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Investigation of the H-bond-mediated aglycone delivery reaction in application to the synthesis of β-glucosides

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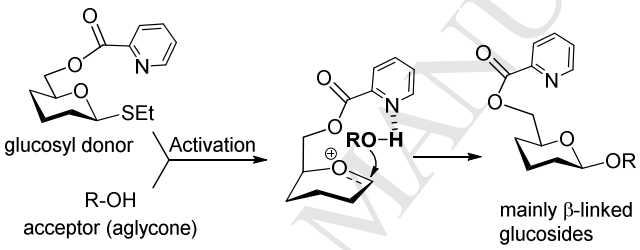
Abstract In an attempt to refine the H-bond-mediated Aglycone Delivery (HAD) glycosylation reaction reported herein is the synthesis of β-glucosides using an ethylthio glucoside donor equipped with the remote 6-*O*-picoloyl substituent. Upon examining various aliphatic, aromatic, and carbohydrate acceptors, it was determined that both electronic and steric factors may greatly affect the stereoselectivity of the HAD reaction with this donor.



Keywords: synthesis, stereoselectivity, glycosylation, oligosaccharides

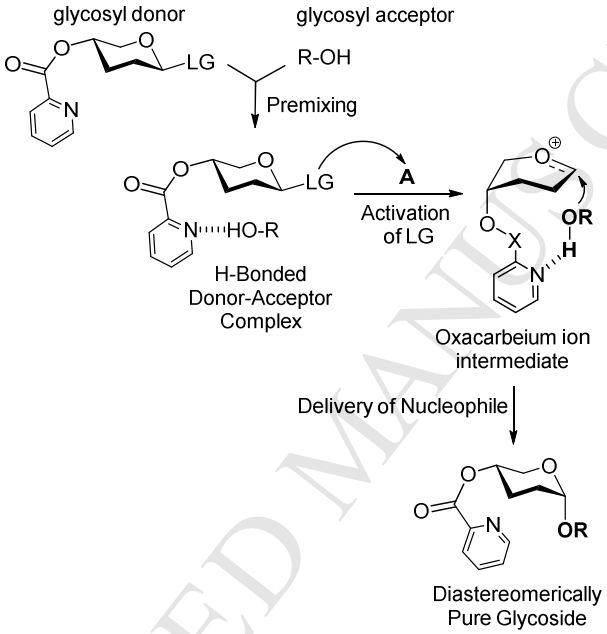
Introduction

The chemical synthesis of glycans still faces many challenges and the biggest and most common problem is chemical glycosylation, the reaction of joining saccharide units via O-glycosidic linkages.[1-3] Due to the inherited mechanistic nature of this reaction, stereocontrol is often difficult to achieve.[4,5] This results in the formation of undesired diastereomers, lowering yields and complicating purification. There are various conditions and methods currently used to control stereoselectivity.[6,7] Among these is the hydrogen-bond-mediated aglycone delivery (HAD) method. First reported in 2012,[8] the HAD method employs a glycosyl donor functionalized with a picoloyl (Pico) or similar moiety, a hydrogen bond accepting protecting group. This picoloyl group forms a hydrogen bond with the free hydroxyl of the glycosyl acceptor, forming an H-bonded donor-acceptor complex (Scheme 1). After addition of the promoter, the donor is activated without disrupting the H-bonded complex, and the acceptor is "delivered" to the anomeric position of the donor resulting in a facially preferential glycosidic bond formation that is *syn*-selective with respect to the picoloyl protecting group.

The HAD reaction has successfully been applied to α-glucosylation using 4-*O*-Pico donor[8] and its utility was demonstrated by the synthesis of linear and branched α-glucans.[9] Also mannosylation with the use of either 3- or 6-*O*-Pico donors proceeded with high β-

stereoselectivity,[10] which was demonstrated by the sinthesis of a β-linked mannan at room temperature.[10] Further expansion of the HAD led to the development of new activation conditions,[11] protecting groups,[12,13] and glycosyl donors with switchable stereoselectivity.[14,15] Mong and co-workers applied 6-*O*-picoloyl-2-deoxy glycosyl donors to stereoselective synthesis of β-glycosides.[16] Yang and co-workers investigated the synthesis of β-D- and β-L-arabinofuranosides,[12] whereas De Meo[17] and Tsai[18] investigated the effect of picoloyl substituents on sialylations.

Scheme 1. Mechanistic depiction of the HAD glycosylation method.

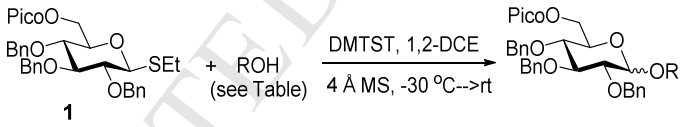


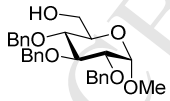
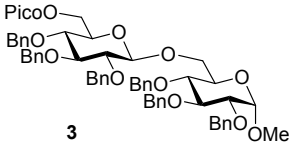
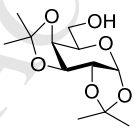
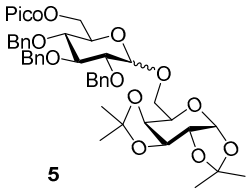
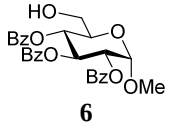
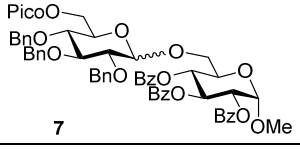
β-Glucosidic bonds are common glycosidic linkages that are often present in natural products[19] and various microbial, plant, and fungal glycan sequences.[20,21] Chemically, β-glucosides are typically formed with high stereoselectivity from glycosyl donors functionalized with an acyl protecting group at the C-2 position capable of the neighboring group participation. Upon activation, these donors form the bicyclic acyloxonium ion intermediate that hinders the nucleophilic attack from the bottom face of the ring.[22] Despite this method's popularity it is prone to byproduct formation, such as an 1,2-*O*-orthoester,[23] and regioselective selective functionalization of the C-2 position can complicate the synthesis of glycosyl donors.[24] In contrast, the HAD method has been shown to form β-glucosides utilizing donors functionalized at the primary C-6 position, offering enhanced synthetic flexibility. However, the preliminary attempts were limited to glycosylation of primary hydroxyl of glucosyl acceptor.[8] To broaden the scope of the HAD-assisted synthesis of β-linked glucosides and disaccharides reported herein is the investigation of thioglucoside donor **1.** Compound **1** equipped with the 6-*O*-picoloyl protecting group has already been shown to perform HAD glycosylations with β-stereoselectively, and its synthesis is known.[8]

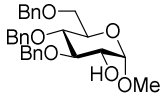
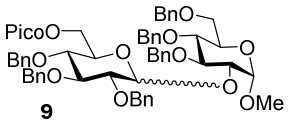
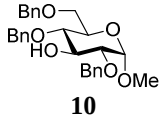
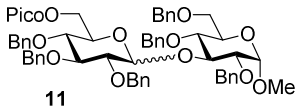
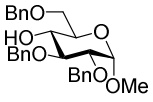
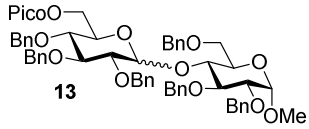
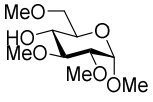
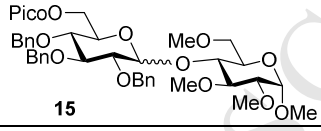
Results and Discussion

Previous glycosylations were performed in the presence of dimethyl(thiomethyl)sulfonium triflate (DMTST) and molecular sieves (4 Å) in 1,2-dichloroethane (1,2-DCE) both under regular (50 mM) and low (5 mM) concentration of donor **1**. DMTST was added at -30 °C, and the reaction mixture was then allowed to warm to room temperature. Thus, under these reaction conditions that became standard for the HAD reactions, glycosylation of acceptor **2**[25,26] with donor **1** proceeded smoothly and β-stereoselectively affording disaccharide **3** in 78-90% yield (entry 1, Table 1). This result was practically the same as that previously reported for this donor-acceptor combination.[8] To expand upon these findings, the glycosylation of other common carbohydrate acceptors with donor **1** were examined and the key findings are summarized in Table 1. The primary acceptor **4** afforded the corresponding disaccharide **5** with respectable yields of 81-91% and complete stereoselectivity (entry 2). Very unexpectedly, the β-stereoselectivity was dramatically decreased when benzoylated primary acceptor **6**[27] was glycosylated. The reaction was still fairly swift (1.5 h), and respectable yields for the synthesis of disaccharide **7** (82-92%) have been achieved, but the stereoselectivity was fairly low (α/β = 1/2.7-2.9, entry 3) in comparison to the results obtained with other primary acceptors (*vide supra*). This last result made us believe that the efficacy of the HAD reaction with donor **1** can be greatly dependent on the electronic properties of the glycosyl acceptor. Thus, with the electro-withdrawing substituents in acceptor **7**, the electron density on the hydroxyl group is decreased in comparison to that of alkylated counterparts. As a result, the hydrogen-bond-donating properties of such electron-poor glycosyl acceptor are reduced and the picoloyl-assisted H-bond-mediated aglycone delivery becomes less prevalent reaction pathway.

Table 1. Glycosylation of primary and secondary glycosyl acceptors with donor **1**



Entry	Acceptor (ROH)	Conc. of **1**, time	Product	yield (α/β ratio)
1	 **2**	5 mM, 2 h 50 mM, 3 h	 **3**	78% (β-only) 90% (β-only)
2	 **4**	5 mM, 1.5 h 50 mM, 1.5 h	 **5**	91% (β-only) 81% (β-only)
3	 **6**	5 mM, 1.5 h 50 mM, 1.5 h	 **7**	82% (1/2.7) 92% (1/2.9)

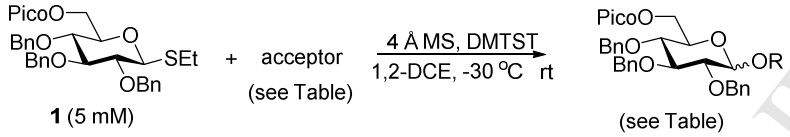
4	 **8**	5 mM, 24 h 50 mM, 24 h	 **9**	42% (1/1.3) 48% (1/2.6)
5	 **10**	5 mM, 24 h 50 mM, 24 h	 **11**	49% (1/2.5) 43% (1/1.0)
6	 **12**	5 mM, 24 h 50 mM, 24 h	 **13**	37% (1/2.5) 31% (1/3.5)
7	 **14**	5 mM, 24 h 50 mM, 24 h	 **15**	38% (1/4.3) 31% (1/2.5)

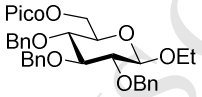
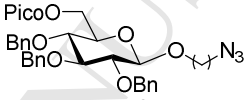
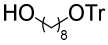
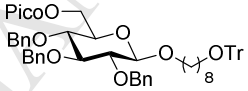
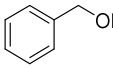
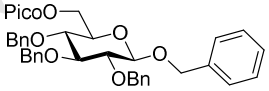
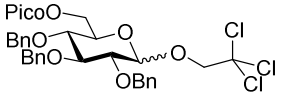
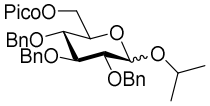
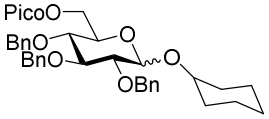
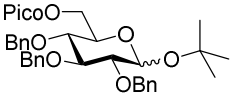
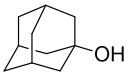
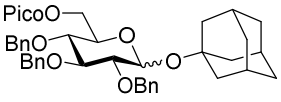
The less reactive, more sterically hindered secondary acceptors also proved to be problematic for the HAD reaction with donor **1**. Poor yields and stereoselectivities, as well as long reaction times, were observed for acceptors **8**,[28] **10**,[29] and **12**[30] (entries 4-6). An improvement in stereoselectivity was seen with the methylated secondary acceptor **14**[31] (entry 7). The reactivity of acceptor **14**, however, was still fairly low leading to long reaction times and low yields. This last result made us believe that the stereoselectivity of the HAD reaction with donor **1** can be also dependent on the steric properties of the glycosyl acceptor. Thus, with the bulky benzyl substituents are present in the glycosyl acceptor, the accessibility of the secondary hydroxyl to form strong H-bonding with bulky picoloyl moiety of the donor is low in comparison to that of less hindered methylated (or primary) counterparts. As a result, the H-bond-donating properties of such hindered glycosyl acceptors are reduced and the picoloyl-assisted delivery becomes a less prevalent stereodirecting pathway. In an attempt to improve results with secondary acceptors, various reaction conditions were investigated in the glycosylation of donor **1** and secondary acceptor **10**. Slightly improved selectivity was observed upon switching to the stronger promoter system of NIS/TfOH. The extended experimental data can be found in the supporting information.

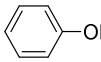
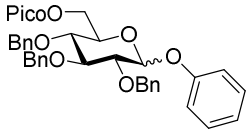
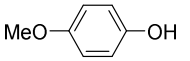
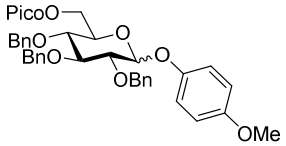
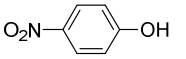
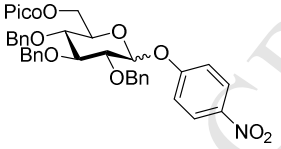
These results were puzzling to us because previously investigated 4-*O*-Pico donor provided excellent *syn*-stereoselectivity for the synthesis of α-glucosides, which was practically independent on the nature of the glycosyl acceptor.[8] On the other hand, the previously investigated 6-*O*-Pico mannosyl donor provided high *syn*-stereoselectivity for the synthesis of β-mannosides.[8,10] To develop a convenient tool-kit for studying this controversial reaction, we turned our attention to glycosylation of small molecule acceptors that could serve a simplified albeit more easily tunable platform for studying possible electronic and steric effects on the outcome of the HAD reaction. The key results of this study performed under low concentration conditions (5 mM of glycosyl donor **1**) are summarized in Table 2. Thus, all initially chosen primary aliphatic acceptors exhibited complete β-selectivity and the corresponding glycosides **16**-**19** we obtained in moderate-to-excellent yields (56-86%, entries 1-4). However, the stereoselectivity was diminished when 2,2,2-trichloroethanol was employed as the glycosyl acceptor. Thus, glycosylation of this more electron poor trichloro-substituted acceptor led to the

formation of glycoside **20** in 77% with decreased selectivity α/β = 1/11.4 (entry 5) in comparison to the complete β-selectivity obtained with non-substituted ethanol (entry 1).

Table 2. Glycosylation of small molecule acceptors to study the effect of steric and electronic factors on the HAD reaction



Entry	Acceptor	Time	Product (yield, α/β ratio)
1	EtOH	0.5 h	 **16** (86%, β-only)
2		0.5 h	 **17** (73%, β-only)
3		0.5 h	 **18** (56%, β-only)
4		0.5 h	 **19** (57%, β-only)
5	Cl_3CCH_2OH	0.5 h	 **20** (77%, 1/11.4)
6		1.5 h	 **21** (77%, 1/3.6)
7		1.5 h	 **22** (63%, 1/2.6)
8		1.5 h	 **23** (78%, 1/1.1)
9		1.5 h	 **24** (56%, 1/4.0)

10		1.5 h	 **25** (81%, 1/4.7)
11		1.5 h	 **26** (63%, 1/5.5)
12		1.5 h	 **27** (52%, 1/1.2)

To investigate the role of steric factors on the stereoselectivity of these reactions, we chose a number of secondary and tertiary small molecule acceptors. The results of these glycosylations are summarized in entries 6-9 (Table 2). Thus, glycosides **21-24** were obtained in 56-78% yields, but the stereoselectivity was even lower than that obtained with 2,2,2-trichloroethanol (α/β = 1/1.0-4.0). To further investigate the effect of electronic factors on the stereoselectivity we chose a series of substituted phenol acceptors. Although stereoselectivity of glycosylation has been a well-documented problem with phenol acceptors,[32] their scalable electronic properties made them attractive targets for our study. The results of these glycosylations are summarized in entries 10-12. Thus, glycosides **25-27** were obtained in 52-81% yields, but the stereoselectivity was modest (α/β = 1/1.2-5.5). Nevertheless, these results reveal a clear correlation between the electronics quantified by relative acidity of the aromatic acceptors and the stereoselectivity of their glycosylation. Specifically, as compared to unsubstituted phenol (pK_a = 10) that afforded glycoside **25** (α/β = 1/4.7, entry 10), a slightly less acidic *p*-methoxyphenol (pK_a = 10.2)[33] showed a modest enhancement of stereoselectivity for the formation of glycoside **26** (α/β = 1/5.5, entry 11). Conversely, glycosylation of a much more acidic *p*-nitrophenol (pK_a = 7.2)[33] led to the formation of glycoside **27** with practically entire loss of stereoselectivity (α/β = 1/1.2, entry 12). In our opinion, this series of results clearly indicate the effect of the glycosyl acceptor on the stereoselectivity outcome of the HAD reaction

Conclusions

The glycosylations of the HAD-capable glycosyl donor **1** with various glycosyl acceptors were investigated. Primary acceptors, both carbohydrate and aliphatic alcohols afforded the glycosylation products with complete β-selectivity. Secondary acceptors and some primary acceptors with the reduced electron density of the hydroxyl group exhibited reduced stereoselectivity. Additionally, secondary carbohydrate acceptors had long reaction times and, in a number of cases, modest yields. Relieving some of the steric crowding in secondary acceptors, such as that noted with the methylated acceptor **14**, led to a slightly improved stereoselectivity. The effect of electronic properties of glycosyl acceptors were further investigated by

glycosylation of a series of phenolic acceptors. These reactions revealed a possible preliminary correlation between the electronics or acidity of the hydroxyl to the stereoselectivity observed. These findings are in agreement with the theory that hydrogen bonding is responsible for the observed selectivity in the HAD reactions. It has been well documented that both acidity and sterics of hydrogen-bond donors, the glycosyl acceptors in this case, can have a great influence on the hydrogen-bond strength.[34] Interestingly, these factors do not seem important when employing 4-*O*-picoloyl donors that previously gave completely α-selective HAD-glycosylations with both primary and secondary acceptors.[8]

EXPERIMENTAL PART

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 (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 rotations were 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.

The synthesis of disaccharides

General procedure. Glycosyl donor **1** (0.05 mmol) and a glycosyl acceptor (0.038 mmol) were dried in high vacuum 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 (1.0 mL or 10.0 mL for 50 mM or 5 mM reaction, respectively) were added and the resulting mixture was stirred under argon for 1 h at rt. The mixture was cooled to -30 °C and DMTST (0.1 mmol) was added. The external cooling was removed, and the reaction mixture was allowed to warm up to rt gradually. Upon completion (see the time listed in Table 1), the solid was filtered off through a pad of Celite and rinsed successively with dichloromethane. The combined filtrate (~30 mL) was washed with sat. aq. $NaHCO_3$ (10 mL) and water (2 × 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). Diastereomeric ratios were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

Methyl *O*-(2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (3) was obtained as a clear syrup from glycosyl donor **1**[8] and acceptor **2**[25,26] in 90% (β-only, 50 mM) and 78% (β-only, 5 mM) yield. The analytical data of the title compound were essentially the same as previously reported.[8,35]

***O*-(2,3,4-Tri-*O*-benzyl-6-*O*-picoloyl-β-D-glucopyranosyl)-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (5)** was obtained as a yellow oil from glycosyl donor **1** and commercial acceptor **4** in 91% (β-only, 50 mM) and 70% (β-only, 5 mM) yield. Analytical

data for **5**: R_f = 0.44 (ethyl acetate/toluene, 2/3, v/v); $[\alpha]_D^{22}$ -9.7 (c = 0.98, $CHCl_3$); ^{1}H NMR: δ, 1.30, 1.30, 1.42, 1.47 (4 s, 12H, 4 x CH_3), 3.50 (dd, 1H, $J_{2',3'}$ = 8.3 Hz, H-2'), 3.64-3.75 (m, 4H, H-3', 4', 5', 6a), 4.06-4.10 (m, 2H, H-5, 6b), 4.19 (dd, 1H, $J_{3,4}$ = 8.0 Hz, H-3), 4.30 (dd, 1H, $J_{2,3}$ = 4.8 Hz, H-2), 4.52 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1'), 4.53-4.63 (m, 4H, H-4, 6a', 6b', ½ CH_2Ph), 4.73 (d, 1H, ^2J = 11.2 Hz, ½ CH_2Ph), 4.80 (d, 1H, ^2J = 10.8 Hz, ½ CH_2Ph), 4.88 (d, 1H, ^2J = 10.8 Hz, ½ CH_2Ph), 4.99 (d, 1H, ^2J = 10.8 Hz, ½ CH_2Ph), 5.06 (d, 1H, ^2J = 11.2 Hz, ½ CH_2Ph), 5.55 (d, 1H, $J_{1,2}$ = 5.0 Hz, H-1), 7.21-7.43 (m, 15H, aromatic), 7.45-7.48 (m, 1H, Pico), 7.81 (dd, 1H, J = 7.6 Hz, Pico), 8.04 (d, 1H, J = 7.8 Hz, Pico), 8.76 (d, 1H, J = 4.8 Hz) ppm; ^{13}C NMR: δ, 24.4, 25.0, 26.0 (×2), 64.4, 67.4, 70.0, 70.4, 70.7, 71.4, 72.8, 74.4, 75.0, 75.8, 77.5, 81.6, 84.6, 96.3, 104.5, 108.5, 109.3, 125.3, 126.6, 127.5, 127.7, 127.9, 128.0, 128.2, 128.4, 128.6, 136.9, 137.7, 138.4, 138.6, 147.8, 150.0, 164.6 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{45}H_{52}NO_{12}$ 798.3489, found 787.3538.

Methyl *O*-(2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (7) was obtained as a clear syrup from glycosyl donor **1** and acceptor **6**[27] in 92% (α/β = 1/2.9, 50 mM) and 82% (α/β = 1/2.7, 5 mM) yield. Analytical data for **7**: R_f = 0.63 (ethyl acetate/toluene, 2/3, v/v); selected ^{1}H NMR data for α-**7**: δ, 3.53 (s, 3H, OCH_3) ppm; selected ^{1}H NMR data for β-**7**: δ, 3.42 (s, 3H, OCH_3), 3.88 (dd, 1H, $J_{5,6a}$ = 7.2 Hz, $J_{6a,6b}$ = 11.1 Hz, H-6a), 4.38-4.43 (m, 1H, H-5), 4.77 (d, 1H, ^2J = 10.8 Hz, ½ CH_2Ph), 4.85 (d, 1H, ^2J = 10.8 Hz, ½ CH_2Ph), 4.94 (d, 1H, ^2J = 10.8 Hz, ½ CH_2Ph), 5.02 (d, 1H, ^2J = 10.8 Hz, ½ CH_2Ph), 5.16 (d, 1H, ^2J = 10.8 Hz, ½ CH_2Ph), 5.52 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 6.20 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 8.80 (d, 1H, J = 4.6 Hz, Pico) ppm; selected ^{13}C NMR data for β-**7**: δ, 55.6, 64.3, 68.8, 69.8, 70.4, 72.0, 72.9, 74.9, 75.0, 75.9, 77.4, 82.2, 84.5, 96.8, 104.0 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{61}H_{57}NNaO_{15}$ 1066.3626, found 1066.3641.

Methyl *O*-(2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-glucopyranosyl)-(1→2)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (9) was obtained as a clear syrup from glycosyl donor **1** and acceptor **8**[28] in 48% (α/β = 1/1.3, 50 mM) and 42% (α/β = 1/2.6, 5 mM) yield. Analytical data for **9**: R_f = 0.57 (ethyl acetate/toluene, 2/3, v/v); selected ^{1}H NMR data for α-**9**: δ, 3.34 (s, 3H, OMe), 7.98 (dd, 1H, J = 7.8 Hz, Pico) ppm; selected ^{1}H NMR data for the β-**9**: δ, 3.45 (s, 3H, OMe), 3.87 (dd, 1H, $J_{2,3}$ = 9.9 Hz, H-2), 8.03 (d, 1H, J = 7.8 Hz, Pico) ppm; selected ^{13}C NMR data for the anomeric region of α/β-**9**: δ, 93.9, 99.3, 99.5, 104.1 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{61}H_{63}NO_{12}Na$ 1024.4248, found 1024.4246.

Methyl *O*-(2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (11) was obtained as a clear syrup from glycosyl donor **1** and acceptor **10**[29] in 43% (α/β = 1/1.0, 50 mM) and 49% (α/β = 1/2.5, 5 mM) yield. Analytical data for **11**: R_f = 0.24 (ethyl acetate/hexane, 2/3, v/v); selected ^{1}H NMR data for α-**11**: δ, 3.31 (s, 3H, OCH_3), 4.12 (dd, 1H, $J_{3',4'}$ = 9.1 Hz, H-3'), 5.57 (d, 1H, $J_{1'2'}$ = 3.1 Hz, H-1'), 7.78 (dd, 1H, J = 7.8 Hz, Pico), 8.05 (d, 1H, J = 7.8 Hz, Pico), 8.74 (d, 1H, J = 4.8 Hz, Pico) ppm; selected ^{1}H NMR data for β-**11**: δ, 3.29 (s, 3H, OCH_3), 7.59 (dd, 1H, J = 7.8 Hz, Pico), 7.86 (d, 1H, J = 7.8 Hz, Pico), 8.70 (d, 1H, J = 3.9 Hz, Pico) ppm; selected ^{13}C NMR data for the anomeric region of α/β-**11**: δ, 97.1, 97.3, 97.7, 102.7 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{61}H_{63}NNaO_{12}$ 1024.4248, found 1024.4246.

Methyl *O*-(2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (13) was obtained as a clear syrup from glycosyl donor **1** and acceptor **12**[30] in 31% (α/β = 1/3.5, 50 mM) and 37% (α/β = 1/2.5, 5 mM) yield. Analytical data for **13**: R_f= 0.30 (ethyl acetate/hexane, 2/3, v/v); selected ^{1}H NMR data for α-**13**: δ, 3.38 (s, 3H, OCH_3), 5.57 (d, 1H, $J_{1',2'}$ = 3.7 Hz, H-1'), 7.75 (dd, 1H, *J* = 7.8 Hz, Pico), 7.98 (d, 1H, *J* = 7.8 Hz, Pico) ppm; selected ^{1}H NMR data for β-**13**: δ, 3.36 (s, 3H, OCH_3), 5.05 (d, 1H, ^2J = 11.3 Hz, ½ CH_2Ph), 7.60 (dd, 1H, *J* = 7.6 Hz, Pico), 7.85 (d, 1H, *J* = 7.8 Hz, Pico) ppm; selected ^{13}C NMR data for the anomeric region of α/β-**13**: δ, 96.5, 97.9, 98.5, 102.7 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{61}H_{63}NNaO_{12}$ 1024.4248, found 1024.4246.

Methyl *O*-(2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-methyl-α-D-glucopyranoside (15) was obtained as a clear syrup from glycosyl donor **1** and acceptor **14**[31] in 31% (α/β = 1/2.5, 50 mM) and 38% (α/β = 1/4.3, 5 mM) yield. Analytical data for α-**15**: R_f = 0.38 (ethyl acetate/dichloromethane, 1/1, v/v); $[\alpha]_D^{22}$ 93.4 (c = 0.88, $CHCl_3$); ^{1}H NMR: δ, 3.27 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 3.33, 3.40 (2 s, 6H, 2 × OCH_3), 3.47-3.50 (m, 7H, H-6b, 2 × OCH_3), 3.62 (dd, 1H, $J_{2',3'}$ = 9.8 Hz, H-2'), 3.69 (dd, 1H, $J_{4',5'}$ = 9.3 Hz, H-4'), 3.74 (dd, 1H, $J_{3,4}$ = 9.1 Hz, H-3), 3.98-4.01 (m, 2H, H-5, 6a), 3.90-3.92 (m, 1H, H-5'), 3.95 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4), 4.00 (dd, 1H, $J_{3',4'}$ = 9.2 Hz, H-3'), 4.53 (dd, 1H, $J_{6a',6b'}$ = 11.8 Hz, H-6a'), 4.62-4.64 (m, 2H, H-6a', ½ CH_2Ph), 4.74 (d, 1H, ^2J = 11.7 Hz, ½ CH_2Ph), 4.83 (d, 1H, ^2J = 11.7 Hz, ½ CH_2Ph), 4.85 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.89 (d, 1H, ^2J = 11.1 Hz, ½ CH_2Ph), 4.97 (d, 1H, ^2J = 10.5 Hz, ½ CH_2Ph), 5.70 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1'), 7.17-7.37 (m, 15H, aromatic), 7.44-7.45 (m, 1H, Pico), 7.79 (dd, 1H, *J* = 7.7 Hz, Pico), 8.01 (d, 1H, *J* = 7.8 Hz, Pico), 8.75 (d, 1H, *J* = 4.6 Hz, Pico) ppm; ^{13}C NMR: δ, 55.1, 58.7, 59.0, 60.1, 64.0, 69.0, 69.2, 70.6, 70.8, 73.2, 75.0, 75.9, 77.1, 79.9, 82.0, 82.1, 83.4, 95.9, 97.1, 125.2, 126.8, 127.8 (× 2), 127.9, 128.0 (× 4), 128.1 (× 2), 128.4 (× 2), 128.5 (× 3), 136.8 (× 2), 137.8, 138.4, 147.7, 150.1 (× 2), 164.6 ppm. Analytical data for β-**15**: R_f = 0.15 (ethyl acetate/dichloromethane, 1/1, v/v); $[\alpha]_D^{22}$ 57.6 (c = 0.74, $CHCl_3$); ^{1}H NMR: δ, 3.09 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 3.26-3.37 (2 s, 6H, 2 × OCH_3), 3.41-3.47 (m, 10H, H-2', 3, 5, 6a, 2 × OCH_3), 3.54-3.56 (m, 1H, H-6b), 3.63-3.73 (m, 4H, H-3', 4, 4', 5'), 4.45 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1'), 4.61-4.63 (m, 3H, H-6a', 6b', ½ CH_2Ph), 4.76 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.80 (d, 1H, ^2J = 11.4 Hz, ½ CH_2Ph), 4.83 (d, 1H, ^2J = 10.9 Hz, ½ CH_2Ph), 4.86 (d, 2H, ^2J = 11.1 Hz, ½ CH_2Ph), 4.94 (d, 1H, ^2J = 10.7 Hz, ½ CH_2Ph), 7.19-7.33 (m, 15H, aromatics), 7.44-7.45 (m, 1H, Pico), 7.78 (dd, 1H, *J* = 7.7 Hz, Pico), 8.03 (d, 1H, *J* = 7.9 Hz, Pico), 8.75 (d, 1H, *J* = 4.5 Hz, Pico) ppm; ^{13}C NMR: δ, 29.7, 55.3, 58.9, 59.3, 60.2, 64.1, 69.6, 70.0, 72.6, 75.0, 75.1, 75.9, 77.4, 77.7, 80.6, 81.1, 82.6, 85.2, 97.7, 102.9, 125.2, 126.8, 127.6, 127.7 (× 2), 127.8 (× 3), 127.9, 128.1 (× 2), 128.3 (× 2), 128.4 (× 2), 128.5 (× 2), 136.8, 137.6, 138.2, 147.8, 150.0 (× 2), 164.5 ppm; HR-FAB MS [M+H]+ calcd for $C_{43}H_{51}NNaO_{12}$ 796.3308, found 796.3341.

The synthesis of glycosides

General procedure. Glycosyl donor **1** (0.05 mmol) was dried in high vacuum for 1 h at rt. Molecular sieves (4 Å, 150 mg), freshly distilled 1,2-dichloroethane (10.0 mL), and an aliphatic or aromatic glycosyl acceptor (0.038 mmol) were added and the resulting mixture was stirred under argon for 1 h at rt. The mixture was cooled to -30 °C and DMTST (0.1 mmol) was added. The external cooling was removed, and the reaction mixture was allowed to warm up to rt gradually. Upon completion (see the time listed in Table 2), the solid was filtered off through a

pad of Celite and rinsed successively with dichloromethane. The combined filtrate (~30 mL) was washed with sat. aq. $NaHCO_3$ (10 mL) and water (2 × 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). Diastereomeric ratios were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-β-D-glucopyranoside (16) obtained as a clear syrup from glycosyl donor **1** and freshly distilled ethanol in 86% yield (β-only). Analytical data for **16**: R_f = 0.21 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D^{22}$ 30.4 (c = 0.41, $CHCl_3$); ^{1}H NMR: δ, 1.18 (t, 3H, OCH_2CH_3), 3.51 (dd, 1H, $J_{2,3}$ = 8.1 Hz, H-2), 3.51-3.67 (m, 4H, H-3, 4, 5, ½ CH_2CH_3), 3.83-3.93 if this is symmetrical, needs just the middle ppm value (m, 1H, ½ CH_2CH_3), 4.38 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.49 (dd, 1H, $J_{5,6a}$ = 4.9 Hz, $J_{6a,6b}$ = 10.9 Hz, H-6a), 4.54-4.59 (m, 2H, H-6b, ½ CH_2Ph), 4.66 (d, 1H, ^2J = 11.0 Hz, ½ CH_2Ph), 4.73 (d, 1H, ^2J = 10.9 Hz, ½ CH_2Ph), 4.82 (d, 1H, ^2J = 10.9 Hz, ½ CH_2Ph), 4.90 (d, 1H, ^2J = 10.9 Hz, ½ CH_2Ph), 7.14-7.30 (m, 15H, aromatic), 7.37-7.42 (m, 1H, Pico), 7.74 (dd, 1H, *J* = 7.7 Hz, Pico), 7.98 (d, 1H, *J* = 7.8 Hz, Pico), 8.70 (d, 1H, *J* = 4.0 Hz, Pico) ppm; ^{13}C NMR: δ, 15.3, 64.5, 65.8, 72.8, 74.9, 75.1, 75.9, 77.6, 82.2, 84.7, 103.5, 125.2, 126.9, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5 (× 3), 136.9, 138.4, 150.0 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{35}H_{37}NNaO_7$ 606.2468, found 606.2468.

4-Azidobutyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-β-D-glucopyranoside (17) was obtained as a colorless syrup from glycosyl donor **1** and 4-azido-1-butanol[36,37] in 73% yield (β-only). Analytical data for **17**: R_f = 0.69 (ethyl acetate/toluene, 2/3, v/v); $[\alpha]_D^{22}$ 30.1 (c = 0.39, $CHCl_3$); ^{1}H NMR: δ, 1.62-1.71 (m, 4H, -CH_2CH_2-), 3.2-3.26 (m, 2H, -CH_2N_3), 3.45 (dd, 1H, $J_{2,3}$ = 8.7 Hz, H-2), 3.52-3.55 (m, 1H, ½ -OCH_2CH_2-), 3.62 (dd, 1H, $J_{4,5}$ = 9.1 Hz, H-4), 3.66-3.70 (m, 1H, H-5), 3.70 (dd, 1H, $J_{3,4}$ = 8.9 Hz, H-3), 3.87-3.89 (m, 1H, ½ -OCH_2CH_2-), 4.41 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.56 (dd, 1H, $J_{5,6a}$ = 5.2 Hz, $J_{6a,6b}$ = 11.9 Hz, H-6a), 4.62 (d, 2H, ^2J = 11.1 Hz, H-6b, ½ CH_2Ph), 4.73 (d, 1H, ^2J = 11.1 Hz, ½ CH_2Ph), 4.80 (d, 1H, ^2J = 10.7 Hz, ½ CH_2Ph), 4.89 (d, 1H, ^2J = 10.9 Hz, ½ CH_2Ph), 4.91 (d, 1H, ^2J = 11.1 Hz, ½ CH_2Ph), 4.95 (d, 1H, ^2J = 10.7 Hz, ½ CH_2Ph), 7.22-7.36 (m, 15H, aromatic), 7.45-7.48 (m, 1H, Pico), 7.82 (dd, 1H, *J* = 7.7 Hz, Pico), 8.04 (d, 1H, *J* = 7.7 Hz, Pico), 8.76 (d, 1H, *J* = 4.5 Hz, Pico) ppm; ^{13}C NMR: δ, 25.6, 26.9, 51.1, 64.4, 69.2, 72.9, 74.9, 75.1, 75.9, 77.7, 82.2, 84.7, 103.5, 125.2, 126.9, 127.8 (× 2), 128.0 (× 5), 128.1 (× 2), 128.4 (× 3), 128.5 (× 6), 136.9, 137.6, 138.3, 147.7, 150.0 ppm; HR-FAB MS [M+Na]+ calcd for $C_{37}H_{40}NNaO_7$ 675.2795, found 675.2798.

8-Trityloxyoctyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-β-D-glucopyranoside (18) was obtained as a yellow syrup from glycosyl donor **1** and 8-trityloxy-1-octanol[38] in 56% yield (β-only). Analytical data for **18**: R_f = 0.56 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D^{22}$ 26.2 (c = 0.42, $CHCl_3$); ^{1}H NMR: δ, 1.19-1.32 (m, 8H, 4 x C-CH_2-C), 1.55-1.62 (m, 4H, 2 x C-CH_2-C), 3.00 (t, 2H, CH_2OTr), 3.47 (dd, 1H, $J_{2,3}$ = 8.7 Hz, H-2), 3.47-3.50 (m, 1H, ½ C-1-OCH_2-), 3.62 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4), 3.67-3.70 (m, 1H, H-5), 3.70 (dd, 1H, $J_{3,4}$ = 8.9 Hz, H-3), 3.85-3.89 (m, 1H, ½ C-1-OCH_2-), 4.42 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.56 (dd, 1H, $J_{5,6b}$ = 5.1, $J_{6a,6b}$ = 11.8 Hz, H-6a), 4.61(d, 2H, ^2J = 10.7 Hz, H-6b, ½ CH_2Ph), 4.71 (d, 1H, ^2J = 10.9 Hz, ½ CH_2Ph), 4.80 (d, 1H, ^2J = 10.9 Hz, ½ CH_2Ph), 4.88 (d, 1H, ^2J = 10.9 Hz, ½ CH_2Ph), 4.94 (d, 1H, ^2J = 10.9 Hz, ½ CH_2Ph), 4.95 (d, 1H, ^2J = 10.8 Hz, ½ CH_2Ph), 7.19-7.43 (m, 31H, aromatic), 7.78 (dd, 1H, *J* = 7.7 Hz, Pico), 8.03 (d, 1H, *J* = 7.8 Hz, Pico), 8.74 (d, 1H, *J* = 4.5 Hz, Pico) ppm; ^{13}C NMR: δ, 26.1, 26.2, 29.3, 29.5, 29.7, 30.0, 63.6, 64.5, 70.3, 72.8, 74.8, 75.1, 75.9, 77.7, 82.2, 84.7, 103.6, 125.2, 126.8 (× 3), 126.9, 127.7

(× 8), 127.9, 128.0 (× 2), 128.1 (× 3), 128.4 (× 4), 128.5 (× 2), 128.7 (× 6), 136.9 (× 2), 137.7, 138.3, 144.5 (× 5), 147.8, 150.0 (× 2), 164.7 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{60}H_{63}NNaO_8$ 948.4452, found 948.4409.

Benzyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-β-D-glucopyranoside (19) was obtained as a colorless syrup from glycosyl donor **1** and benzyl alcohol in 57% yield (β-only). Analytical data for **19**: R_f = 0.28 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D^{22}$ 8.3 (c = 0.99, $CHCl_3$); ^{1}H NMR: δ, 3.48 (dd, 1H, $J_{2,3}$ = 8.2 Hz, H-2), 3.58-3.67 (m, 3H, H-3, 4, 5), 4.47 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 4.55-4.58 (m, 3H, H-6a, 6b, ½ CH_2Ph), 4.65 (d, 1H, ^2J = 11.0 Hz, ½ CH_2Ph), 4.72 (d, 1H, ^2J = 10.7 Hz, ½ CH_2Ph), 4.83 (d, 1H, ^2J = 11.2 Hz, ½ CH_2Ph), 4.85-4.91 (m, 3H, 1.5 × CH_2Ph), 7.18-7.26 (m, 15H, aromatic), 7.39-7.42 (m, 1H, Pico), 7.75 (dd, 1H, J = 7.4 Hz, Pico), 8.00 (d, 1H, J = 7.8 Hz, Pico), 8.71 (d, 1H, J = 3.3 Hz, Pico) ppm; ^{13}C NMR: δ, 64.4, 71.1, 72.9, 74.9, 75.0, 75.9, 77.6, 82.2, 84.7, 102.2, 125.2, 126.9, 127.7, 127.8, 127.9 (× 2), 128.0 (× 2), 128.1 (× 4), 128.2 (× 2), 128.4 (× 4), 128.5 (× 4), 136.9, 137.1, 137.6, 138.2, 138.3, 147.8, 150.1, 164.7 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{40}H_{39}NNaO_7$ 668.2625, found 668.2632.

2,2,2-Trichloroethyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-glucopyranoside (20) was obtained as a clear syrup from glycosyl donor **1** and 2,2,2-trichloroethanol in 77% yield (α/β = 1/11.4). Analytical data for **20**: R_f = 0.31 (ethyl acetate/hexane, 2/3, v/v); selected ^{1}H NMR data for β-**20**: δ, 3.57-3.77 (m, 4H, H-2, 3, 4, 5), 4.17 (d, 1H, ^2J = 11.9 Hz, ½ CH_2CCl$_3$), 4.43 (d, 1H, ^2J = 11.9 Hz, ½ CH_2CCl$_3$), 4.60-4.83 (m, 6H, H-1, 6a, 6b, 3 × ½ CH_2Ph,), 4.89 (d, 1H, ^2J = 10.8 Hz, ½ CH_2Ph), 4.99 (d, 1H, ^2J = 10.2 Hz, ½ CH_2Ph), 5.11 (d, 1H, ^2J = 10.6 Hz, ½ CH_2Ph), 7.23-7.40 (m, 15H, aromatic), 7.47-7.51 (m, 1H, Pico), 7.84 (dd, 1H, J = 7.7 Hz, Pico), 8.04 (d, 1H, J = 7.7 Hz, Pico), 8.77-8.79 (m, 1H, Pico) ppm; selected ^{13}C NMR data for β-**20**: δ, 62.9, 63.7, 72.7,74.6, 74.7, 75.5, 76.8, 80.1, 81.3, 83.9, 95.9, 103.4, 124.8, 126.6, 127.4 (× 2), 127.5 (× 3), 127.6, 127.7 (× 2), 128.0 (× 8), 136.5, 137.0, 137.5, 137.8, 147.2, 149.61, 164.2 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{35}H_{35}Cl_3NO_7$ 686.1478, found 686.1450.

Isopropyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-glucopyranoside (21) was obtained as a clear syrup from glycosyl donor **1** and freshly distilled isopropanol in 77% yield (α/β = 1/3.6). Analytical data for **21**: R_f = 0.60 (ethyl acetate/toluene, 2/3, v/v); selected ^{1}H NMR data for α-**21**: δ, 1.15-1.16 (m, 6H, CH(CH_3)$_2$), 3.95 (sep, 1H, CH(CH$_3$)$_2$), 4.04-4.08 (m, 2H, H-3, 5), 5.02 (d, 1H, ^2J = 10.5 Hz, ½ CH_2Ph), 7.99 (d, 1H, J = 7.8 Hz, Pico) ppm; selected ^{1}H NMR data for β-**21**: δ, 1.21-1.22 (m, 6H, CH(CH_3)$_2$), 3.45 (dd, 1H, $J_{2,3}$ = 8.9 Hz, H-2), 3.95 (sep, 1H, CH(CH$_3$)$_2$), 4.49 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.55 (dd, 1H, $J_{5,6a}$ = 5.4 Hz, $J_{6a,6b}$ = 11.6 Hz, H-6a), 4.70 (d, 1H, ^2J = 10.8 Hz, ½ CH_2Ph), 4.79 (d, 1H, ^2J = 10.6 Hz, ½ CH_2Ph), 4.88 (d, 1H, ^2J = 10.8 Hz, ½ CH_2Ph), 8.04 (d, 1H, J = 5.8 Hz, Pico) ppm; selected ^{13}C NMR data for the sugar region of α/β-**21**: δ, 64.6, 68.6, 69.4, 72.8, 72.9, 73.2, 74.9, 75.0, 75.2, 75.9, 77.7, 77.8, 80.0, 82.1, 82.2, 84.8, 94.7, 102.3 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{36}H_{39}NNaO_7$ 597.2727, found 620.2625.

Cyclohexyl 2,3,4-Tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-glucopyranoside (22) was obtained as a clear syrup from glycosyl donor **1** and cyclohexanol in 63% yield (α/β = 1/2.0). Analytical data for **22**: R_f = 0.45 (ethyl acetate/hexane, 2/3, v/v); selected ^{1}H NMR data for α-**22**: δ, 4.06 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 4.12 (m, 1H, H-5), 8.01 (d, 1H, J = 7.7 Hz, Pico) ppm; selected ^{1}H NMR data for β-**22**: δ, 3.48 (dd, 1H, $J_{2,3}$ = 8.5 Hz, H-2), 3.68-3.71 (m, 2H, H-3, 5), 4.54 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.71 (d, 1H, ^2J = 10.9 Hz, ½ CH_2Ph), 4.79 (d, 1H, ^2J = 10.8 Hz, ½ CH_2Ph), 4.88 (d,

1H, ^{2}J = 10.9 Hz, ½ CH_2Ph), 8.05 (d, 1H, J = 7.6 Hz, Pico) ppm; selected ^{13}C NMR data for the sugar region of α/β-**22**: δ, 64.4, 64.6, 68.7, 72.7, 73.0, 74.9, 75.0, 75.2, 75.9, 77.8, 77.9, 78.4, 80.0, 82.1, 82.2, 84.8, 94.6, 102.1 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{39}H_{43}NNaO_7$ 660.2937, found 660.2946.

***t*-Butyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-glucopyranoside (23)** was obtained as a clear syrup from glycosyl donor **1** and *t*-butanol in 78% yield (α/β = 1/1.1). Analytical data for **23**: R_f = 0.31 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D^{22}$ 70.1 (c = 0.96, $CHCl_3$); selected ^{1}H NMR data for α-**23**: δ, 3.61 (dd, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 4.07 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 4.20-4.22 (m, 1H, H-5), 5.13 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 8.01 (d, 1H, J = 7.8 Hz, Pico) ppm; selected ^{1}H NMR data for β-**23**: δ, 3.45 (dd, 1H, $J_{2,3}$ = 8.5 Hz, H-2), 8.03 (d, 1H, J = 7.7 Hz, Pico) ppm; selected ^{13}C NMR data for the sugar region of α/β-**23**: δ, 64.6, 64.8, 68.3, 72.7, 73.1, 75.0, 75.8, 78.1 (× 2), 82.0, 82.3, 85.1, 91.3, 97.8 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{37}H_{41}NNaO_7$ 634.2781, found 634.2771.

1-Adamantyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-glucopyranoside (24) was obtained as a clear syrup from glycosyl donor **1** and 1-adamantanol in 56% yield (α/β = 1/10). Analytical data for **24**: R_f = 0.69 (ethyl acetate/toluene, 2/3, v/v); selected ^{1}H NMR data for α-**24**: δ, 4.07 (dd, 1H, $J_{3,4}$ = 9.1 Hz, H-3), 4.24-4.27 (m, 1H, H-5), 5.24 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 8.02 (d, 1H, J = 7.8 Hz, Pico) ppm; selected ^{1}H NMR data for β-**24**: δ, 3.45 (dd, 1H, $J_{2,3}$ = 8.8 Hz, H-2), 3.51 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4), 3.69 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 3.69-3.73 (m, 1H, H-5), 4.60 (d, 1H, ^{2}J = 11.0 Hz, ½ CH_2Ph), 4.77 (d, 1H, ^{2}J = 10.9 Hz, ½ CH_2Ph), 4.88 (d, 1H, ^{2}J = 11.0 Hz, ½ CH_2Ph), 4.93 (d, 1H, ^{2}J = 10.7 Hz, ½ CH_2Ph), 4.99 (d, 1H, ^{2}J = 10.9 Hz, ½ CH_2Ph), 8.05 (d, 1H, J = 7.8 Hz, Pico) ppm; selected ^{13}C NMR data for α-**24**: δ, 64.8, 72.6, 74.9, 75.4, 75.9, 78.2, 82.2, 85.1, 96.2 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{43}H_{47}NNaO_7$ 712.3250, found 712.3265.

Phenyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-glucopyranoside (25) was obtained as a clear syrup from glycosyl donor **1** and phenol in 81% yield (α/β = 1/4.7). Analytical data for **25**: R_f = 0.36 (ethyl acetate/hexane, 2/3, v/v); selected ^{1}H NMR data for β-**25**: δ, 4.10-4.15 (m, 1H, H-5), 4.27 (dd, 1H, $J_{3,4}$ = 9.8 Hz, H-3), 5.45 (d, 1H, $J_{1,2}$ = 2.8 Hz, H-1), 8.75 (d, 1H, J = 5.0 Hz, Pico) ppm; selected ^{13}C NMR data for the sugar region of α/β-**25**: δ, 64.4, 73.1, 75.1, 76.0, 77.3, 77.7, 82.0, 84.7, 95.0, 101.6 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{39}H_{37}NO_7Na$ 654.2467, found 654.2479.

***p*-Methoxyphenyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-glucopyranoside (26)** was obtained as a clear oil from glycosyl donor **1** and *p*-methoxyphenol in 63% yield (α/β = 1/5.5). Analytical data for **26**: R_f = 0.24 (ethyl acetate/hexane, 2/3, v/v); selected ^{1}H NMR data for α-**26**: δ, 4.17 (m, 1H, H-5), 4.25 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 5.34 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 8.75 (d, 1H, J = 4.5 Hz, Pico) ppm; selected ^{1}H NMR data for β-**26**: δ, 4.98 (d, 1H, ^{2}J = 10.8 Hz, ½ CH_2Ph), 5.07 (d, 1H, ^{2}J = 10.8 Hz, ½ CH_2Ph), 7.82 (dd, 1H, J = 7.4 Hz, Pico), 8.03 (d, 1H, J = 7.8 Hz, Pico), 8.80 (d, 1H, J = 4.4 Hz, Pico) ppm; ^{13}C NMR data for the anomeric region of α/β-**26**: δ, 95.9, 102.7 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{40}H_{39}NO_8Na$ 684.2573, found 684.2576.

***p*-Nitrophenyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-glucopyranoside (27)** was obtained as a clear syrup from glycosyl donor **1**[7] and *p*-nitrophenol in 52% yield (α/β = 1/1.2). Analytical data for **27**: R_f = 0.30 (ethyl acetate/hexane, 2/3, v/v); selected ^{1}H NMR data for α-**27**: δ, 3.76 (dd, 1H,

$J_{2,3}$ = 9.4 Hz, H-2), 4.22 (dd, 1H, $J_{3,4}$ = 9.1 Hz, H-3), 5.40 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 8.71 (d, 1H, J = 7.3 Hz, Pico) ppm; selected ^{1}H NMR data for β-**27**: δ, 4.43 (dd, 1H, ^{2}J = 11.7 Hz, H-6a), 5.07 (d, 1H, $J_{1,2}$ = 10.6 Hz, H-1), 8.83 (d, 1H, J = 7.3 Hz, Pico) ppm; selected ^{13}C NMR data for the sugar region of α/β-**27**: δ, 63.8, 64.1, 70.2, 73.5, 75.2, 75.3, 76.0, 76.2, 77.3, 79.6, 79.6, 81.6, 82.0, 84.6, 94.9, 100.4, ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{39}H_{36}N_2NaO_9$ 699.2319, found 699.2287.

ASSOCIATED CONTENT

Supporting Information. Additional experimental details, ^{1}H and ^{13}C NMR spectra for all new compounds have been supplied as the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org."

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Author Contributions

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Highlights

- The glycosylations of the HAD-capable glycosyl donor showed a great variation of the results depending on the nature of glycosyl acceptors used
- Primary acceptors, both carbohydrate and aliphatic alcohols afforded the glycosylation products with complete β-selectivity.
- Both steric and electronic factors may have a strong effect on the stereoselectivity of HAD glycosylations for the synthesis of β-glucosides