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Letter

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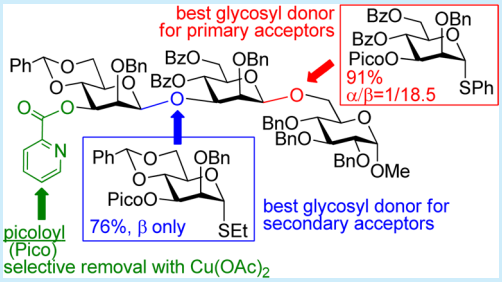
Hydrogen-Bond-Mediated Aglycone Delivery: Focus on β-Mannosylation

Salvatore G. Pistorio, Jagodige P. Yasomanee, and Alexei V. Demchenko*

Department of Chemistry and Biochemistry, University of Missouri—St. Louis, One University Boulevard, St. Louis, Missouri 63121, United States

Supporting Information

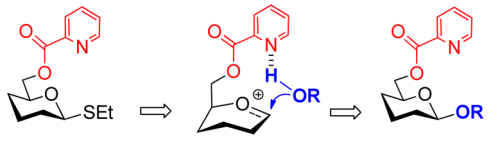
ABSTRACT: *O*-Picoloyl groups at remote positions can mediate the course of glycosylation reactions by providing high facial selectivity for the H-bond-mediated attack of the glycosyl acceptor. A new practical method for the stereoselective synthesis of β-mannosides at ambient temperature is presented.



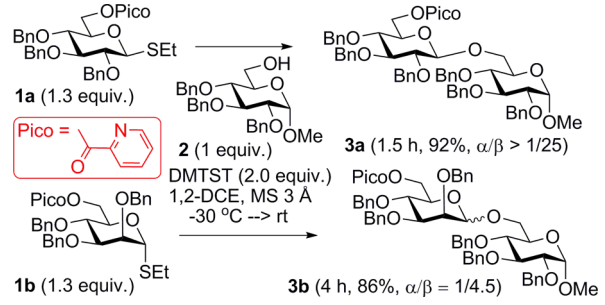
The vast majority of complex carbohydrates consist of monosaccharide residues connected via *O*-glycosidic linkages.[1,2] Uncontrolled chemical *O*-glycosylations often lead to low yields and/or mixtures of anomers. The goal of stereocontrolling glycosylation has been a major inspiration and driving force of progress in the field. The synthesis of 1,2-*cis* glycosides, which cannot be assisted by conventional neighboring acyl group participation,[3] is more challenging. Many factors affect the stereoselectivity of glycosylation, but none can guarantee complete 1,2-*cis* stereoselectivity.[4] Therefore, all individual factors and combinations thereof are typically considered when glycosylations are attempted.

Among a variety of unconventional protecting groups that have been introduced in recent years to control the stereoselectivity of glycosylations,[5−7] the neighboring 2-*O*-picolinyl group formally participates in glycosylation and provides 1,2-*trans* products stereoselectively as a result of the *anti* attack by the glycosyl acceptor.[8,9] Remarkably, when placed at remote positions (C-3, C-4, and C-6), picolinyl and similar picoloyl substituents also provide high selectivity but act via a different mode. All glycosylations proceed with stereoselectivity consistent with *syn* attack because the remote picolinyl moiety acts as an H-bond acceptor for the incoming nucleophile (Scheme 1).[10] Therefore, since this remote protecting group assistance is not directly correlated with the orientation of the substituent at C-2, this approach should in principle be suitable for the assisted synthesis of either 1,2-*cis*- or 1,2-*trans*-linked glycosides.

Scheme 1. 6-*O*-Picoloyl-Assisted β-D-Glycosylation



Scheme 2. Synthesis of β-Glucosides vs β-Mannosides



For instance, as illustrated in Scheme 2, glycosidation of the 6-picoloyl (Pico) glucosyl donor **1a** with acceptor **2** in the presence of dimethyl(methylthio)sulfonium triflate (DMTST)[11] afforded disaccharide **3a** in 92% yield and complete β-selectivity.[10] A similar DMTST-promoted glycosylation with mannosyl donor **1b** was significantly less stereoselective (α/β = 1/4.5) and afforded the corresponding disaccharide **3b** in 86% yield.[10]

Further screening of the reaction conditions showed that the NIS/TfOH promoter system provides a better environment for β-mannosylation with donor **1b**. Under these reaction conditions, disaccharide **3b** was obtained in 87% yield and enhanced β-selectivity (α/β = 1/9.5, Table 1, entry 1).[10] The synthesis of β-mannosides has been regarded as one of the greatest challenges of glycochemistry.[12,13] Some promising methods have been established by Crich[14−20] and others,[21−23] but these are typically limited to specific types of glycosyl donor and require extreme reaction conditions or indirect methods[24−26] to ensure that reactions proceed highly stereoselectively. Building upon promising preliminary results, herein

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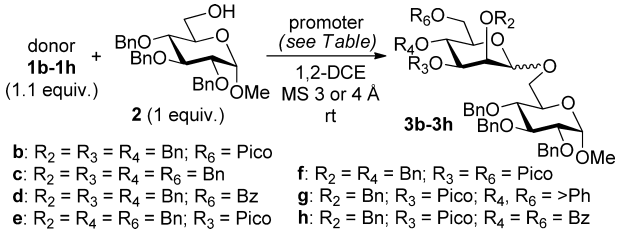
Table 1. Comparative Investigation of Mannosyl Donors 1b–1h



b: $R_2 = R_3 = R_4 = Bn$; $R_6 = Pico$
c: $R_2 = R_3 = R_4 = R_6 = Bn$
d: $R_2 = R_3 = R_4 = Bn$; $R_6 = Bz$
e: $R_2 = R_4 = R_6 = Bn$; $R_3 = Pico$
f: $R_2 = R_4 = Bn$; $R_3 = R_6 = Pico$
g: $R_2 = Bn$; $R_3 = Pico$; R_4, R_6 = >Ph
h: $R_2 = Bn$; $R_3 = Pico$; $R_4 = R_6 = Bz$

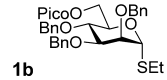
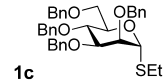
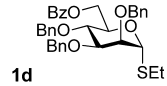
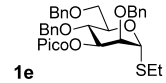
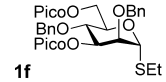
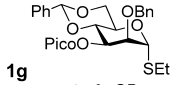
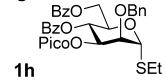
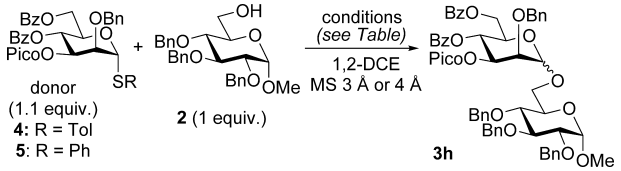
entry	donor	promoter, time	product (yield, α/β ratio)
1[10]	 **1b**	DMTST, 4 h NIS/TfOH, 2.5 h	**3b** (86%, 1/4.5) **3b** (87%, 1/9.5)
2	 **1c**	DMTST, 72 h NIS/TfOH, 72 h	**3c** (65%, 1/1.4) **3c** (67%, 1/1.0)
3	 **1d**	DMTST, 24 h NIS/TfOH, 24 h	**3d** (68%, 1/1.0) **3d** (70%, 1/1.0)
4	 **1e**	DMTST, 30 min NIS/TfOH, 20 min	**3e** (92%, 1/7.0) **3e** (89%, 1/8.0)
5	 **1f**	DMTST, 50 min NIS/TfOH, 3 h	**3f** (72%, 1/10.0) **3f** (86%, 1/8.7)
6	 **1g**	DMTST, 40 min NIS/TfOH, 40 min	**3g** (73%, 1/5.7) **3g** (73%, 1/6.5)
7	 **1h**	DMTST, 1.5 h NIS/TfOH, 1 h	**3h** (86%, 1/12.1) **3h** (72%, 1/12.3)

Table 2. Investigation of *S*-Tolyl 4 and *S*-Phenyl 5 Glycosyl Donors



entry	donor (concn)	conditions	time	yield, α/β ratio of **3h**
1	**4** (5 mM)	DMTST, rt	2 h 50 min	89%, 1/9.5
2	**4** (5 mM)	NIS/TfOH, rt	12 h	86%, 1/9.5
3	**5** (50 mM)	DMTST, rt	7 h	73%, 1/5.0
4	**5** (50 mM)	NIS/TfOH, rt	1h 10 min	97%, 1/8.8
5	**5** (5 mM)	DMTST, rt	2 h 50 min	91%, 1/18.5
6	**5** (5 mM)	NIS/TfOH, rt	12 h	96%, 1/7.2
7	**5** (5 mM)	DMTST, -30 °C	5 h	87%, 1/17.6
8	**5** (1 mM)	DMTST, rt	2 h	80%, 1/14.0

we present our systematic study of H-bond mediated aglycone delivery reaction as applied to β-mannosylation.

As the starting comparison point, known per-*O*-benzylated glycosyl donor **1c**[27] was coupled with glycosyl acceptor **2** in the presence of DMTST or NIS/TfOH under high dilution reaction conditions that became the standard for *O*-picoloylated glycosyl donors: 5.0 mM concentration in 1,2-dichloroethane. Previously, we conducted all reactions at −30 → rt or +42 °C.[10] Herein, we observed no significant temperature dependence and conducted all reactions at rt. Thus, a glycosylation reaction between donor **1c** and acceptor **2**[28,29] gave the corresponding disaccharide **3c**[30] in good yield, but no selectivity was observed in the case of either promoter (Table 1, entry 2). Similarly, glycosidation of 6-*O*-benzoyl donor **1d**[31] provided disaccharide **3d** with no stereoselection (entry 3). Since D-mannose has two remote substituents projecting above the pyranose ring (O-3 and O-6), we were curious to compare 6-*O*-picoloyl donor **1b** with its 3-*O*-picoloyl counterpart **1e**. Encouragingly, donor **1e** gave excellent yields (89–92%) and high β-stereoselectivity (α/β = 1/7–8, entry 4). Further screening of protecting groups included the 3,6-di-*O*-picoloyl donor **1f**, the 4,6-*O*-benzylidene donor **1g**, and the 4,6-di-*O*-benzoyl donor **1h**. Among this 3-*O*-picoloyl donor series, the best results were achieved with donor **1h**, which afforded the corresponding disaccharide **3h** in good yield and with high stereoselectivity (α/β > 1/12, entry 7).

Having identified the most promising glycosyl donor **1h** of the ethyl thioglycoside series, we conducted further studies with similarly protected *p*-tolyl and phenyl thioglycoside series, **4** and **5**, respectively. In addition to studying the effect of the anomeric leaving groups, this in-depth study involved screening promoters (DMTST and NIS/TfOH), concentration (1–50 mM), and temperature (rt and −30 °C). Although all experiments summarized in Table 2 proceeded with high selectivity (α/β > 1/5), the most beneficial conditions for β-mannosylation of acceptor **2** include glycosyl donor **5** (5 mM in 1,2-dichloromethane) activated with DMTST at rt. Resultantly, disaccharide **3h** was obtained in excellent yield and stereoselectivity (91%, α/β = 1/18.5, entry 5).

Following this, we decided to investigate whether these mannosyl donors would also be suitable for stereoselective couplings with the secondary glycosyl acceptors **6**, **8**, and **14**. Concerning glycosyl donors of the ethyl thioglycoside series, the best results for glycosylation of primary glycosyl acceptor **2** were obtained with **1e**, **1f**, and **1h** (see Table 1). Unfortunately, when applied to glycosylations of secondary acceptors **6** and **8**,[19] none of these donors performed up to our expectations (Table 3, entries 1–4). Although the corresponding disaccharides **7** and **9–11** were obtained in respectable yields of 72–87%, stereoselectivity was much lower (α/β = 1/2.9–5.2, Table 3) in comparison to that achieved with the primary acceptor **2**.

In contrast, the glycosyl donor **1g**, which was not very effective with the primary acceptor **2**, showed respectable results in coupling reactions with the secondary glycosyl acceptors. Thus, coupling of the donor **1g** with the 4-OH acceptor **6** afforded disaccharide **12** in good yields 71–83% and commendable β-stereoselectivity ($\alpha/\beta \sim$ 1/10, entry 5). Similar results were obtained in glycosylations of acceptors **8** and **14**, which led to the formation of disaccharides **13** and **15**, respectively, in 71–88% yield with high stereoselectivity (α/β = 1/6–10, entries 6 and 7). Similarly protected *S*-tolyl **16** and *S*-phenyl **17** donors provided disaccharide **12** with even higher yields (80–96%) albeit with lower stereoselectivity (α/β = 1/5.4–8, entries 8 and 9) in comparison to that obtained with their *S*-ethyl counterpart **1g**.

Having investigated the synthesis of both primary and secondary β-mannosides, we felt well equipped to evaluate an oligosaccharide synthesis to probe the protecting/leaving group combinations and conditions. For this purpose, we obtained disaccharide **3h** (91%, α/β = 1/18.5) using the best conditions for primary glycosyl acceptor **2**: *S*-phenyl donor **5** activated with DMTST at rt. The β-linked disaccharide was separated and subjected to selective removal of 3′-*O*-picoloyl group, which was selectively affected in the presence of copper(II) acetate to give the 3′-OH derivative **18** (Scheme 3). The latter was glycosylated with donor **1g**, which was found the most suitable for

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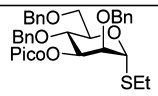
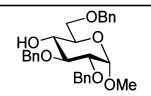
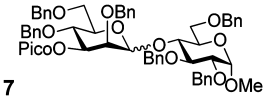
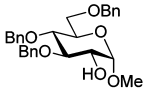
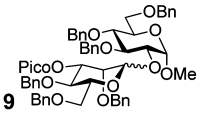
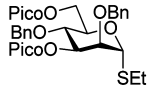
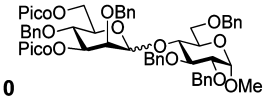
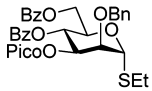
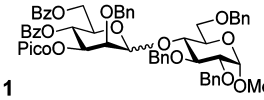
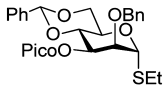
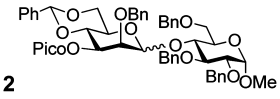
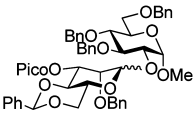
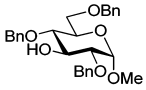
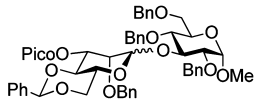
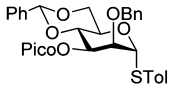
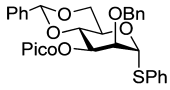
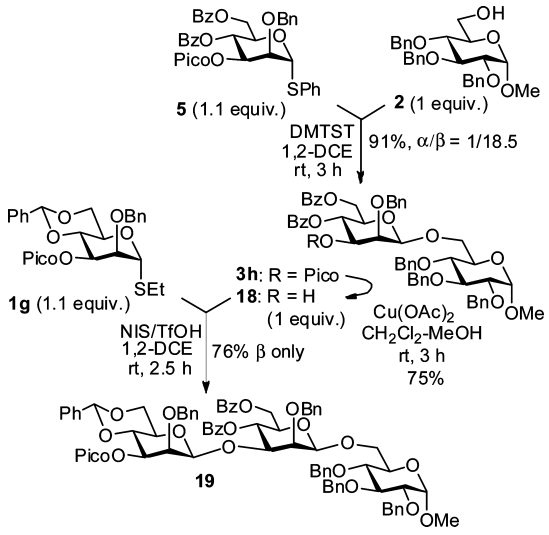
Table 3. Glycosylation of Secondary Glycosyl Acceptors 6, 8, and 14

entry	donor	acceptor	promoter, time	product	yield, α/β ratio
1	 **1e**	 **6**	NIS/TfOH, 30 min	 **7**	80%, 1/2.9
2	**1e**	 **8**	NIS/TfOH, 30 min	 **9**	78%, 1/4.9
3	 **1f**	**6**	DMTST, 2 h NIS/TfOH, 3 h	 **10**	73%, 1/2.9 87%, 1/2.9
4	 **1h**	**6**	DMTST, 1.5 h NIS/TfOH, 1.5 h	 **11**	86%, 1/5.2 72%, 1/3.5
5	 **1g**	**6**	DMTST, 40 min NIS/TfOH, 2 h	 **12**	71%, 1/10.0 83%, 1/9.8
6	**1g**	**8**	DMTST, 1.5 h	 **13**	78%, 1/7.3
7	**1g**	 **14**	DMTST, 2 h NIS/TfOH, 2 h	 **15**	71%, 1/6.0 88%, 1/10
8	 **16**	**6**	DMTST, 24 h NIS/TfOH, 2 h[b]	**12**	80%, 1/5.4 96%, 1/8.0
9	 **17**	**6**	DMTST, 2.5 h NIS/TfOH, 12 h[c]	**12**	86%, 1/5.5 89%, 1/7.4

[a]Unless noted otherwise, performed under standard conditions: 5 mM concentration of donor, 1,2-dichloroethane (10 mL), rt. [b]Performed at 50 mM concentration of donor, no reaction at 5 mM. [c]Performed at 50 mM concentration of donor, lower stereoselectivity obtained at 5 mM.

Scheme 3. Synthesis of Trisaccharide 19



glycosylation of secondary hydroxyls. This coupling was promoted in the presence of NIS and TfOH and resulted in the formation of trisaccharide **19** in 76% yield and, to our delight, with complete β-stereoselectivity ($\alpha/\beta > 1/25$).

In conclusion, we have discovered that a remote 3-*O*-picoloyl group can effectively mediate β-mannosylation reactions with high facial *syn* selectivity for attack of the glycosyl acceptor. The applicability of this approach was demonstrated for the synthesis of an oligosaccharide containing both primary and secondary β-mannosidic linkages. Further application of this new stereoselective glycosylation reaction to other targets and systems is currently underway in our laboratory.

■ 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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: demchenkoa@umsl.edu.

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Notes

The authors declare no competing financial interest.

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