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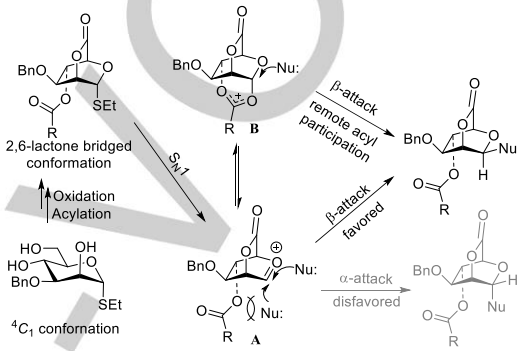
β-Stereoselective Mannosylation with a 2,6-Lactone-bridged Thiomannosyl Donor by Remote Acyl Group Participation

Huanfang Xu,‡ Long Chen,‡ Qi Zhang, Yingle Feng, Yujia Zu and Yonghai Chai*

Abstract: Stereoselective β-mannosylation has been recognized as one of the greatest challenges of carbohydrate chemistry. Herein, we described a practical method for stereoselective construction of β-mannosides by using a 2,6-lactone-bridged thiomannosyl donor via the remote acyl group participation as well as the steric effect of *O*-4 substituent. The two effects are enabled through the conversion of a regular mannopyranosyl $^4C_1$ conformation into a 2,6-lactone bridged conformation. The lactone donor could be readily prepared in 3 steps on a gram scale and the β-mannosylation proceeded smoothly with high stereoselectivity for primary, secondary and tertiary alcohol acceptors. In addition, this strategy was successfully applied to the synthesis of a naturally occurring trisaccharide.

In recent decades, great efforts have been devoted to the development of efficient and stereoselective glycosylation methodologies due to the biological significance of glycoconjugates.[1] However, the stereoselective construction of β-mannosides is still challenging since both the anomeric effect and the steric effect of the *C*-2 axial substituent on the mannopyranosyl ring favor the formation of β-mannosides.[2] To overcome this obstacle, different strategies[3] have been developed. The 4,6-*O*-benzylidene method, established by Crich and co-workers,[4] is one of the most powerful tools for the installation of β-mannosides. The updated 4,6-*O*-benzylidene versions[5] and 4,6-*O*-silylene version[6] have also been proven to be effective for β-mannosylation. Another impactful protocol for the synthesis of β-mannosides is the intramolecular aglycone delivery (IAD) method, which was introduced by Hindsgaul and co-works[7] and further extensively studied by Stork,[8] Ito and Ogawa et al.[9] Recently, some innovative strategies have also been introduced into the construction of β-mannosyl linkages including hydrogen-mediated aglycone delivery (HAD) method,[10] glycosyl-acceptor-derived boronic ester-promoted method[11] and $^1C_4$ conformation-based neighboring-group participation (NGP) method.[12] Although significant progress has been made in the construction of β-mannoside, practical and highly selective approaches are still in great demand.

In this context, we developed an efficient protocol for β-mannosylation with the use of 2,6-lactone-bridged thiomannosides as donors predominantly via the *O*-4 remote acyl group participation, which proved to play an important role in the glycosylation[13], as well as the steric effect of *O*-4 substitutes (Scheme 1). Considering the axial or pseudo-axial hydroxy group at *C*-4 position, when acylated, could provide a remote acyl participation, we employed a 2,6-lactone bridge to switch the *C*-4 hydroxyl group, which is at the equatorial position in a regular mannopyranosyl $^4C_1$ conformation, to the axial or pseudo-axial position. Furthermore, the bulky substituent at *O*-4 position might sterically disfavour the α-face attack by a nucleophilic acceptor, resulting in higher β-selectivity.



Scheme 1. Our strategy for β-mannosylation using a 4-*O*-acyl 2,6-lactone-bridged thiomannosyl lactone as donor: 1). Upon activation, thiomannoside forms the oxocarbenium cation **A**, which is then attacked by an acceptor from β-face (β-attack) or from α-face (α-attack). The α-attack is disfavored due to the steric repulsion between *O*-4 substituent and the nucleophilic acceptor; 2). α-attack is blocked due to the formation of dioxocarbenium ions **B** via *O*-4 acyl group remote participation.

Notably, at our final stage of manuscript preparation, Sasaki and co-workers reported their novel method for β-mannosylation by using 2,6-lactone donors without acyl group in the *O*-4 position. The stereoselectivity is believed to arise mainly from S_N2(-like) displacement of the α-nucleofuge at the anomeric position with the glycosyl cation generated from the donor being sterically β-directing. In their case, the highest β-stereoselectivity was obtained when α-trichloroacetimidates were used as donors. But unfortunately, the synthetic yields of this kind of α-trichloroacetimidate donors were quite low (32% from the hemiacetal precursor, 4-di-*O*-benzyl-D-mannopyranurono-2,6-lactone; 5% from the starting material, allyl mannoside).[14]

Our study commenced with the synthesis of various 2,6-lactone-bridged mannoside donors bearing different *O*-4 acyl group and *C*-1 leaving group. Trichloroacetimidates **5a** and **5b** were first chosen as the target donors (Scheme 2a). Using Stahl's oxidative protocol[15], 3-*O*-benzyl protected allyl mannoside **1**[14] was converted into lactone **2**, in which the *C*-4 hydroxyl group locates at our expected axial or pseudo-axial position. After acylation, followed by deprotection of allyl group, hemiacetals **4a** and **4b** were prepared successfully. However, the final trichloroacetimidation was in the grip of unacceptable yields, and the desired donor **5a** or **5b** was only obtained in 13% or 10%, respectively. The low yields may be attributed to two reasons. First, during the reaction, considerable side-products **6a** or **6b** was always formed although various reaction conditions were examined. Second, trichloroacetimidates containing the 2,6-lactone moiety were found to be very fragile

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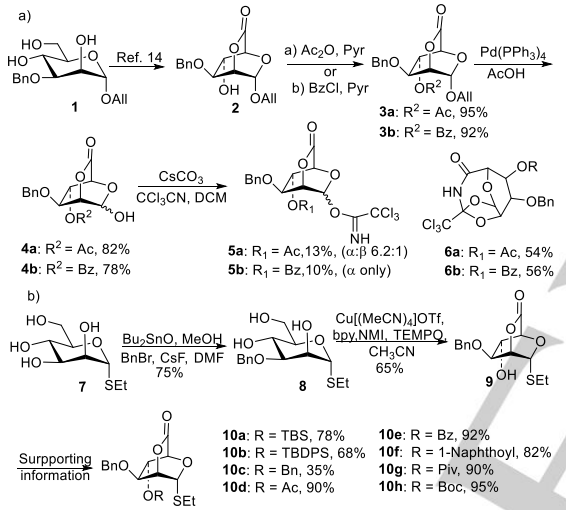
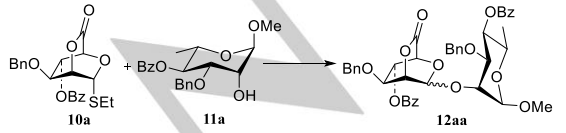
and would partially decompose during workup and column chromatography. Actually, when R^2 is benzyl group, the similar unsatisfied result was received (34%, from 4-Di-*O*-benzyl-D-mannopyranurono-2,6-lactone, see Supporting Information, **5c** and **6c**), which is consistent with data reported by Sasaki et al[13]. To solve the problem, we then turned our effort to the synthesis of donors **10a-h**, in which the *C*-1 leaving group is ethylthio ether (Scheme 2b). Starting from the commercially available ethyl-1-thio-α-*D*-mannopyranoside **7**, several 2,6-lactone-bridged thiomannosyl donors were easily prepared in practical total yields on a gram scale by a 3-steps strategy. With the treatment of $^{n}Bu_2SnO$ and benzyl bromide, **7** was first regioselectively benzylated[16] to give 3-*O*-benzylmannoside **8**, which was then oxidized to lactone **9** by using Stahl's protocol[15]. The *C*-1 hydroxyl group in **9** was readily to be modified with different protecting agents, affording the desired 2,6-lactone-bridged thiomannosyl donors bearing various *O*-4 substituents.



Scheme 2. Synthesis of donnors **5a-b** and **10a-h**.

With the donors in hand, we explored the β-mannosylation using donor **10a** as model reaction. As shown in Table 1, the glycosylation of **10a** with acceptor **11a** led to the expected β-mannoside product in excellent yield with high stereoselectivity under the optimized reaction condition (Table 1, entry 8). The β-anomeric configuration of the product was determined by the NOE correlation between H_1 and H_3 and further unequivocally confirmed by X-ray single crystal diffraction analysis (Figure 1).

Table 1 Optimization of the reaction conditions with **10a** and **11a**[a]



Entry	Promoter	Solvent	Temp./Time	Yield[b] (β/α)[c]
1	NIS/TfOH	DCM	0 °C/13 h	32% (>20:1)
2	NIS/TMSOTf	DCM	0 °C/13 h	40% (>20:1)
3	NIS/AgOTf	DCM	0 °C/1 h	54% (>20:1)
4	NIS/AgOTf	Toluene	0 °C/4 h	NR
5	NIS/AgOTf	THF	0 °C/4 h	Trace
6	NIS/AgOTf	CH_3CN	0 °C/4 h	Trace
7[d]	NIS/AgOTf	DCM	0 °C/50 min	68% (>20:1)
8[e]	NIS/AgOTf	DCM	0 °C/40 min	88% (>20:1)
9[e]	NIS/$AgClO_4$	DCM	0 °C/2 h	74% (>20:1)

[a] Reaction of **10a** (1 equiv), **11a** (1.5 equiv), NIS (1 equiv), catalyst (0.2 equiv) and 4Å MS in a mentioned solvent (c = 0.1 mol·L^{-1}) under Ar atmosphere. [b] Yield of the isolated product. [c] Ratios determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Reaction of **10a** (1.2 equiv), **11a** (1 equiv), NIS (1.2 equiv), AgOTf (0.3 equiv) and 4Å MS. [e] Reaction of **10a** (1.5 equiv), **11a** (1 equivl), NIS (1.5 equiv), Ag(I) salt (0.5 equiv) and 4Å MS.

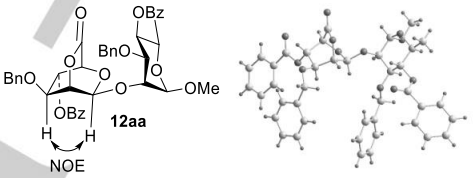
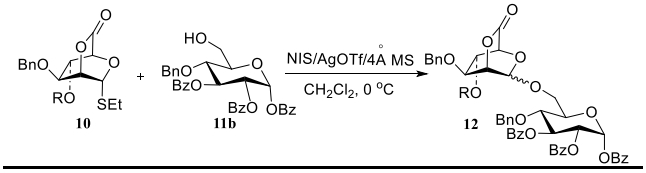


Figure 1. NOE correlation between H_1-H_3 and X-ray crystal structure of the disaccharide ***β*-12aa**.

The efficiency and stereoselectivity of our synthesized 2,6-lactone-bridged thiomannosyl donors **10a-g** were then evaluated using **11b** as acceptor under the above-mentioned optimized condition (Table 2). The glycosylation of 4-*O*-TBS donor **10a** with **11b** gave the corresponding mannoside with a 2:1 ratio of β/α-anomer (Table 2, entry 1). Enhanced β-selectivity was obtained when bulkier donor **10b** bearing a TBDPS group in the *O*-4 position was employed (β/α = 4:1, Table 2, entry 2), which indicates that increasing the α-face (namely *O*-4 positional) steric hindrance of the donor may sterically disfavor α-face nucleophilic attack and thus resulted in higher β-selectivity. To our delight, with the use of *O*-4 acyl protected donors, such as **10d**-**g**, the β-selectivity could be further improved (β/α 7-10:1 *vs* 2-4:1,Table 2, entries 4-7 *vs* 1-3). This outcome implies that the remote participation of 4-*O*-acyl group may play a significant β-directing role and contributes extra β-selectivity in the mannosylation. Furthermore, when bulky Piv group was introduced into the 4-*O* position of the donor, the best result was achieved (β/α = 10:1, Table 2, entry 7), which provides evidence that both the remote participation and the steric effect of *O*-4 substitute contribute to the β-selectivity of mannosylation.

Table 2 Optimization of the reaction conditions with **10a** and **11a**[a]

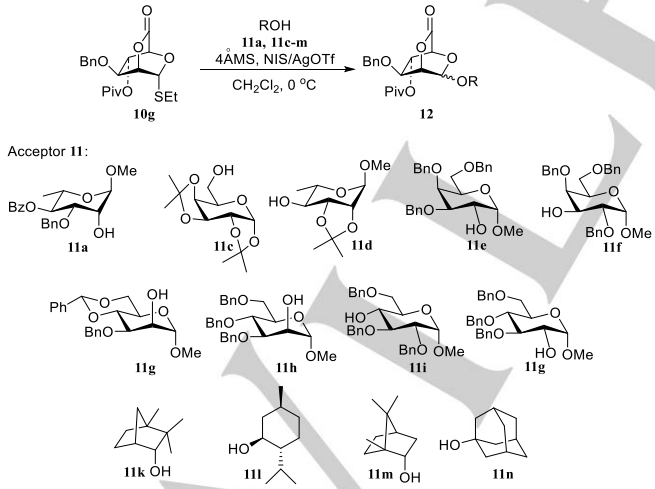


Entry	Donor (R)	Product	Yield[b]	β/α[c]
1	**10a** (4-*O*-TBS)	**12ab**	78 %	2:1
2	**10b** (4-*O*-TBDPS)	**12bb**	82 %	4:1
3	**10c** (4-*O*-Bn)	**12cb**	86 %	3:1
4	**10d** (4-*O*-Ac)	**12db**	76 %	7:1
5	**10e** (4-*O*-Bz)	**12eb**	68 %	9:1
6	**10f** (4-*O*-1-Naphthoyl)	**12fb**	57 %	8:1
7	**10g** (4-*O*-Piv)	**12gb**	73 %	10:1

[a] Reaction of donor (1.5 equiv), **11b** (1 equiv), NIS (1.5 equiv) and AgOTf (0.5 equiv). [b] Yield of the isolated product. [c] Ratios determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

Next, different alcohol acceptors were subjected to the glycosylation with the optimal donor **10g**. As summarized in Table 3, the glycosylation of **10g** with most of secondary alcohols proceeded smoothly, providing the corresponding disaccharides in good yield with excellent β-selectivity (Table 3, entries 1, 3-13). The β-mannosylation of primary alcohol **11c** (Table 3, entry 2) and tertiary alcohol **11n** (Table 3, entry 13) also delivered the desired disaccharides with commendable β/α selectivity.

Table 3 Glycosylations of Donor **10e** with Acceptors **11a−n**[a]

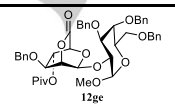
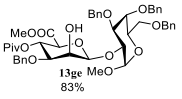
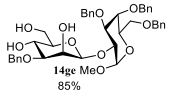
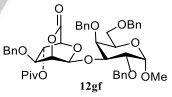
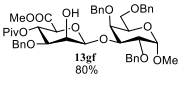
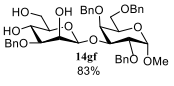
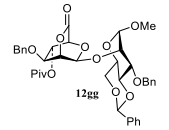
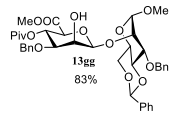
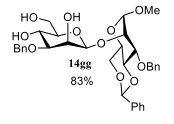
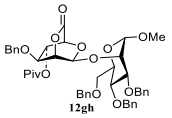
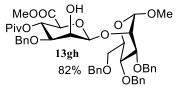
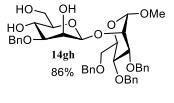
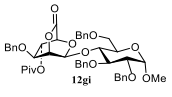
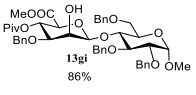
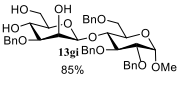


Entry	Acceptor	Product	Yield (%)[b]	β/α[c]
1	**11a**	**12ga**	88	>20:1
2	**11c**	**12gc**	62	10:1
3	**11d**	**12gd**	65	>20:1
4	**11e**	**12ge**	72	>20:1
5	**11f**	**12gf**	81	>20:1
6	**11g**	**12gg**	82	>20:1
7	**11h**	**12gh**	78	>20:1
8	**11i**	**12gi**	58	>20:1
9	**11j**	**12gj**	74	>20:1
10	**11k**	**12gk**	74	20:1
11	**11l**	**12gl**	70	11:1
12	**11m**	**12gm**	77	16:1
13	**11n**	**12gn**	65	12:1

[a] Reaction of **10e** (1.5 equiv), acceptor (1 equiv), NIS (1.5 equiv) and AgOTf (0.5 equiv). [b] Yield of the isolated product. [c] Ratios determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

Opening the lactone disaccharides by a catalytic amount of NaOMe or by reduction with $LiBH_4$ generated mannuronic methyl esters **13** or mannosides **14** with the restoration of the conformation to $^4C_1$ (Table 4). The β-configuration of the disaccharides with restored $^4C_1$ conformation were confirmed by their $J_{C\text{-}1,H\text{-}1}$ coupling values which are smaller than 160 Hz.[17]

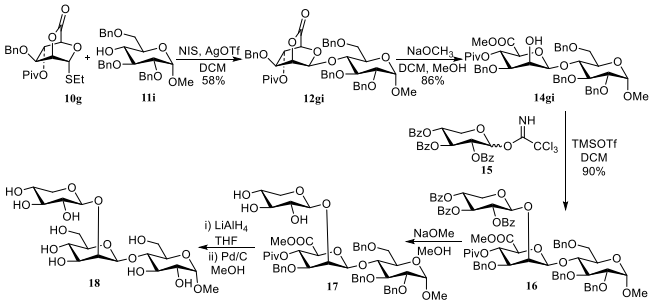
Table 4 Opening of the lactone dissacharides[a]

Entry	Lactone	Product[b] Yield	Product[c] Yield
1			
2			
3			
4			
5			

[a] Yield of the isolated product. [b] Deprotection by NaOMe (0.05 equiv). [c] Reduction by $LiBH_4$ (4 equiv).

After the development of this new donor for β-mannosylation, we set out to synthesize trisaccharide **18**, which is a component of the *Hyriopsis schlegelii* glycosphingolipid.[18] As depicted in Scheme 4, β-mannosylation of donor **10g** with acceptor **11i** provided the disaccharide **12gi** in 58% yield with excellent β-selectivity. The trisaccharide **16** was obtained via the base-

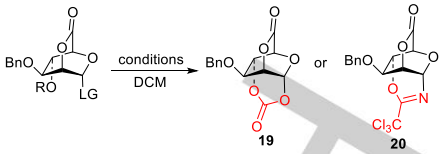
catalyzed opening of the lactone disaccharide with NaOMe, followed by glycosylation with imidate **15**. Reduction of **17** with $LiAlH_4$ and subsequent global debenzylation in the presence of Pd/C under hydrogen atmosphere accomplish the synthesis of the target molecule **18**, the characterization data of which are in accordance with those reported in the literature.[19]



Scheme 4. Synthesis of trisaccharide **18**.

Several trapping experiments were also carried out to further understand the factors influencing the stereoselectivity, especially the β-directing effect by remote participation of *O*-4 acyl group in the donors (Table 5). We selected *O*-4 Boc and tricloroacetimidoyl protected lactone donors to trap anomeric oxocarbenium ion intermediates by the intramolecular nucleophilic attack of the Boc group or the tricloroacetimidoyl group. The trapping of intramolecular electrophilic centers by the Boc group results in the formation of cyclic carbonates[20],[21] and by the tricloroacetimidoyl group results in the formation of cyclic oxazolines or oxazines.[13a],[13d],[22] This strategy was well established and used for providing support for the neighboring-group participation and remote participation of acyl group in the glycosyl donors. In our trapping experiments, although no cyclic carbonate **19** was obtained in the reaction of Boc protected mannosyl thioether **10h** and triflate **10i** with different promoters (Table 5, entries 1-5), we were capable of attaining stable tricyclic product **20**, the structure of which was firmly confirmed by NMR, HRMS and single-crystal X-ray analysis (Figure 2), when using 4-*O*-tricloroacetimidoyl-mannosyl trichloroimidate **10k** under the conditions of catalytic amounts of TMSOTf (Table 5, entry 7). The result of these trapping experiments serves as strong proof for the remote participation of *O*-4 acyl group. Moreover, the concentration-depending experiment shows that the β-selectivity of this mannosylation reaction only improved slightly as the concentration increased [β/α 8.5:1 (*c* 0.05 M) *vs* 10:1 (*c* 0.1 M) *vs* 12:1 (*c* 1 M)], indicating that the S_N2(-like) pathway is not the predominant pathway for our 2,6-lactone-bridged thiomannosyl donors with the treatment of NIS/AgOTf (see Supporting Information, Table S-1).

Table 5 Trapping experiments.



Entry	Donor	R	LG	Conditions	Result
1				NIS, AgOTf[a]	removal of Boc
2	**10h**		SEt	BSP, Tf_2O, TTBP[b]	no reaction
3		Boc		BSP, Tf_2O[c]	removal of Boc
4				BSP, Tf_2O[c]	no reaction
5	**10i**		Tol	$AuCl_3$[d]	removal of Boc
6	**10j**		SEt	BSP, Tf_2O[c]	no reaction
7	**10k**	tricloroacetimidoyl	trichloroimidate	TMSOTf[e]	**20** (73%)

[a] Donor (1 equiv), NIS (1 equiv), AgOTf (0.5 equiv). [b] Donor (1 equiv), BSP (1.1 equiv), TTBP (2.5 equiv), Tf_2O (1.1 equiv). [c] Donor (1 equiv), BSP (1.1 equiv), Tf_2O (1.1 equiv). [d] Donor (1 equiv), $AuCl_3$ (0.5 equiv). [e] Donor (1 equiv), TMSOTf (0.3 equiv).

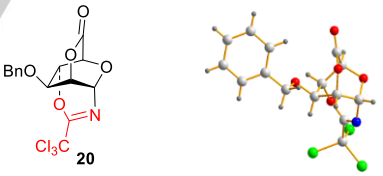


Figure 2. X-ray crystal structure of the key intermediate.

In conclusion, we have developed an efficient β-mannosylation method using a 2,6-lactone-bridged thiomannosyl donor via remote acyl group participation as well as *O*-4 steric effect. The lactone donor could be rapidly prepared on a gram scale in 3 steps and the glycosylation of the lactone donor with primary, secondary and tertiary alcohol acceptors proceeds smoothly with high β-selectivity. The easy availability of the donor and the high β-selectivity for mannosides enable this method to be an alternative to those reported in the literatures for the construction of β-mannosides. The utility of the method has been demonstrated by the synthesis of the trisaccharide, a component of the *Hyriopsis schlegelii* glycosphingolipid.

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Keywords: mannosylation • 2,6-lactone bridge • remote acyl group participation • stereoselectivity • steric effect

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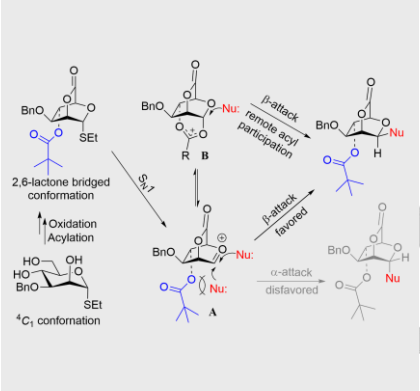
Layout 1:

COMMUNICATION

Stereoselective β-mannosylation was achieved using a 2,6-lactone-bridged thiomannosyl donor via *O*-4 remote acyl group participation and the assistance of *O*-4 substituent's steric effect. The glycosylation proceeded smoothly with high stereoselectivity for primary, secondary and tertiary alcohol acceptors. The novel donor could be readily prepared in 3 steps on a gram scale.



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β-Stereoselective Mannosylation with a 2,6-Lactone-bridged Thiomannosyl Donor by Remote Acyl Group Participation