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Effect of Remote Picolinyl and Picoloyl Substituents on the Stereoselectivity of Chemical Glycosylation

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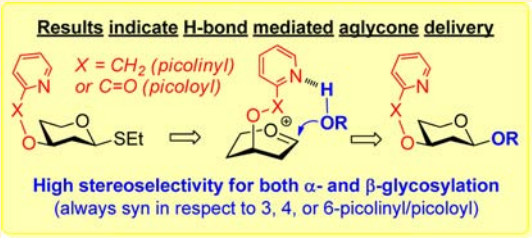
Supporting Information

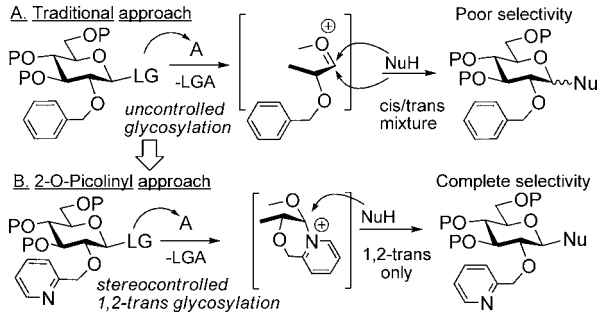
ABSTRACT: *O*-Picolinyl and *O*-picoloyl groups at remote positions (C-3, C-4, and C-6) can mediate glycosylation reactions by providing high or even complete facial selectivity for the attack of the glycosyl acceptor. The set of data presented herein offers a strong evidence of the intermolecular H-bond tethering between the glycosyl donor and glycosyl acceptor counterparts while providing a practical new methodology for the synthesis of either 1,2-*cis* or 1,2-*trans* linkages. Challenging glycosidic linkages including α-gluco, β-manno, and β-rhamno have seen obtained with high or complete stereocontrol.



INTRODUCTION

Complex carbohydrates consist of monosaccharide units, which are connected via *O*-glycosidic linkages into elaborate oligosaccharide networks.[1,2] Chemically, the *O*-glycosidic linkage is formed by a glycosylation reaction, which in the most general sense is a promoter/activator (A)-assisted monomolecular nucleophilic displacement of the leaving group (LG) of a glycosyl donor with a hydroxyl moiety of a glycosyl acceptor (NuH, Scheme 1).[3,4] Other functional groups

Scheme 1. Traditional Glycoside Synthesis Using Conventional 2-*O*-Benzyl Protection versus 2-*O*-Picolinyl-Assisted 1,2-*trans*-Glycosylation



on both glycosyl donor and acceptor are temporarily masked with protecting groups (P). Upon the leaving group departure, the flattened oxacarbenium ion is formed, which often leads to anomeric mixtures (Scheme 1A).[5] Therefore, particular care has to be taken with regards to the stereoselectivity of glycosylation.

The aim of stereocontrolling of glycosylation has been approached in a variety of ways, and the participation of a neighboring acyl-type group has been widely used to obtain 1,2-*trans* glycosides.[6] Recently, our group has expanded methods available for 1,2-*trans* glycosylation by developing the neighboring 2-*O*-picolinyl (2-pyridylmethyl, Pic) participating group.[7,8] It was demonstrated that 2-*O*-picolinyl-assisted glycosylations proceed via a formal six-membered ring intermediate leading to the formation of 1,2-*trans* glycosides with complete stereocontrol (Scheme 1B). Other unconventional methods for participation-assisted or stereodirected glycosylation have also been recently introduced.[9−15]

RESULTS AND DISCUSSION

Upon discovering complete 1,2-*trans* stereoselectivity obtained via the 2-*O*-picolinyl participation, we decided to broaden the scope of this method and investigate whether a similar effect can be achieved with remote picolinyl groups. Herein, we report the study of a series of novel glycosyl donors equipped with picolinyl and picoloyl (2-pyridinecarbonyl, Pico) groups at remote positions (C-3, C-4, and C-6). The major emphasis of this study is to investigate the effect that these remote substituents may have on the stereoselectivity of glycosylation. As shown in Chart 1, our original expectation was to obtain anti substitution due to the anticipated participation of the remote Pic/Pico moieties.

As the starting comparison point, known glycosyl donors per-*O*-benzylated and 2-*O*-picolinyl-substituted thioglycosides, **1a**[16] and **1b**,[8] respectively, were coupled with glycosyl acceptor **2**[17] under reaction conditions that became standard for 2-*O*-picolinyl glycosyl donors: dimethyl(methylthio)sulfonium triflate (DMTST),[18] 1,2-dichloroethane, −30 → 42 °C.[8] Glycosidation of donor **1a** was nonstereoselective, and the corresponding disaccharide **3a**[19] was isolated in 92% yield (α/β = 1/1.9, entry 1, Table 1). As expected, glycosidation of 2-*O*-picolinyl donor **1b** provided disaccharide **3b**[8] with anticipated

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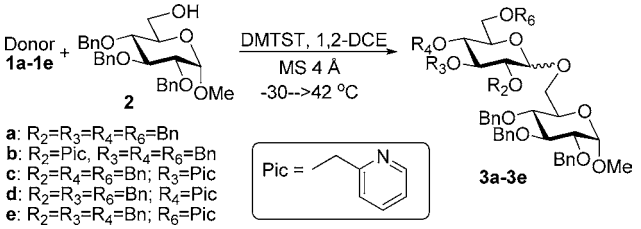
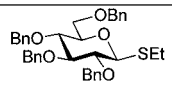
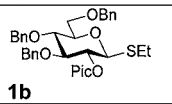
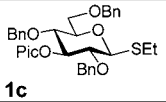
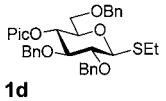
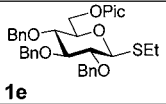
Chart 1. Expected Versus Detected Stereoselectivity that was Found to be Always Syn with Respect to the Remote Picolinyl Group

Table 1. Comparative Investigation of Glycosyl Donors 1a–1e



Entry	Donor	Time	Yield	Product	α/β Ratio
1	 **1a**	15 min	92%	**3a**	1 / 1.9
2	 **1b**	20 h	83%	**3b**	β only
3	 **1c**	4 h	84%	**3c**	1 / 5.8
4	 **1d**	4 h	88%	**3d**	1.2 / 1
5	 **1e**	5 h	93%	**3e**	1 / 2.4

complete β-stereoselectivity in 83% yield (entry 2). Rather unexpectedly, 3-*O*-picolinyl thioglycoside **1c** gave disaccharide **3c** in a relatively high β-selectivity (84%, α/β = 1/5.8, entry 3). In further probing positional isomers 4-*O*-picolinyl donor **1d** and 6-*O*-picolinyl donor **1e** (entries 4 and 5), we noticed that in all cases the product was preferentially forming in the syn orientation to that of the picolinyl substituent rather than anti as it was originally anticipated (Chart 1). Thus, 4-*O*-picolinyl donor **1d** (the substituent at C-4 is projecting below the ring) showed slight preference toward the formation of α-**3d** (α/β = 1.2/1, 88%, entry 4). Conversely, glycosidation of 6-*O*-picolinyl donor **1e** (substituent projecting above the ring) gave disaccharide **3e** with some β-stereoselectivity (α/β = 1/2.4, 93%, entry 4).

Clearly, the level of stereoselectivity observed in these preliminary experiments was not exceptionally high. Nevertheless, these results suggest that the nature of the remote picolinyl effect is perhaps of a more complex origin than the anticipated direct participation. It is possible that the remote picolinyl groups affect glycosylation reactions via a mode different from that observed for the neighboring 2-*O*-picolinyl group (complete 1,2-*trans* selectivity, anti with respect to picolinyl, via the direct participation).[7,8] Intrigued by the unexpected preliminary results, we began the study that would improve our understanding of the mode by which the remote picolinyl substituents affect both 1,2-*cis* and 1,2-*trans* stereoselectivity of glycosylation.

One explanation for the syn stereoselectivity observed in all preliminary glycosylations is that instead of the anticipated direct participation at the anomeric center, the remote picolinyl moiety acts as a platform for a hydrogen-bond-mediated aglycone delivery (Chart 2). If the remote picolinyl group

Chart 2. Possible Rationalization for the Stereoselectivity Observed

indeed acts as the H-bond acceptor for NuH, the benefit of such an action would be 2-fold. First, the hydrogen-bond tethering would provide enhanced (if not complete) facial selectivity by delivering the glycosyl acceptor from the same face (syn) with respect to the H-bond acceptor (consistent with results described in Table 1). Second, picolinyl moiety would accelerate the entire reaction by positioning both reaction components in a close proximity to each other and also may facilitate deprotonation, the last essential step of the glycosylation of neutral aglycones.[3] It should be noted that intramolecular hydrogen bonding between picolinyl group and the neighboring acetamido group has been reported by Crich.[20]

To test this hypothesis, elucidate the reaction pathway, and, consequently, improve the stereoselectivity of glycosylations, we began a systematic study. Table 2 summarizes our major findings, whereas the complete set of data is available as a part of the Supporting Information. Having assumed that the orientation of the anomeric substituent would be significant for the proposed H-bond-mediated aglycone delivery to take place, we investigated donor α-**1c**. Indeed, nearly a 3-fold enhancement of β-selectivity (α/β = 1/14.5, entry 1, Table 2) was observed in comparison to that obtained with β-**1c** (α/β = 1/5.8, entry 3, Table 1). Even more dramatically, a 5-fold enhancement of β-selectivity was obtained with 6-*O*-picolinyl donor α-**1e** (α/β = 1/11.8, entry 2, Table 2) in comparison to that obtained with β-**1e** (α/β = 1/2.4, entry 5, Table 1). For comparison, the use of α- or β-**1a** showed practically no difference in stereoselectivity obtained (see the Supporting Information).

We also hypothesized that if the H-bonding between the donor and acceptor counterparts indeed was taking place in the reaction medium, the effect of dilution would help to enhance the stereoselectivity due to decreased probability of the nonstereoselective attack of unbound nucleophiles. To test this hypothesis, we performed a glycosylation reaction between donor **1c** and acceptor **2** at a 10-fold dilution with 1,2-dichloroethane, 5 mM donor concentration versus 50 mM in standard experiments. This coupling was even faster than that of the standard concentration (3 h vs 4 h), and a 3-fold enhanced stereoselectivity was obtained under high dilution

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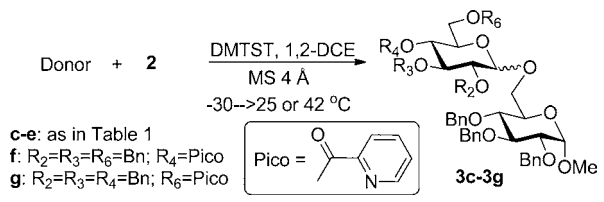
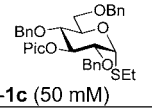
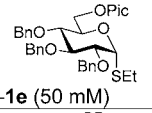
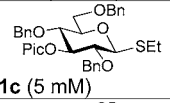
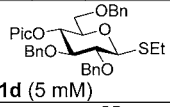
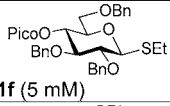
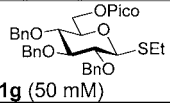
Table 2. Refining the Stereoselectivity Obtained with Picolinyl and Picoloyl-Protected Donors 1c−1g



Entry	Donor (conc.)	Time	Yield	Product	α/β Ratio
1	 α-**1c** (50 mM)	3.5 h	89%	**3c**	1 / 14.5
2	 α-**1e** (50 mM)	4 h	71%	**3e**	1 / 11.8
3	 **1c** (5 mM)	3 h	85%	**3c**	1 / 15.6
4	 **1d** (5 mM)	5 h	86%	**3d**	5.3 / 1
5	 **1f** (5 mM)	4 h	73%	**3f**	>25 / 1
6	 **1g** (50 mM)	1.5 h	96%	**3g**	>1 / 25

conditions (α/β = 1/5.8, entry 3, Table 1 vs α/β = 1/15.6, entry 3, Table 2). Interestingly, applying much higher dilution, up to 50-fold (1 mM), even faster glycosidation of **1c** (2.5 h) was observed, whereas glycosidation of donor **1a** was practically ineffective. In this context, Yu and co-workers have recently reported a strong concentration effect on *N*-glycosylation, wherein it was attributed to the long-range participation effect.[21] Kononov and co-workers also observed a very interesting correlation between concentration and stereoselectivity.[22] We rationalize this minor effect of high dilution on the rate of glycosidation of **1c** by the existence of the preassembled donor−acceptor pairs. In the absence of the H-bond tethering, like in conventional glycosylations, glycosyl donor and acceptor counterparts are less reactive because they are separated by solvent molecules.

It should be noted that, although the comparison of all reactions was performed at standard temperature of −30 → 42 °C, experiments at lower or ambient temperatures showed a very similar trend and very minor effect on stereoselectivity. Conversely, we observed a significant loss of stereoselectivity if the reactions were performed at 50 °C from the beginning (see the Supporting Information). A result of particular interest was obtained in the high dilution experiments wherein reaction at 50 °C was significantly less stereoselective and much slower (incomplete at 18 h) than those at −30 °C or ambient temperature (3 h).

At this stage, we also incorporated a series of glycosyl donors equipped with *O*-picoloyl (2-pyridinecarbonyl, Pico) substituent.[23,24] In general, these glycosyl donors showed comparable stereoselectivity and dilution effect trend to that observed with the picolinyl substituent. On one occasion, however, a significant enhancement in 1,2-*cis* stereoselectivity was observed when the picoloyl substituent was used instead of picolinyl at the C-4 position. While reactions with 4-*O*-picolinyl donor **1d** performed at high dilution gave unexceptional stereoselectivity of α/β = 5.3/1 (entry 4, Table 2), 4-*O*-picoloyl donor **1f** led to disaccharide **3f** with complete α-stereoselectivity (entry 5). To elucidate whether or not this enhancement of stereoselectivity is due to an electron-withdrawing (or a remote participating) effect of the carbonyl group, we tested the corresponding 4-*O*-benzoylated donor. This glycosylation was modestly β-stereoselective, indicating that the carbonyl group effect by itself is of very minor, if any, influence. In this context, nonstereoselective reactions were observed with glycosyl donors equipped with 3-pyridylmethyl (*m*-picolinyl) and 4-pyridylmethyl (*p*-picolinyl) groups at C-4 (see the Supporting Information for details).

Further study of the 6-*O*-picoloyl substituent in donor **1g** showed excellent 1,2-*trans* stereoselectivity, and the resulting disaccharide **3g** was obtained as pure β-linked diastereomer (entry 6). In our opinion, the set of data summarized in Table 2 provides a strong evidence of the syn delivery effect of picolinyl and picoloyl substituents while offering a practical new methodology for highly stereoselective synthesis of both 1,2-*trans* and 1,2-*cis* linked disaccharides. Although picoloyl substituent is a weaker H-bond acceptor than its picolinyl counterpart, very comparable results have been observed with these two groups. In our opinion, the strength of the H-bonding is not the deciding factor for excellent stereoselectivity. It is possible that the key importance of the H-bonded acceptor is to provide correct geometry for the aglycone delivery. Arguably, preferential *trans*-ester conformation of picoloyl group may offer the beneficial orientation for the H-bonding-mediated delivery. Indeed, glycosidation of donors equipped with *m*-picoloyl (3-pyridinecarbonyl) and *p*-picoloyl (4-pyridinecarbonyl) was sluggish and nonstereoselective.

Encouraged by these results, we decided to expand the scope of the H-bond-mediated stereoselective glycosylations to a broader range of substrates and investigated a variety of sugar series, common galactose, mannose, and rhamnose, as well as secondary glycosyl acceptors. The abbreviated results with the emphasis on the synthesis of traditionally challenging 1,2-*cis* linkages[25,26] are listed in Table 3 (see the Supporting Information for additional experiments). Complete β-stereoselectivity obtained in galactosylation with 4-*O*-picolinyl/picoloyl glycosyl donors (**1i**/**1j**) is also noteworthy (entry 1, Table 3). This directing effect represents a dramatic change in comparison to the nonstereoselective glycosidation of per-*O*-benzylated galactosyl donor **1h**. Most remarkably, the high β-stereoselectivity obtained with 4-*O*-picoloyl ester differs drastically from that reported by Boons and co-workers in studying a series of 4-*O*-acylated galactosyl donors wherein high α-selectivity was achieved.[27] This result is also very indicative of the existence of the H-bond-mediated glycosylation. Although not particularly high, a respectable β-stereoselectivity (α/β = 1/9.5) was recorded for β-mannosylation with **1k** in the presence of NIS/TfOH (entry 2). We also obtained complete β-stereoselectivity upon rhamnosylation with 3-*O*-picoloyl donor **1l** (entry 3). Secondary glycosyl acceptors **4**,[28] **6**,[29] and **8**[30] were glycosylated with glucosyl donor **1f** equipped with 4-*O*-picoloyl substituent to provide consistently high α-stereoselectivity, particularly at a 10-fold dilution (5 mM, entries 4−6).

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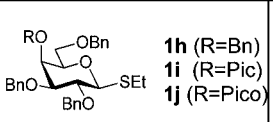
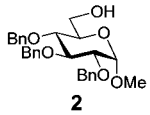
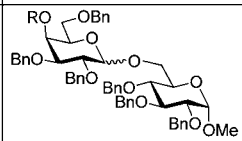
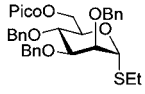
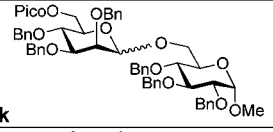
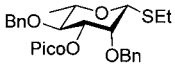
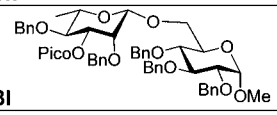
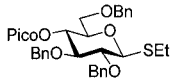
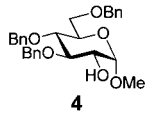
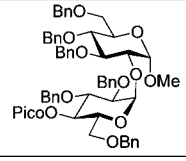
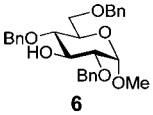
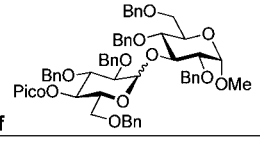
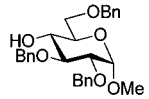
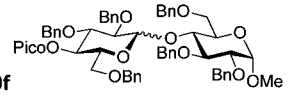
Table 3. Broadening the Scope of the Picolinyl/Picoloyl-Assisted Stereoselective Glycosylation[a]

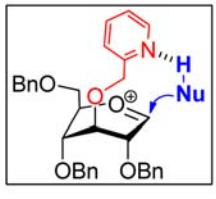
Entry	Donor	Acceptor, concentration	Time	Yield	Product	Ratio α/β
1	 **1h** (R=Bn) **1i** (R=Pic) **1j** (R=Pico)	 **2** 50 mM 5 mM 5 mM	45 min 3 h 1 h	87% 83% 95%	 **1h** (R=Bn) **1i** (R=Pic) **1j** (R=Pico)	1 / 1.0 >1 / 25 >1 / 25
2	 **1k**	**2** 5 mM 5 mM	4 h 2.5 h[b]	86% 87%	 **3k**	1 / 4.5 1 / 9.5
3	 **1l**	**2** 50 mM	15 min	94%	 **3l**	>1 / 25
4	 **1f**	 **4** 50 mM	5 h	93%	 **5f**	>25 / 1
5	**1f**	 **6** 50 mM 5 mM	6 h 16 h	87% 81%	 **7f**	10 / 1 >25 / 1
6	**1f**	 **8** 50 mM 5 mM	16 h 24h	94% 81%	 **9f**	12 / 1 21 / 1

[a]Unless noted otherwise, the reactions were performed under standard conditions: DMTST, 1,2-dichloroethane, −30 → 25 °C. [b]Performed in the presence of NIS/TfOH.

Encouraged by these results, we performed further study to test the hypothesis of the intermolecular H-bonding and its key involvement into the glycosylation process. The outcome of the following experiments, along with previously discussed temperature effect, is summarized in Chart 3 (see the Supporting Information for complete details). First, consistent with the documented phenomenon that hydrogen bonding can be disturbed by the addition of DMSO,[31] reactions in the presence of DMSO were much less stereoselective with both α- and β-directing glycosyl donors (see the Supporting Information for details). The contribution of glycosyl sulfoxonium ion intermediates that could be forming in the presence of DMSO[32] remains to be investigated. However, in our opinion, simple formation of other activated species may not have a direct effect on the stereoselectivity of H-bond-mediated glycosylation.

Chart 3. A Survey of Effects That Reduce Stereoselectivity by Disrupting the H-Bonding

Standard glycosidation of donor **1c**: α/β = 1/15.6 (5 mM)



Modification	α/β
heat at 50 °C	1/7.1
added DMSO (1 equiv.)	1/4.9
excess DMTST (6 equiv.)	1/9.8
added TfOH (1 equiv.)	1/8.1
replace H with TMS	1/2.0
4,6-*O*-benzylidene	1/2.1

Decrease of selectivity was also detected by using m- and p-picolinyl/picoloyl groups, donor preactivation or by concomitant addition of acceptor and promoter

Second, a significant loss of stereoselectivity was observed when reactions were performed in the presence of a large excess of DMTST (6 equiv to donor). Also, the addition of TfOH (1 equiv with respect to the donor) along with DMTST (2 equiv) significantly decreased the stereoselectivity. We believe that the effect of excess electrophilic reagents in the reaction medium could be due to blocking the H-bond acceptor (pyridyl nitrogen) with SMe^+ released from DMTST or by protonation. This effect was observed under both 50 and 5 mM reaction conditions.

Third, the use of the TMS-protected counterpart of glycosyl acceptor **2** gave very low stereoselectivity for both *α*- and *β*-directing glycosyl donors. This result clearly supports the essentiality of the acceptor proton and the presence of hydrogen bonding for the enhanced *syn* selectivity. It is possible that these reactions still proceed via sequential TMS-deprotection followed by glycosylation, but the generated acceptor has no time to establish H-bonding with the donor. Our further study showed that it is essential to premix the donor and acceptor counterparts (1 h standard time) before adding DMTST. Alternatively, if the donor is preactivated before the addition of the acceptor or acceptor and DMTST are added concomitantly, no stereoselectivity is observed.

Fourth, being inspired by previous studies by Vasella and, more recently, Crich, we have determined the reduced temperature coefficient for equimolar **2**/**1d** and **2**/**1f** combinations in $CDCl_3$ to be −3.1 and −0.9 ppb K^{-1},

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respectively, at the linear regression region of the $\Delta\delta/\Delta T$ plots for δ_{OH} at 50 mM concentration.[20,33,34] These data provide an indication that the H-bonding may exist between glycosyl acceptor and donor. We have also observed a linear dependence of δ_{OH} in ^{1}H NMR spectra of **2** recorded at different concentrations for equimolar acceptor−donor pairs in $CDCl_3$ at room temperature (see the Supporting Information). The linear dependence obtained for both 4-picolinyl donor **1d** and 4-*O*-picoloyl donor **1f** is very indicative of the intermolecular hydrogen bonding, as previously shown by Vasella[33,35] and Crich[20] for substituted 2-aminosugars.

Last, we found that the stereoselectivity diminishes dramatically in case of glycosyl donors protected with 4,6-*O*-benzylidene (see the Supporting Information). It is possible that the induced rigidity of the pyranose ring prevents conformational changes necessary to form the all-axial oxacarbenium intermediate.[5,36−38] This result indicates that the conformational flexibility of the pyranose ring might be essential to ensure efficient H-bond-mediated aglycone delivery.

CONCLUSIONS

We discovered that remote *O*-picolinyl and *O*-picoloyl groups can mediate glycosylation reactions by providing high or even complete facial selectivity for the attack of the glycosyl acceptor. In our opinion, the set of data presented herein provides a strong evidence for the hydrogen bonding between glycosyl donor and acceptor[39−42] while providing a practical new methodology for stereoselective glycosylation. The applicability of this approach was demonstrated and found to be consistently effective for the synthesis of various glycosides including α- and β-glucosides, β-galactosides, β-mannosides, and β-rhamnosides and works well with both primary and secondary glycosyl acceptors. Further application of this new stereoselective glycosylation reaction to other targets and to the synthesis of oligosaccharides along with further investigation of the mechanism and the kinetic profile of this reaction are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Procedure for Glycosylation in the Presence of DMTST. A mixture of a glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in $(ClCH_2)_2$ (2.6 mL, 50 mM or 26 mL, 5 mM) was stirred under argon for 1 h. The mixture was cooled to −30 °C, DMTST[18] (0.26 mmol) was added, and the resulting mixture was allowed to warm to room temperature over a period of 1 h. The external heating was then applied, and the reaction mixture was stirred at 42 °C for the time specified in tables. Alternative procedure involved stirring at room temperature or as indicated in tables. Upon completion, Et_3N (0.3 mL) was added, and the resulting mixture was stirred for 30 min. The mixture was then diluted with CH_2Cl_2 (10 mL, 50 mM reaction only), the solid was filtered off, and the residue was washed sucessively with CH_2Cl_2. The combined filtrate (∼30−40 mL) was washed with 20% aqueous $NaHCO_3$ (10 mL) and water (3 × 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−hexane gradient elution). Anomeric ratios (or anomeric purity) were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

ASSOCIATED CONTENT

Supporting Information

Additional experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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