding disaccharide **5** in 90% yield and complete β-stereoselectivity (entry 3). To be able to perform the reaction at -50 °C we used DCM as the reaction solvent because 1,2-DCE is known to freeze at -35 °C. With these preliminary observations, we decided to investigate the solvent and the temperature effects on glycosidation of benzylated 3-Pico donor **1**. Over the course of this study, a steady drop in stereoselectivity was observed when the reaction temperature was increased from -50 °C (α/β = 1/23) to room temperature (α/β = 1/3.5, entries 4-9). This result was consistent with the proposed reaction pathway taking place via the intermediacy of glycosyl triflate, which is expected to be more stable at low temperatures.[8] It should be noted that the yield has also decreased following the reaction temperature increase from -50 °C (85%) to room temperature (59%, entries 4-9). We explained this by the occurrence of the competing hydrolysis reaction, judged by the formation of significant quantities of the hemiacetal side product, which is accelerated at higher temperatures.

Table 1. Optimization of the reaction solvent and temperature for glycosidation of **1**



Entry	Donor (50 mM)	Promoter (equiv) conditions, time	Product, yield, α/β ratio
1	 **1** (5 mM)	DMTST (2) 4Å MS, 1,2-DCE -30 °C → rt, 3 h	**3**, 90%, 1/2.6

10.1002/chem.201905278

2	**1**	NIS(1.2)/TfOH(2.5) 4Å MS, 1,2-DCE -30 °C, 30 min	**3**, 85%, 1/23
3	 **4**	NIS(1.2)/TfOH(2.5) 4Å MS, DCM -50 °C, 30 min	**5**, 90%, < 1/25
4	**1**	NIS(1.2)/TfOH(2.5) 4Å MS, DCM -50 °C, 30 min	**3**, 85%, 1/23
5	**1**	NIS(1.2)/TfOH(2.5) 4Å MS, DCM -30 °C, 30 min	**3**, 85%, < 1/25
6	**1**	NIS(1.2)/TfOH(2.5) 4Å MS, DCM -10 °C, 30 min	**3**, 70%, 1/11.5
7	**1**	NIS(1.2)/TfOH(2.5) 4Å MS, DCM 0 °C, 30 min	**3**, 66%, 1/8.3
8	**1**	NIS(1.2)/TfOH(2.5) 4Å MS, DCM 10 °C, 30 min	**3**, 70%, 1/5.6
9	**1**	NIS(1.2)/TfOH(2.5) 4Å MS, DCM rt, 30 min	**3**, 59%, 1/3.5
10	**1**	NIS(1.2)/TfOH(2.5) 4Å MS, DCM -50 °C, 30 min Preactivation	**3**, 41%, 1/20

To gain further insight into the mechanism responsible for the excellent stereoselectivity observed, we performed glycosylation by preactivation of the donor with the promoter followed by the addition of the acceptor. Previously, it has been demonstrated that preactivation causes a complete loss of stereoselectivity in the HAD reactions.[3] This was attributed to the necessity to form the hydrogen-bonded donor-acceptor pair for the HAD effect to take place. The reaction performed via preactivation of glycosyl donor **1** in the presence of excess TfOH provided comparably high stereoselectivity, albeit reduced yield (41%, entry 10). This lower yield was due to competing hydrolysis side reaction that resulted in the formation of the corresponding

10.1002/chem.201905278

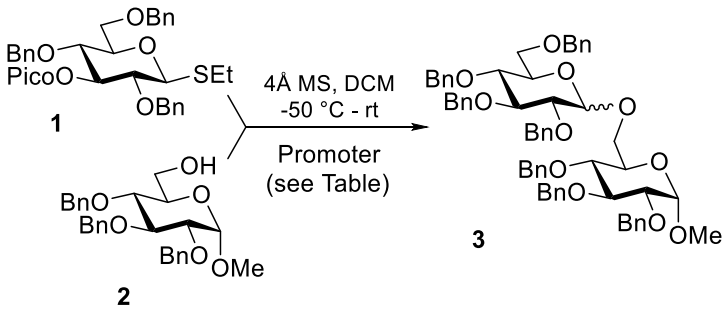
hemiacetal derivative. This result further reinforces the idea that this reaction that does not follow the HAD pathway under these promoter conditions.

We then investigated the effect of the promoter on the outcome of glycosylation. The promoter systems of NIS/TfOH and NBS/TfOH were previously examined and both were found to produce the glucosyl triflate intermediate by NMR.[6] The application of these promoter systems in glycosylation are surveyed in entries 1 and 2 of Table 2. In most cases, the optimized conditions (excess of electrophilic reagent) resulted in fast reactions that produced disaccharide **3** in high yields. Other reactions that employed standard catalytic amounts of electrophilic promoter were allowed to warm up to room temperature as was done with the HAD reactions. All sluggish reactions were stopped after 24 h. In the case of NIS or NBS, both sets of experiments showed a remarkable increase in stereoselectivity as we moved from the conventional ratio to excess TfOH (entries 1 and 2).

We then wondered whether the availability of the proton provided by TfOH is essential for these reactions. First, we replaced TfOH with trimethylsilyl triflate (TMSOTf) which has been reported to coordinate to the Pico group.[9] NIS/TMSOTf-promoted reactions showed the identical outcome (entry 3) to that achieved with NIS/TfOH (entry 1). On the other hand, NIS/AgOTf promoted reactions afforded only a modest improvement over HAD reactions upon increase from the catalytic amount (α/β = 1/2.3) to excess of AgOTf (α/β = 1/7.0, entry 4). We believe that the modest increase in stereoselectivity can be attributed to the slow release of TfOH over the course of this reaction. As a result of this study, we concluded that a sufficiently available Pico coordinating source, excess TfOH or TMSOTf, is required to achieve excellent stereoselectivity.

10.1002/chem.201905278

Table 2. Investigation of promoters for glycosidation of donor **1** with acceptor **2**



Entry	Promoter (equiv), time	Yield of **3**, α/β ratio
1	NIS(2)/TfOH(0.2), 24 h NIS(1.2)/TfOH(2.5), 30 min	89%, 1/3.0 85%, 1/23
2	NBS(2)/TfOH(0.2), 24 h NBS(1.2)/TfOH(2.5), 3 h	12%,[a] 1/3.1 79%, < 1/25
3	NIS(2)/TMSOTf(0.2), 24 h NIS(1.2)/TMSOTf(2.5), 30 min	79%, 1/2.6 86%, < 1/25
4	NIS(2)/AgOTf(0.2), 24 h NIS(1.2)/AgOTf(2.5), 30 min	69%, 1/2.3 92%, 1/7.0
5	NIS(2)/AgOTs(0.2), 24 h NIS(1.2)/AgOTs(2.5), 24 h	22%, 1/1.0 37%, 1.6/1
6	NIS(2)/MsOH(0.2), 24 h NIS(1.2)/MsOH(2.5), 24 h	No reaction[b] 56%, 1/1.3
7	NIS(2)/$HN(Tf)_2$(0.2), 24 h NIS(1.2)/$HN(Tf)_2$(2.5), 30 min	62%, 1/1.0 94%, 1/1.0
8	IDCH(2)/TfOH(0.2), 24 h IDCH(1.2)/TfOH(2.5), 30 min IDCH(1.2)/TfOH(3.2), 30 min	No reaction 83%, 1/7.2 82%, 1/13.3

[a] - Glycosyl bromide was formed as the major by-product;
[b] – 6-*O*-Mesylated acceptor was obtained along with unreacted starting materials

Subsequently, we endeavored to identify the role of the counter-ion in the reaction. For this purpose, we selected several co-promoters as replacements for TfOH. Alternative sulfonates, methanesulfonic acid (MsOH) and silver p-toluenesulfonate (AgOTs), were chosen along with trifluormethanesulfonamide ($HN(Tf)_2$). AgOTs was selected over *p*-toluenesulfonic acid because the latter exists as a monohydrate, which could be problematic in water sensitive glycosylation reactions. $HN(Tf)_2$ was investigated because it has a similar pK_a to TfOH, -12.3 and -11.4,

10.1002/chem.201905278

respectively,[10] but it is unable to produce the anomeric triflate intermediate. As a result of this study summarized in entries 5-7 (Table 2), these additives were practically ineffective in enhancing the stereoselectivity of glycosylations. This result reinforces the importance of the triflate counter-anion. . However, we cannot exclude other factors that could be of relevance to the excellent stereoselectivity observed

We then turned our attention to studying possible effect of succinimide as a side-product or as a counter ion on the outcome of this glycosylation reaction. For this purpose, we changed the iodonium source from NIS to iodonium(di-γ-collidine)hexafluorophosphate (IDCH).[11] IDCH was chosen as an alternative source of iodonium ion instead of the more common IDCP (perchlorate) because of the presence of the nucleophilic perchlorate counter ion has been known to influence the stereoselectivity of glycosylation reactions.[8, 12] Over the course of the study summarized in entry 8, we observed a modest stereoselectivity improvement using the optimized reaction conditions. Interestingly, further improvement in stereoselectivity was achieved when the amount of TfOH was tripled in respect to IDCH. To rationalize this result, we hypothesized that excess acid is required to quench the conjugate base of the iodonium source, two equivalents of collidine in case of IDCH, and still have a full equivalent to be able to interact with the Pico group of the glycosyl donor. From these experiments we were able to determine that NIS is not directly involved in the reaction pathway further reinforcing our hypothesis that the reaction proceeds via the intermediacy of glycosyl triflate.

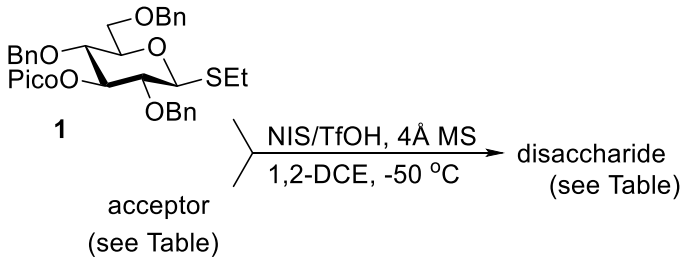
We next sought to expand the acceptor scope for these reaction conditions. As listed in Table 3, glycosyl donor **1** was glycosidated with various secondary acceptors **6**, **8**, **10** and electronically deactivated primary acceptors **12**, **14**, and **16** using the optimized conditions. Both yields and stereoselectivities for the formation of disaccharides **7**, **9**, and **11** derived from the

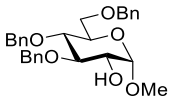
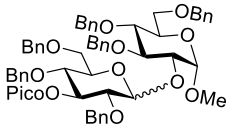
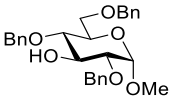
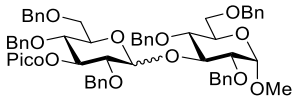
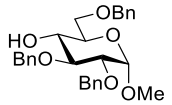
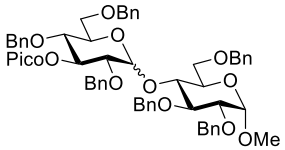
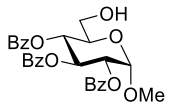
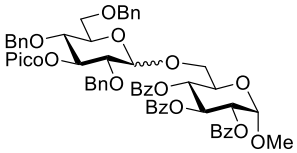
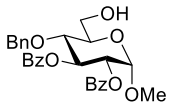
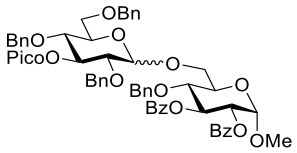
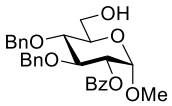
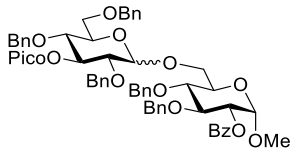
standard secondary acceptors were poor, demonstrating only improved reaction time (entries 1-3). This result was expected because secondary acceptors have been known to perform poorly in S_N2-like reactions in general, and as substrates for glycosyl triflates in particular.[13] Albeit insignificant, we note a reversal of the stereoselectivity in glycosylations to produce disaccharides 7 and 9 under standard versus novel reaction conditions (entries 1 and 2). Alternatively, the optimized conditions exhibited moderate to high stereoselectivities for glycosylation of relatively deactivated primary acceptors to from the respective disaccharides **13**, **15**, and **17** with stereoselectivities ranging from α/β = 1/7.7 to α/β >1/25 (entries 4-6). Interestingly, the nucleophilicity of the acceptor seemed to be directly proportional to the observed stereoselectivity. This trend could be followed by varying the number of deactivating benzoyl substituents in glycosyl acceptors **12**, **14**, and **16**. This is to be expected from an S_N2-like reaction pathway, and has shown to be a factor in the stereoselectivities obtained from glycosyl triflates.[14]

To further expand the scope of this reaction, we investigated the glycosidation of other picoloylated donors of the D-galacto and D-manno series. These results are summarized in Table 4. Galactosyl donor **18** afforded a lower improvement in stereoselectivity compared to the drastic improvement achieved with glucosyl donor **1** (Table 4, entries 2 vs. 1). Nevertheless, the reaction still seemed to follow a similar trend and the corresponding disaccharide **19** was obtained in a good yield and the stereoselectivity improved from α/β = 1/2.5, achieved under standard conditions, to α/β = 1/9.0 under the new conditions (entry 2). The same cannot be said of the mannosyl donor **20**, which exhibited a complete reversal in stereoselectivity (entry 3).

10.1002/chem.201905278

Table 3. Glycosidation of donor **1** with different glycosyl acceptors



Entry	Acceptor	Time, yield, α/β ratio[a]	Product
1	 **6**	24 h, 57%, 2.1/1 1.5 h, 78%, 1/1.5	 **7**
2	 **8**	24 h, 68%, 1/1.7 1.5 h, 53%, 3.0/1	 **9**
3	 **10**	24 h, 40%, 1/2.0 1.5 h, 44%, 1/1.7	 **11**
4	 **12**	3 h, 67%, 1/2.4 30 min, 92%, 1/7.7	 **13**
5	 **14**	3 h, 87%, 1/3.0 30 min, 80%, 1/16.7	 **15**
6	 **16**	3 h, 86%, 1/2.6 30 min, 79%, >1/25	 **17**

[a] – first set of data is for reaction under standard conditions NIS(2)/TfOH(0.2) and the second set of data is for the new conditions NIS(1.2)/TfOH(2.5)

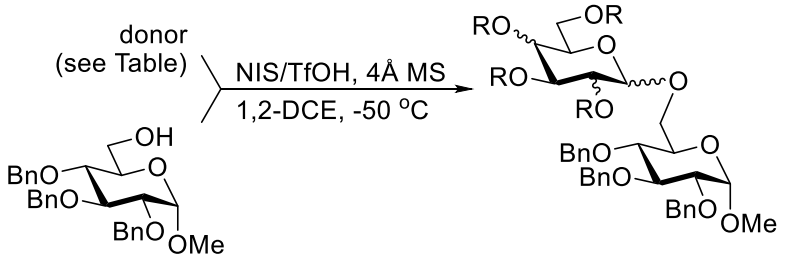
10.1002/chem.201905278

It is important to note that, similar to glucosyl donor **1**, the stereoselectivities obtained with donors **18** and **20** were found to be proportional to the ratios of NIS/TfOH employed, suggesting that the TfOH might have a similar effect on the reaction pathway involving these substrates (see the Supporting Information Table 1S for further details). We next investigated whether the new reaction conditions can be applied to glycosyl donors bearing the Pico group at other remote positions. Interestingly, glucosyl donors functionalized with 4- or 6-Pico group showed practically no change in stereoselectivity (entries 4 and 5). These results demonstrate that the newly optimized conditions provide dramatic stereoselectivity enhancement only when the Pico group is at the C-3 position of the glycosyl donor. This is believed to be due to the increased proximity of the electron withdrawing group at C-3 to the anomeric center. The stabilizing effect electron withdrawing groups have on glycosyl triflate intermediates has been shown to be dependent on the functional group location and it is optimal from the C-3 position.[15] Considering that the HAD glycosylation method is optimal with donors functionalized with 4- or 6-Pico groups,[4a, 16] these results also reinforce a different reaction pathway by which 3-Pico protected glycosyl donors may react.

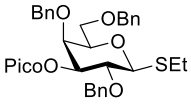
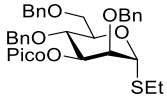
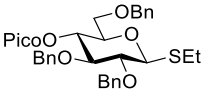
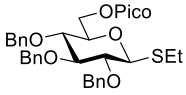
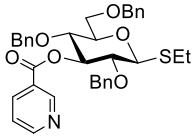
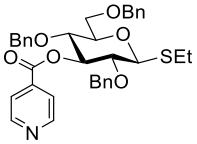
The HAD method has previously been shown to suffer by the presence of excess protic acid and/or preactivation of the glycosyl donor, both of which are well tolerated in this new reaction pathway. In addition, switching from the donor equipped with the Pico group to its regioisomers, 3-*O*-nicotinoyl (Nico) protected donor **26** and 3-*O*-*iso*-nicotinoyl (^{i}Nico) protected donor **28**, led to the complete loss of stereoselectivity in the HAD reaction.[3] In the presence of excess TfOH, protonation of the Pico group is expected to be optimal due to the stabilizing effects of the resulting five-member ring between the nitrogen and carbonyl oxygen. However, the Nico and ^{i}Nico protecting groups are still expected to be protonated and may exhibit a similar affect under these conditions.

10.1002/chem.201905278

Table 4. Investigation of various glycosyl donor under new reaction conditions



2

Entry	Donor	Product, reaction time, yield, α/β ratio[a]
1	**1**	**3**, 24 h, 89%, 1/3.0 **3**, 30 min, 92%, 1/23
2	 **18**	**19**, 24 h, 89%, 1/2.5 **19**, 30 min, 76%, 1/9.0
3	 **20**	**21**, 24 h, 82%, 1/3.8 **21**, 30 min, 79%, 5.4/1
4	 **22**	**23**, 24 h, 86%, 1.2/1 **23**, 30 min, 89%, 1/1.8
5	 **24**	**25**, 2 h, 89%, 1/10 **25**, 30 min, 75%, 2.6/1
6	 **26**	**27**, 24 h, 62%, 1/1.3 **27**, 30 min, 66%, 1/6.0
7	 **28**	**29**, 24 h, 70%, 1/1.3 **29**, 30 min, 82%, 1/4.0

[a] – first set of data is for reaction under standard conditions NIS(2)/TfOH(0.2) and the second set of data is for the new conditions NIS(1.2)/TfOH(2.5)

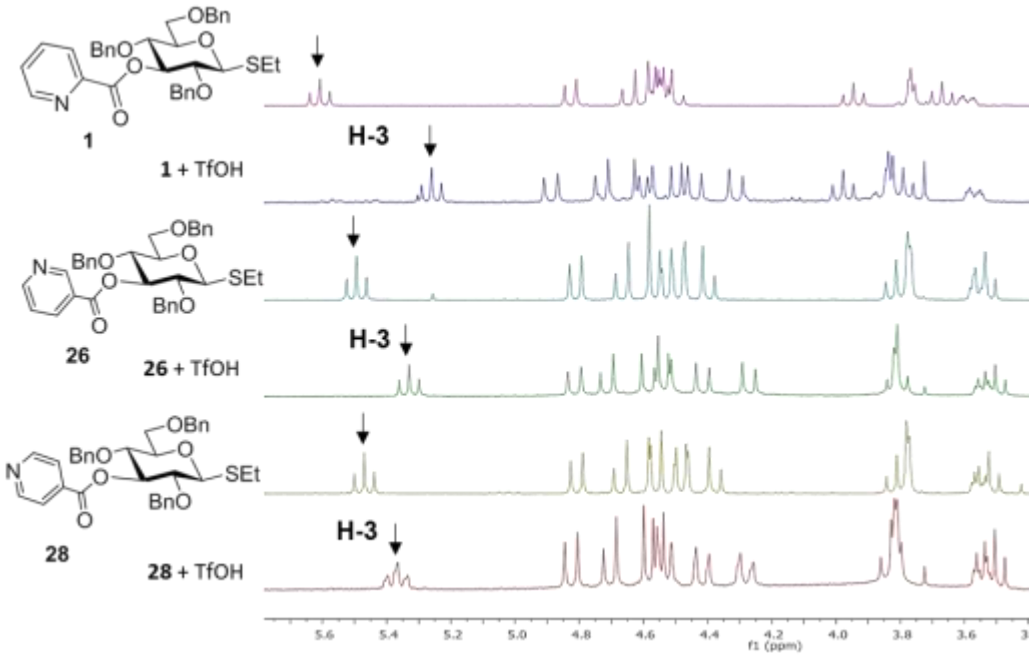
Predictably, we observed a reduction in stereoselectivity with the Nico and *i*Nico donors, **26** and **28** (entries 6 and 7), compared to the Pico donor **1**. However, these substrates still exhibit

10.1002/chem.201905278

improved β-stereoselectivity using the optimized reaction conditions compared to no stereoselectivity obtained with catalytic TfOH (HAD conditions). These results further suggest that reactions under the newly optimized conditions do not proceed through the HAD pathway.

Comparing the results in Table 4 for Pico, Nico and ^{i}Nico protecting groups; it appears that the same mechanistic pathway is occurring with each donor but to different degrees. These variations are believed to arise from different stabilities of the protonated protecting groups, altering the stereoselectivity. In an attempt to identify changes correlating to the protonation that varies among the donors in a similar manner to stereoselectivity we turned spectroscopic studies. ^{1}H NMR analysis of each donor in the presence of TfOH (1.0 equiv) was performed to determine possible chemical shift changes indicative of protonation. As reported in the preceding article,[6] chemical shift changes are not observed for the 3-*O*-benzoylated or per-*O*-benzylated thioglycoside donors.

Figure 1. Chemical shifts comparison of 3-Pico, 3-Nico, and 3-^{i}Nico donors **1**, **26** and **28** in the presence of TfOH



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These spectroscopic studies revealed that in the presence of TfOH, several proton signals experience chemical shift changes. Among these was the upfield shift of the δ H-3 proton. Previously this chemical shift change was postulated and qualitatively proven to be a result of π-π or cation-π interactions with the neighboring benzyl substituents and the electronically deficient protonated pyridine ring.[6] Since each donor substrate contains the same number and location of benzyl groups, the TfOH induced chemical shift changes for each sample should be a function of the electronic nature of the substituent at C-3. To this extent the change in δ H-3 for each sample was found to follow the same trend as the stereoselectivities obtained in their glycosidations (**1**, Δδ H-3 = 0.32 ppm; **26**, Δδ H-3 = 0.17 ppm; **28**, Δδ H-3 = 0.10 ppm, Figure 1). These results indicate that the Pico group experiences a stronger electronic effect compared to that of the Nico and ^{i}Nico substituents, suggesting a correlation between the C-3 electronics and the observed stereoselectivity.

In conclusion, excellent β-stereoselectivity for the glycosylation with 3-Pico glucosyl donors, without the use of participating group, was expanded upon. This method utilizes the optimized NIS/TfOH promoter conditions previously reported.[6] Protonation of the Pico group was determined to be crucial in this reaction. Further investigation using IDCH as the iodonium source confirmed the necessity to have sufficient amount of TfOH to quench the conjugate base and protonate the donor. Furthermore, the stability or extent of the protonated pyridine ring was also found to be a key factor in obtaining high stereoselectivity. The stability of the five-membered ring formed between the nitrogen and neighboring carbonyl oxygen of the protonated Pico group affords dramatically improved stereoselectivity compared to the Nico and ^{i}Nico counterparts. The identity of the glycosyl donor and acceptor was also shown to be a determining factor in this reaction. The nucleophilicity of the acceptor was found to be proportional to the stereoselectivity

10.1002/chem.201905278

obtained, suggesting an S_N2-like mechanism. Changing the donor substrate led to a variety of results. Moving the Pico group to other remote positions was not well tolerated. Galactosyl donors functionalized with 3-Pico showed good stereoselectivity while mannosyl donors showed a preference for the α-product. Since these stereoselectivities follow a similar trend with the NIS/TfOH ratio as the glucosyl donor, it is suspected that the reaction pathway is somewhat similar in the case of D-galacto series but differs drastically in the case of the D-manno series. The mechanistic pathway was thoroughly investigated and, in our estimation, we have provided significant evidence for the formation and importance of the protonated Pico-dependent glycosyl triflate intermediate.

Experimental

General. Column chromatography was performed on silica gel 60 (70-230 mesh), reactions were monitored by TLC on Kieselgel 60 F254. The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. CH_2Cl_2 and $ClCH_2CH_2Cl$ (1,2-DCE) were distilled from CaH_2 directly prior to application. Molecular sieves (3 or 4 Å) used for reactions were crushed and activated in *vacuo* at 390 °C for an initial 8 h and then for 2-3 h at 390 °C directly prior to application. Optical rotation was measured at 'Jasco P-2000' polarimeter. Unless noted otherwise, ^{1}H NMR spectra were recorded in $CDCl_3$ at 300 or 600 MHz, ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 MHz. High resolution mass spectrometry (HRMS) was carried out on ESI-TOF mass spectrometer.

Synthesis of glycosyl donors

Ethyl 2,4,6-tri-*O*-benzyl-3-*O*-picoloyl-1-thio-β-D-glucopyranoside (1) was synthesized according to the reported procedure and its analytical data was essentially the same as reported previously.[6]

Ethyl 2,4,6-tri-*O*-methyl-3-*O*-picoloyl-1-thio-β-D-glucopyranoside (4) was synthesized according to the reported procedure and its analytical data was essentially the same as reported previously.[6]

Ethyl 2,4,6-tri-*O*-benzyl-3-*O*-picoloyl-1-thio-β-D-galactopyranoside (18). Picolinic acid (0.10 g, 0.80 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (0.155 g, 0.80 mmol), and 4-dimethylaminopyridine (0.01 g, 0.08 mmol) were added to a solution of ethyl 2,4,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside[17] (0.20 g, 0.40 mmol) in and the resulting mixture was stirred under argon for 30 min at rt. The reaction mixture was diluted with CH_2Cl_2 (~100 mL) and washed with sat. aq. $NaHCO_3$ (30 mL) and water (3 x 10 mL). The organic phase was separated, dried with magnesium sulfate, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate – toluene gradient elution) to give the title compound as a white amorphous solid in 93% yield. The analytical data for **18**: R_f = 0.60 (ethyl acetate/toluene, 2/3, v/v); $[\alpha]_D^{21}$ 40.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.37 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.83 (m, 2H, SCH_2CH_3), 3.63-3.73 (m, 2H, H-6a, 6b), 3.85 (m, 1H, H-5), 4.08 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 4.23 (dd, 1H, $J_{4,5}$ = 3.0 Hz, H-4), 4.47 (d, 1H, *J* = 11.9 Hz, C*H*Ph), 4.55 (d, 1H, *J* = 11.0 Hz, C*H*Ph), 4.77 (m, 2H, $J_{1,2}$ = 8.4 Hz, H-1, C*H*Ph), 4.74 (d, 1H, ^2J = 11.7 Hz, C*H*Ph), 4.75 (d, 1H, *J* = 10.7 Hz, C*H*Ph), 4.93 (d, 1H, *J* = 10.7 Hz, C*H*Ph), 5.31 (dd, 1H, $J_{3,4}$ = 3.0 Hz, H-3), 7.18-7.37 (m, 15H, aromatic), 7.53 (m, 1H, Pico-H), 7.83 (m, 1H, Pico-H), 7.93 (d, 1H, *J* = 7.8 Hz, Pico-H), 8.83 (d, 1H, *J* = 4.7 Hz, Pico-H) ppm; ^{13}C NMR: δ, 15.1, 25.1, 68.4, 73.5,

74.4, 74.9, 75.6, 76.9, 78.3, 85.4, 125.3, 127.0, 127.6, 127.7, 127.8, 127.9 (x2) 128.2 (x9), 128.5 (x2), 136.9, 137.8, 137.9, 138.1, 147.6, 150.2, 164.3 ppm; ESI-TOF $[M+Na]^+$ calcd for $C_{35}H_{37}NNaO_6S$ 622.2239, found 622.2236.

Ethyl 2,4,6-tri-*O*-benzyl-3-*O*-picoloyl-1-thio-β-D-mannopyranoside (20) was synthesized according to the reported procedure and its analytical data was essentially the same as reported previously.[4b]

Ethyl 2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-1-thio-β-D-glucopyranoside (22) was synthesized according to the reported procedure and its analytical data was essentially the same as reported previously.[3]

Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-1-thio-β-D-glucopyranoside (24) was synthesized according to the reported procedure and its analytical data was essentially the same as reported previously.[3]

Ethyl 2,4,6-tri-*O*-benzyl-3-*O*-nicotinoyl-1-thio-β-D-glucopyranoside (26). Nicotinic acid (0.10 g, 0.80 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (0.155 g, 0.80 mmol), and 4-dimethylaminopyridine (0.01 g, 0.08 mmol) were added to a solution of ethyl 2,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside[18] (0.20 g, 0.80 mmol) in CH_2Cl_2 (10 mL), and the resulting mixture was stirred under argon for 30 min at rt. The reaction mixture was diluted with CH_2Cl_2 (~ 100 mL) and washed with sat. aq. $NaHCO_3$ (30 mL) and water (3 x 10 mL). The organic phase was separated, dried with magnesium sulfate, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate – toluene gradient elution) to give the title compound as a white amorphous solid in 90% yield. The analytical data for **26**: R_f = 0.40 (ethyl acetate/toluene, 2/3, v/v); $[\alpha]_D^{21}$ -27.0 (*c* 0.8, $CHCl_3$); ^{1}H NMR: δ, 1.37 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.83 (m, 2H, SCH_2CH_3), 3.68 (m, 2H, H-6a, 6b), 3.85 (m, 1H, $J_{5,6a}$ = 6.6 Hz, H-5),

4.08 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 4.23 (dd, 1H, $J_{4,5}$ = 3.0 Hz, H-4), 4.46-4.76 (m, 5H, H-1, 4 × C*H*Ph), 4.75 (d, 1H, ^2J = 10.6 Hz, C*H*Ph), 4.94 (d, 1H, ^2J = 10.7 Hz, C*H*Ph), 5.33 (dd, 1H, $J_{3,4}$ = 9.6 Hz, H-3), 7.18-7.35 (m, 15H, aromatic), 7.53 (m, 1H, Pico-H), 7.81 (m, 1H, Pico-H), 7.93 (d, 1H, J = 7.8 Hz, Pico-H), 8.84 (d, 1H, J = 4.6 Hz, Pico-H) ppm; ^{13}C NMR: δ, 15.1, 25.2, 68.5, 73.6, 74.4, 74.9, 75.8, 78.1, 78.9, 79.2, 85.2, 123.1, 125.8, 127.7 (x3), 127.9 (x2), 128.0 (x2), 128.2 (x4), 128.3 (x2), 128.4, 137.1, 137.3, 137.4, 137.9, 150.8, 153.3, 164.1 ppm; ESI-TOF $[M+Na]^+$ calcd for $C_{35}H_{37}NNaO_6S$ 622.2239, found 622.2232.

Ethyl 2,4,6-tri-*O*-benzyl-3-*O*-*iso*-nicotinoyl-1-thio-β-D-glucopyranoside (28). Iso-Nicotinic acid (0.10 g, 0.80 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.155 g, 0.80 mmol), and 4-dimethylaminopyridine (0.01 g, 0.08 mmol) were added to a solution of ethyl 2,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside[18] (0.20 g, 0.80 mmol) in CH_2Cl_2 (10 mL), and the resulting mixture was stirred under argon for 30 min at rt. The reaction mixture was diluted with CH_2Cl_2 (~ 100 mL) and washed with sat. aq. $NaHCO_3$ (30 mL) and water (3 x 10 mL). The organic phase was separated, dried with magnesium sulfate, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate – toluene gradient elution) to give the title compound as a white amorphous solid in 89% yield. The analytical data for **28**: R_f = 0.45 (ethyl acetate/toluene, 2/3, v/v); $[\alpha]_D^{21}$ -37.0 (*c* 0.9, $CHCl_3$); ^{1}H NMR: δ, 1.42 (t, 3H, J = 7.4 Hz, SCH_2CH_3), 2.86 (m, 2H, SCH_2CH_3), 3.61 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-2) 3.64 (m, 1H, H-5), 3.85 (m, 2H, H-6a, 6b), 3.88 (dd, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 4.46 (d, 1H, ^2J = 11.2 Hz, C*H*Ph), 4.54-4.65 (m, 4H, H-1, 3 × C*H*Ph), 4.75 (d, 1H, ^2J = 12.1 Hz, C*H*Ph), 4.88 (d, 1H, ^2J = 11.2 Hz, C*H*Ph), 5.56 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 7.04-7.44 (m, 16H, aromatic), 8.13 (m, 1H, Nico-H), 8.82 (d, 1H, J = 4.8 Hz, Nico-H), 9.04 (s, 1H, Nico-H) ppm; ^{13}C NMR: δ, 15.2, 25.4, 68.5, 73.6, 74.4, 74.9, 75.8, 78.5, 78.9, 79.2, 85.3, 122.9 (x2), 127.9 (x2), 128.0 (x4), 128.3 (x7), 128.5 (x2), 137.0, 137.3,

137.4, 137.9, 150.5 (x2), 164.1 ppm; ESI-TOF $[M+Na]^+$ calcd for $C_{35}H_{37}NNaO_6S$ 622.2239, found 622.2241.

Synthesis of disaccharides

General procedure for glycosylation. Glycosyl donor (0.05 mmol) and glycosyl acceptor (0.038 mmol) were dried *in vacuo* for 1 h at rt. Molecular sieves (4 Å, 60 mg or 150 mg for 50 mM or 5 mM reaction, respectively) and freshly distilled 1,2-dichloroethane or dichloromethane (1.0 mL for 50 mM reaction or 10.0 mL for 5 mM) were added and the resulting mixture was stirred under argon for 1 h at rt. The mixture was cooled (-30 °C or -50°C) and the promoter was added. The external cooling was removed, and the reaction mixture was allowed to warm gradually to rt for reactions longer than 2 h. Upon completion (see the time listed in Tables), the solid was filtered off through a pad of Celite and rinsed successively with dichloromethane. The combined filtrate (~ 30 mL) was washed with either sat. aq. $NaHCO_3$ (10 mL) or 10% NaS_2O_3 (10 mL, for NIS-promoted reactions) and water (2 x 10 mL). The organic phase was separated, dried with magnesium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate – hexanes gradient elution) to afford the corresponding disaccharide. Diastereomeric ratios were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

Methyl *O*-(2,4,6-tri-*O*-benzyl-3-*O*-picoloyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (3) was obtained as a white amorphous solid from glycosyl donor **1** and acceptor **2** in 85% (α/β = 1/23). Analytical data for **3** was in accordance with that reported previously.[6]

Methyl *O*-(2,4,6-tri-*O*-methyl-3-*O*-picoloyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (5) was obtained as a white amorphous solid from glycosyl donor **4** and acceptor **2** in 90% (α/β > 1/25). Analytical data for **5** was in accordance with that reported previously.[6]

Methyl *O*-(2,4,6-tri-*O*-benzyl-3-*O*-picoloyl-α/β-D-glucopyransyl)-(1→2)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (7) was obtained as a clear syrup from glycosyl donor **1** and glycosyl acceptor **6** in 78% yield (α/β = 1/1.5). Selected analytical data for **α-7**: R_f = 0.55 (ethyl acetate/toluene, 2/3, v/v); ^{1}H NMR: δ, 5.06 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1'), 6.04 (dd, 1H, $J_{3',4'}$ = 9.4 Hz, H-3'), 8.09 (d, 1H, *J* = 7.7 Hz, Pico-H), 8.80 (d, 1H, *J* = 3.9 Hz, Pico-H) ppm; ^{13}C NMR: δ, 94.2, 96.5 ppm. Selected analytical data for **β-7**: R_f = 0.55 (ethyl acetate/toluene, 2/3, v/v); ^{1}H NMR: δ, 5.57 (dd, 1H, $J_{3',4'}$ = 9.4 Hz, H-3'), 7.90 (d, 1H, *J* = 7.8 Hz, Pico-H), 8.76 (d, 1H, *J* = 4.7 Hz, Pico-H) ppm; ^{13}C NMR: δ, 99.8, 104.0 ppm; ESI-TOF $[M+Na]^+$ calcd for $C_{61}H_{63}NNaO_{12}$ 1024.4248, found 1024.4262.

Methyl *O*-(2,4,6-tri-*O*-benzyl-3-*O*-picoloyl-α/β-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (9) was obtained as a clear syrup from glycosyl donor **1** and glycosyl acceptor **8** in 68% yield (α/β = 1/1.7). Selected analytical data for **α-9**: R_f = 0.60 (ethyl acetate/toluene, 2/3, v/v); ^{1}H NMR: δ, 4.02 (dd, 1H, $J_{4',5'}$ = 9.6 Hz, H-4'), 5.71 (d, 1H, $J_{1',2'}$ = 3.4 Hz, H-1'), 8.04 (d, 1H, *J* = 7.7 Hz, Pico-H) ppm; ^{13}C NMR: δ, 97.2, 97.5 ppm. Selected analytical data for **β-9**: R_f = 0.60 (ethyl acetate/toluene, 2/3, v/v); ^{1}H NMR: δ, 5.15 (d, 1H, ^2J = 10.7 Hz, C*H*Ph), 5.28 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1'), 5.68 (dd, 1H, $J_{3',4'}$ = 9.5 Hz, H-3'), 8.11 (d, 1H, *J* = 7.8 Hz, Pico-H) ppm; ESI-TOF $[M+Na]^+$ calcd for $C_{61}H_{63}NNaO_{12}$ 1024.4248, found 1024.4254.

Methyl *O*-(2,4,6-tri-*O*-benzyl-3-*O*-picoloyl-α/β-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (11) was obtained as a clear syrup from glycosyl donor **1** and glycosyl

acceptor **10** in 44% yield (α/β = 1/2.0). Selected analytical data for **α-11**: R_f = 0.55 (ethyl acetate/toluene, 2/3, v/v); ^{1}H NMR: δ, 5.03 (d, 1H, ^2J = 11.7 Hz, C*H*Ph), 5.76 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1'), 5.82 (dd, 1H, $J_{3',4'}$ = 9.8 Hz, H-3') ppm; ^{13}C NMR: δ, 96.5, 97.8 ppm; Selected analytical data for **β-11**: R_f = 0.55 (ethyl acetate/toluene, 2/3, v/v); ^{1}H NMR: δ, 5.12 (d, 1H, ^2J = 11.3 Hz, C*H*Ph), 5.44 (dd, 1H, $J_{3',4'}$ = 9.4 Hz, H-3') ppm; ^{13}C NMR: δ, 98.5, 102.6 ppm; ESI-TOF $[M+Na]^+$ calcd for $C_{61}H_{63}NNaO_{12}$ 1024.4248, found 1024.4260.

Methyl *O*-(2,4,6-tri-*O*-benzyl-3-*O*-picoloyl-α/β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (13) was obtained as a clear syrup from glycosyl donor **1** and methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside **12**[19] in 92% yield (α/β = 1/7.7). Analytical data for **β-13**: R_f = 0.60 (ethyl acetate/ toluene, 2/3, v/v); ^{1}H NMR: δ, 3.46 (s, 3H, OCH_3), 3.57 (m, 1H, H-5'), 3.66 (dd, 1H, $J_{2',3'}$ = 9.6 Hz, H-2'), 3.77 (m, 2H, H-6a', 6b'), 3.92 (dd, 1H, $J_{6a,6b}$ = 11.0 Hz, H-6a), 4.00 (dd, 1H, $J_{4',5'}$ = 9.6 Hz, H-4'), 4.17 (dd, 1H, H-6b), 4.45 (m, 1H, $J_{5,6a}$ = 6.3 Hz, H-5), 4.46-4.70 (m, 5H, 5 x C*H*Ph), 4.67 (d, 1H, $J_{1',2'}$ = 6.8 Hz, H-1'), 4.96 (d, 1H, ^2J = 12.0 Hz, C*H*Ph), 5.27-5.34 (m, 2H, H-1, 2), 5.53 (dd, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 5.62 (dd, 1H, $J_{3',4'}$ = 9.5 Hz, H-3'), 6.24 (dd, 1H, $J_{3,4}$ = 9.7 Hz, H-3), 7.05-8.02 (m, 33H, aromatic), 8.81 (d, 1H, J = 6.4 Hz, Pico-H) ppm; ^{13}C NMR: δ, 55.6, 68.2, 69.1, 69.8, 70.5, 72.2, 73.5, 74.1, 74.5, 74.8, 75.8, 77.3, 79.2, 96.9, 104.0, 125.5, 126.8, 127.3, 127.6 (x2), 127.8 (x2), 127.9 (x2), 128.0 (x4), 128.2 (x2), 128.3 (x4), 128.4 (x4), 128.9, 129.1, 129.2, 129.7 (x2), 130.0 (x4), 133.1, 133.3, 133.5, 136.8, 137.6, 138.0, 138.2, 147.9, 149.7, 164.3, 165.5, 165.8 (x2) ppm; ESI-TOF $[M+Na]^+$ calcd for $C_{61}H_{57}NNaO_{15}$ 1066.3626, found 1066.3625.

Methyl *O*-(2,4,6-tri-*O*-benzyl-3-*O*-picoloyl-α/β-D-glucopyranosyl)-(1→6)-2,3-di-*O*-benzoyl-4-*O*-benzyl-α-D-glucopyranoside (15) was obtained as a clear syrup from glycosyl donor **1** and methyl 2,3-di-*O*-benzoyl-4-*O*-benzyl-α-D-glucopyranoside **14**[20] in 80% (α/β = 1/16.7) yield.

Analytical data for **β-15**: R_f = 0.60 (ethyl acetate/toluene, 2/3, v/v), ^{1}H NMR: δ, 3.43 (s, 3H, OCH_3), 3.57 (m, 1H, $J_{5',6a'}$ = 2.8 Hz, H-5'), 3.74 (dd, 1H, $J_{2',3'}$ = 9.6 Hz, H-2'), 3.83-3.90 (m, 3H, H-6a, 6a', 6b'), 3.93 (dd, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 4.01 (dd, 1H, $J_{4',5'}$ = 9.6 Hz, H-4'), 4.10 (m, 1H, $J_{5,6a}$ = 2.0 Hz, H-5), 4.30 (dd, 1H, H-6b), 4.52 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1'), 4.54-4.78 (m, 7H, 7 x C*H*Ph), 5.00 (d, 1H, ^2J = 11.6 Hz, C*H*Ph), 5.17-5.22 (m, 2H, H-1, 2), 5.66 (dd, 1H, $J_{2',4'}$ = 9.5 Hz, H-3'), 6.10 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 7.09-8.08 (m, 33H, aromatics), 8.82 (d, 1H, J = 4.4 Hz, Pico-H) ppm; ^{13}C NMR: δ, 55.3, 68.4, 68.6, 69.9, 70.6, 72.3, 72.7, 73.5, 74.5, 74.6, 74.8, 75.0, 79.0, 77.2, 79.3, 96.9, 104.0, 125.5, 126.9, 127.4, 127.6 (x2), 127.7 (x2), 127.8 (x4), 128.0 (x2), 128.2 (x4), 128.4 (x8), 129.1, 129.6 (x2), 129.9 (x2), 133.1, 133.3 (x2), 136.9, 137.5, 137.6, 138.0, 138.1, 147.7, 149.8, 164.4, 165.6, 166.0 ppm; ESI-TOF $[M+Na]^+$ calcd for $C_{61}H_{59}NNaO_{14}$ 1052.3833, found 1052.3816.

Methyl *O*-(2,4,6-tri-*O*-benzyl-3-*O*-picoloyl-α/β-D-glucopyranosyl)-(1→6)-2-*O*-benzoyl-3,4-di-*O*-benzyl-α-D-glucopyranoside (17) was obtained as a clear oil from glycosyl donor **1** and methyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-α-D-glucopyranoside **16** in 79% yield (α/β >1/25). Analytical data for **β-17**: R_f = 0.60 (ethyl acetate/toluene, 2/3, v/v); ^{1}H NMR: δ, 3.33 (s, 3H, OCH_3), 3.55 (m, 1H, H-5'), 3.62-6.68 (m, 2H, H-2', 4), 3.73-3.77 (m, 3H, H-6a, 6a', 6b'), 3.92 (dd, $J_{4',5'}$ = 9.5 Hz, H-4'), 3.92-3.96 (m, 1H, H-5), 4.16-4.26 (m, 2H, H-3, 6b), 4.46-4.58 (m, 5H, H-1', 4 x C*H*Ph), 4.63 (dd 1H, ^2J = 11.7 Hz, C*H*Ph), 4.67 (d, 1H, ^2J = 12.1 Hz, C*H*Ph), 4.73 (d, 1H, ^2J = 11.3 Hz, C*H*Ph), 4.78-4.79 (m, 2H, 2 x C*H*Ph), 4.86 (d, 1H, ^2J = 11.5 Hz, C*H*Ph), 5.05 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 5.11 (dd, 1H, $J_{2,3}$ = 9.8 Hz, H-2), 5.57 (dd, 1H, $J_{3,4}$ = 9.4 Hz, H-3'), 6.99-7.49 (m, 28H, aromatic), 7.58 (m, 1H, Pico-H), 7.81 (m, 1H, Pico-H), 7.97 (d, 1H, J = 7.8 Hz, Pico-H), 8.05 (m, 2H, aromatic), 8.75 (d, 1H, J = 4.7 Hz, Pico-H) ppm; ^{13}C NMR: δ, 55.1, 68.6, 70.1, 73.5, 74.0, 74.5, 74.9, 75.0, 75.5, 76.0, 77.2, 78.1, 79.1, 80.1, 97.0, 103.8, 125.5, 126.8,

10.1002/chem.201905278

127.3, 127.6 (x2), 127.8 (x3), 127.9 (x6), 128.0 (x2), 128.1 (x2), 128.2 (x2), 128.3 (x2), 128.4 (x2), 128.4 (x3), 129.7, 129.8 (x2), 133.3, 136.9, 137.6, 137.8, 138.1 (x3), 147.7, 149.7, 164.3, 166.0 ppm; ESI-TOF $[M+Na]^+$ calcd for $C_{61}H_{61}NNaO_{13}$ 1038.4041, found 1038.4049.

Methyl *O*-(2,4,6-tri-*O*-benzyl-3-*O*-picoloyl-α/β-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (19) was obtained as a clear oil from glycosyl donor **18** and glycosyl acceptor **2** in 76% yield (α/β = 1/9). Analytical data for **β-19**: R_f = 0.70 (ethyl acetate/toluene, 2/3, v/v); ^{1}H NMR: δ, 3.37 (s, 3H, OCH_3), 3.51 (dd, 1H, $J_{4,5}$ = 9.9 Hz, H-4), 3.55-3.59 (m, 1H, H-2), 3.67-3.81 (m, 4H, H-5', 6a, 6a', 6b), 3.90 (m, 1H, H-5), 4.02-4.09 (m, 2H, H-2', 3), 4.17-4.24 (m, 2H, H-4', 6b'), 4.50 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1'), 4.52-4.87 (m, 10H, 10 × C*H*Ph), 4.65 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.94 (d, 1H, ^2J = 11.4 Hz, C*H*Ph), 5.03 (d, 1H, ^2J = 10.8 Hz, C*H*Ph), 5.28 (dd, 1H, $J_{3',4'}$ = 10.1 Hz, H-3'), 7.08-7.84 (m, 33H, aromatic), 8.84 (d, 1H, J = 4.6 Hz, Pico-H) ppm; ^{13}C NMR: δ, 55.2, 67.8, 68.3, 70.0, 73.0, 73.3, 73.4, 74.4, 74.7, 74.9, 75.8, 76.5, 77.2, 78.2, 79.7, 82.0, 97.9, 104.1, 125.2, 126.9, 127.4, 127.5, 127.6 (x2), 127.7 (x4), 127.9 (x6), 128.1 (x6), 128.2, 128.4 (x4), 128.5 (x2), 137.0, 137.8, 138.1 (x2), 138.2, 138.8, 147.4, 150.0, 164.1 ppm; ESI-TOF $[M+Na]^+$ calcd for $C_{61}H_{63}NNaO_{12}$ 1024.4248, found 1024.4243.

Methyl *O*-(2,4,6-tri-*O*-benzyl-3-*O*-picoloyl-α/β-D-mannopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (21) was obtained as a white amorphous solid from glycosyl donor **20** and acceptor **2** in 82% yield (α/β = 1/3.8). Analytical data for **21** was in accordance with that reported previously.[4b]

Methyl *O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α/β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (23) was obtained as a white amorphous solid from glycosyl donor **22** and acceptor **2** in 86% yield (α/β = 1.2/1). Analytical data for **23** was in accordance with that reported previously.[3]

Methyl *O*-(2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (25) was obtained as a white amorphous solid from glycosyl donor **24** and acceptor **2** in 89% yield (α/β = 1/10). Analytical data for **25** was in accordance with that reported previously.[3]

Methyl *O*-(2,4,6-tri-*O*-benzyl-3-*O*-nicotinoyl-α/β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (27) was obtained as a clear syrup from glycosyl donor **26** and glycosyl acceptor **2** in 66% yield (α/β = 1/6). Selected analytical data for **α-27**: R_f = 0.60 (ethyl acetate/toluene, 2/3, v/v); ^{1}H NMR: δ, 5.11 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1'), 5.80 (dd, 1H, $J_{3',4'}$ = 9.0 Hz, H-3') ppm. Selected analytical data for **β-27**: R_f = 0.60 (ethyl acetate/toluene, 2/3, v/v); ^{1}H NMR: δ, 3.92 (m, 1H, H-5'), 4.07 (dd, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 4.26 (dd, 1H, H-6b), 5.04 (d, 1H, ^2J = 10.7 Hz, C*H*Ph), 5.48 (dd, 1H, $J_{3',4'}$ = 9.4 Hz, H-3') ppm; ^{13}C NMR: δ, 98.0, 103.8 ppm; ESI-TOF $[M+Na]^+$ calcd for $C_{61}H_{63}NNaO_{12}$ 1024.4248, found 1024.4252.

Methyl *O*-(2,4,6-tri-*O*-benzyl-3-*O*-*iso*-nicotinoyl-α/β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (29) was obtained as a clear syrup from glycosyl donor **28** and glycosyl acceptor **2** in 82% yield (α/β = 1/4). Selected analytical data for **α-29**: R_f = 0.50 (ethyl acetate/toluene, 2/3, v/v); ^{1}H NMR: δ, 5.12 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1'), 5.78 (dd, 1H, $J_{3',4'}$ = 9.7 Hz, H-3') ppm. Selected analytical data for **β-29**: R_f = 0.50 (ethyl acetate/toluene, 2/3, v/v); ^{1}H NMR: δ, 4.07 (dd, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 4.23 (dd, 1H, H-6b), 5.04 (dd, 1H, ^2J = 10.7 Hz, C*H*Ph), 5.45 (dd, 1H, $J_{3',4'}$ = 9.5 Hz, H-3') ppm; ^{13}C NMR: δ, 98.1, 103.9 ppm; ESI-TOF $[M+Na]^+$ calcd for $C_{61}H_{63}NNaO_{12}$ 1024.4248, found 1024.4245.

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ASSOCIATED CONTENT

Supporting Information

Additional experimental data and NMR spectra for all new compounds. This material is available free of charge via the Internet at

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

Notes

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