

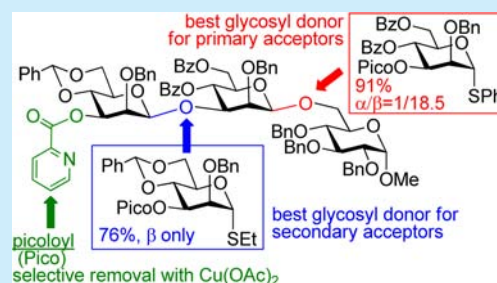
Hydrogen-Bond-Mediated Aglycone Delivery: Focus on β -Mannosylation

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S Supporting Information

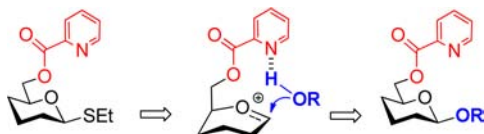
ABSTRACT: *O*-Picoloyl groups at remote positions can mediate the course of glycosylation reactions by providing high facial selectivity for the H-bond-mediated attack of the glycosyl acceptor. A new practical method for the stereoselective synthesis of β -mannosides at ambient temperature is presented.



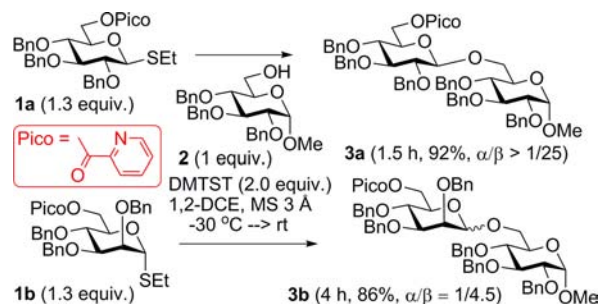
The vast majority of complex carbohydrates consist of monosaccharide residues connected via *O*-glycosidic linkages.^{1,2} Uncontrolled chemical *O*-glycosylations often lead to low yields and/or mixtures of anomers. The goal of stereocontrolling glycosylation has been a major inspiration and driving 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 ($\alpha/\beta = 1/4.5$) 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 ($\alpha/\beta = 1/9.5$, 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: R₂ = R₃ = R₄ = Bn; R₆ = Pico
 c: R₂ = R₃ = R₄ = R₆ = Bn
 d: R₂ = R₃ = R₄ = Bn; R₆ = Bz
 e: R₂ = R₄ = Bn; R₃ = Pico
 f: R₂ = R₄ = Bn; R₃ = R₆ = Pico
 g: R₂ = Bn; R₃ = Pico; R₄, R₆ = >Ph
 h: R₂ = Bn; R₃ = Pico; R₄ = R₆ = 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

4: R = Tol
 5: R = Ph

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	1 h 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 stereo-selection (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 ($\alpha/\beta = 1/7$ –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 ($\alpha/\beta > 1/12$, 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 ($\alpha/\beta > 1/5$), 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%, $\alpha/\beta = 1/18.5$, 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 ($\alpha/\beta = 1/2.9$ –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 ($\alpha/\beta = 1/6$ –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 ($\alpha/\beta = 1/5.4$ –8, entries 8 and 9) in comparison to that obtained with their S-ethyl counterpart **1g**.

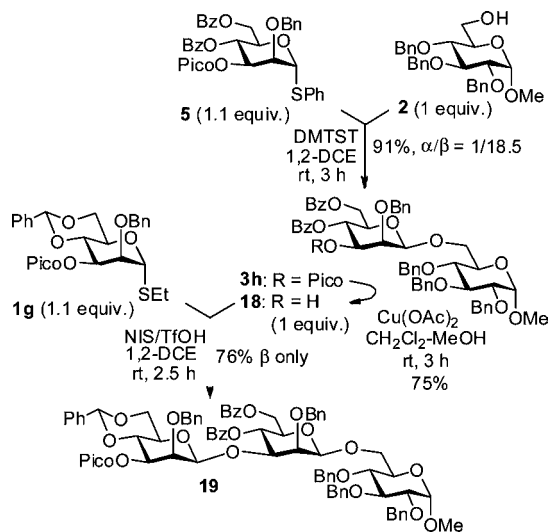
Having investigated the synthesis of both primary and secondary β -mannosides, we felt well equipped to evaluate an oligosaccharide synthesis to probe the protecting/leaving group combinations and conditions. For this purpose, we obtained disaccharide **3h** (91%, $\alpha/\beta = 1/18.5$) using the best 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

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

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

^aUnless noted otherwise, performed under standard conditions: 5 mM concentration of donor, 1,2-dichloroethane (10 mL), rt. ^bPerformed at 50 mM concentration of donor, no reaction at 5 mM. ^cPerformed at 50 mM concentration of donor, lower stereoselectivity obtained at 5 mM.

Scheme 3. Synthesis of Trisaccharide 19



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

S 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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glycosylation of secondary hydroxyls. This coupling was promoted in the presence of NIS and TfOH and resulted in

Notes

The authors declare no competing financial interest.

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