β-L-Rhamnosylation and β-D-Mannosylation Mediated by 4-O-Ester Groups in Weakly Nucleophilic Environment

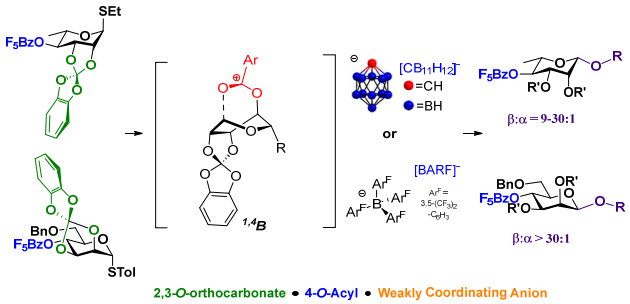
Yongliang Zhang,[a+] Changsheng Chen,[a+] Yongtao Gao,[a+] Min Yang,[b] Zehuan He,[a] Bangzhi Zhang,[d] Guofeng Gu,[a] Bencan Tang,[c] and Feng Cai[a,d*]

[a] Y. Zhang, C. Chen, Y. Gao, Z. He, Prof. G. Gu, Prof. F. Cai, National Glycoengineering Research Center and Shandong Key laboratory of Carbohydrate Chemistry and Glycobiology, Shandong University, 72 Binhai Rd. Qingdao, 266237, China, E-mail: fcai@sdu.edu.cn

[b] Dr. M. Yang, Center for Analysis and Characterization, School of Physical Science and Technology, ShanghaiTech University, 393 Huaxia Middle Rd, Shanghai 201210, China

[c] Prof. B. Tang, Faculty of Science and Engineering, The University of Nottingham Ningbo China, 199 Taikang E Rd, Ningbo 315100, China

[d] Prof. B. Zhang, Key Laboratory of Preclinical Study for New Drugs of Gansu Province, School of Basic Medical Sciences, Lanzhou University, Lanzhou 730000, China



ABSTRACT: *Eq*-4-O-acyl group directed β-rhamnosylation and β-mannosylation are achieved in carborane or BARF anion formed weakly nucleophilic environment with the assistance of a 2,3-orthocarbonate group. The 4-O-acyl group plays a critical role in directing the β-selectivity, and the weakly coordinating anion is essential to amplify this direction. The orthocarbonate group could be readily removed with 1,3-propanediol in the presence of $BF_3.Et_2O$.

β-L-Rhamnosides and β-D-mannosides are two distinct types of glycosides. β-L-Rhamnoside is a common polysaccharide building block widely distributed in bacterial polysaccharides, such as lipopolysaccharides,[1] exopolysaccharides,[2] and capsular polysaccharides.[3] β-D-Mannosides mainly occur in the common pentasaccharide core of the *N*-linked oligosaccharides,[4] and are also found as subunits of glycosphingolipids,[5] lipopolysaccharides or other polysaccharides from microbial cell walls.[6] While they are not quite related in biological occurrences, the stereocontrolled synthesis of either β-rhamnopyranosides or β-mannopyranosides confronts similar synthetic challenges because of their similar chemical structures. They are one of the most difficult goals in oligosaccharide synthesis. None of the anomeric effect, the axial orientation of 2-*O*-substituent, or the 2-*O*-acyl neighboring group participation prefers β-selectivity. Many approaches have been investigated including using electron-deficient 2-*O*-substituents,[7] regenerating 2-*O*-axial hydroxyl after glycosylation,[8] utilizing 1,2-*O*-*cis*-stannylene acetal donors,[9] and with heterogeneous Kornigs-Knorr glycosylation[10] but with limitations. The 4,6-*O*-benzylidene restricted the conformation of mannopyranoside affording excellent β-selectivity.[11] Lately, 2,6- or 3,6-lactone restricted mannopyranosides were also proved to facilitate β-selective mannosylation.[12, 13] However, missing the 6-oxygen occludes the above β-mannosylation being applied to β-rhamnosylation. Manipulation of the rhamnopyranoside conformation was also investigated,[14] but comparable results have yet achieved through these strategies.

Different strategies have been developed in solving both β-mannosylation and β-rhamnosylation. Using a natural occurred β-L-Rhap-(1→4)-D-Glcp linkage as a benchmark, yields and β-selectivity of these strategies are shown in **Fig 1a** including a two-step 2-naphthylmethyl-mediated intramolecular aglycone delivery (IAD) (**Fig. 1**,

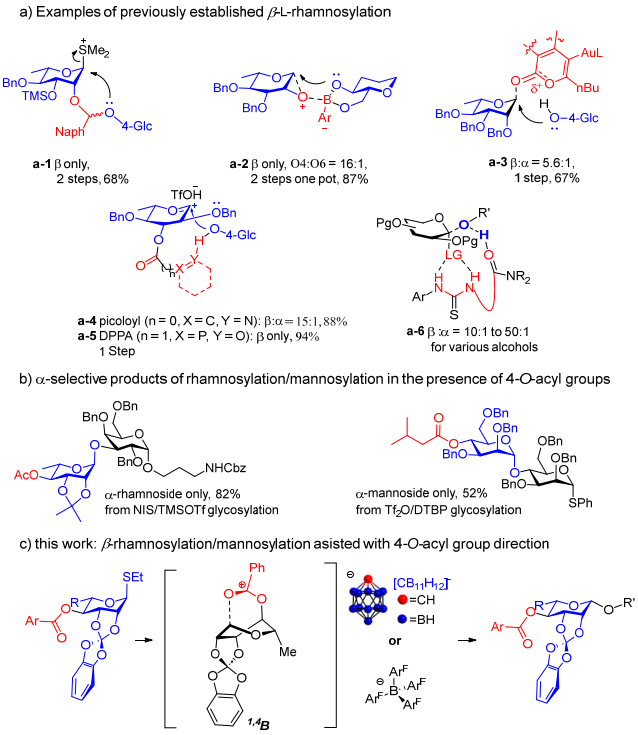


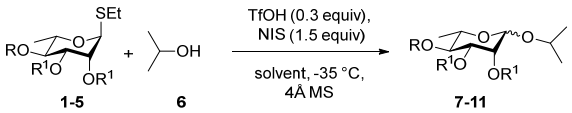
Figure 1 a) Examples of previously established β-rhamnosylation; b) 4-O-acyl groups barely contributing the β-selectivity in previous glycosylations; c): proposed β-rhamnosylation with the assistance of a 4-O-acyl and a 2,3-O-fused ring in this work.

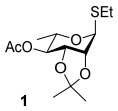
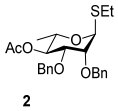
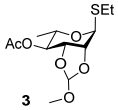
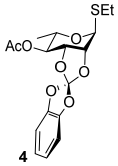
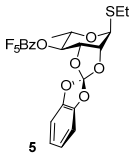
a-1, β only, 68%),[15] 1,2-anhydro-rhamnoside coupled with sugar boronates (**Fig. 1**, **a-2**, β only, regioselectivity *O*4:*O*6 = 16:1, 87%),[16] gold(I)-BARF-catalyzed S$_N$2-like glycosylation,[17] (**Fig. 1**, **a-3**, β:α = 5.6:1, 67%),[18] and hydrogen bond mediated aglycone delivery (HAD) including picoloyl_type groups (**Fig. 1**, **a-4**, β:α = 15:1, 88%)[19] and 2-(diphenylphosphinoyl)acetyl group.[20] (**Fig. 1**, **a-5**, β only, 94%), and these strategies also work well in β-mannosylation.[17, 21] Other than substrate control, external chirality from bis-thiourea could also efficiently catalyze β-L-rhamnosylation and β-D-mannosylation (**Fig. 1**, **a-6**).[22]

Here, we are interested in addressing this challenge through 4-*O*-acyl group direction. Acyl group directed glycosylation has been extensively investigated, and a 2-acyl or a distal *eq*-3-O-, *ax*-3-O-, *ax*-4-O, or 6-O-acyl group is capable of directing the corresponding 1,2-, 1,3-, 1,4-, or 1,6-*trans* glycosylation with good to excellent selectivities.[23] However, a general acyl group directed glycosylation strategy is incomplete due to missing eq-4-O-acyl group direction. β-Mannosylation and β-rhamnosylation through *eq*-4-O-acyl group direction are unfeasible, rather, α-glycosides are predominating products even in the presence of 4-*O*-acyl group (Fig. 1b)[24] although several surrogate strategies are used for some glycosides.[12, 25, 26] The dioxacarbenium ion from *eq*-4-O-acyl group has been observed under high vacuum as "naked" glycosyl cations.[27] However, "naked" glycosyl cations are inaccessible in solution since most current glycosylation methods involve triflate or other stronger nucleophilic anions as counter anions of oxocarbeniums via covalent bonds or closed ion pairs (CIPs).[28] Non-coordinating anions are weaker nucleophiles used in many metal-catalyzed reactions and several glycosylation as counterions,[17, 18, 29] but have not been used in conjunction with acyl group direction. We propose that non-coordinating anions readily interact with oxocarbenium cations and allow formation of dioxacarbenium ions akin to "naked" glycosyl cations even in solutions. In this study, we demonstrate that *eq*-4-O-acyl group-directed 1,4-*trans* selectivity can be achieved under non-coordinating anions provided weakly nucleophilic environments in conjunction with a suitable 2,3-*O*-ring substitution.

Starting with 2,3-*O*-isopropylidene-4-*O*-acetyl thiorhamnoside (**1**), we found that NIS/TfOH promoted glycosylation of **1** and isopropanol (**6**) preferred β-selectivity in Et_2O solution, which is consistent with Pedersen's observation[30] (**Table 1**, entry 1, and supporting information, **Table S1**).

Table 1. Optimization of 2,3,4-O-substituents.



Entry	Donor	Solvent	Yield (%)[a]	β:α[b]
1	 1	Et_2O	92	**7** (2.0:1)
		Et_2O:CH_2Cl_2 (3:1)	95	(2.0:1)
2	 2	Et_2O:CH_2Cl_2 (3:1)	96	**8** (1.6:1)
3	 3	Et_2O:CH_2Cl_2 (3:1)	85	**9** (2.2:1)
4	 4	Et_2O:CH_2Cl_2 (3:1)	95	**10** (2.6:1)
5	 5	Et_2O:CH_2Cl_2 (3:1)	95	**11** (3.0:1)

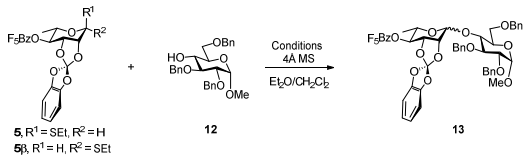
[a] isolated yield. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture.

In the absence of 2,3-*O*-ring fusion, 2,3-di-*O*-benzylated **2** gave poorer stereoselectivity demonstrating the significance of 2,3-*O*-ring fusion (**Table 1**, entry 2). We thus screened existing 2,3-*O*-fusion protections but none could further improve the β-selectivity (supporting information, **Table S2**). To our surprise, 2,3-*O*-orthoester **3** afforded slightly increased β-selectivity (2.2:1, **Table 1**, entry 3). After excluding the steric effect from the less bulky monosubstituted ring (supporting information, **Table S2**), we anchored the role of the extra-oxygen of orthoester. Since it is unstable and possesses a stereoelectronic effect, we prepared donors **4**-**5** bearing a stable and symmetrical orthocarbonate, 2,3-*O*-benzo[1',3']dioxol-2'-ylidene, via a reaction of rhamnoside 2,3-diol with commercially available 2,2-dichlorobenzo[1,3]dioxole[31] in the presence of pyridine (supporting information). Delightfully, donor **4** with 4-*O*-acetyl protection gave a better β-selectivity (β:α = 2.6:1), which was further improved with donor **5** bearing the pentaflurobenzoyl (F_5Bz) protection (β:α = 3.0:1, **5**) (**Table 1**, entry 4-5). The anomeric configuration of **11α** or **β** was determined through the direct bonded C1-H1 coupling constant ($^1J_{C1\text{-}H1}$, **11β**: $^1J_{C1\text{-}H1}$ = 156.6 Hz; **11α**: $^1J_{C1\text{-}H1}$ = 171.0 Hz, supporting information).[32]

In the rhamnosylation of less reactive alcohols, such as 4-hydroxyl glucoside (**12**), the selectivity is not ideal. The NIS activation mainly afforded α-rhamnoside (β:α = 1:4.7) (**Table 2**, entry 1). We therefore examined different reaction conditions. Activation with *p*-TolSCl/AgOTf [11, 33] afforded more β-rhamnoside (β:α = 1:1.4) (**Table 2**, entry 2). We next explored reaction conditions under weakly nucleophilic conditions. In conjunction with sulfenyl chloride, an array of silver salts with non-coordinating counter anions including $AgSbF_6$, $AgBAr^F{}_4$ (silver BARF), and $AgCB_{11}H_{12}$ (silver carborane)[34] in the order of decreasing nucleophilicity were evaluated. Encouragingly, when treated with *p*-TolSCl/$AgSbF_6$ or *p*-TolSCl/$AgBAr^F{}_4$ at -30 °C, improved β-selectivity was obtained (α:β = 1:3.5 or 1:4, respectively) (**Table 2**, entries 3 and 4). Furthermore, decreasing the glycosylation temperature to -78 °C, *p*-TolSCl/$AgBAr^F{}_4$ can still activate donor and afford much improved β-selectivity (α:β = 1:16, **Table 2**, entry 5). At -78 °C, $AgCB_{11}H_{12}$ provided the highest β-selectivity (α:β = 1:22, **Table 2**, entry 7), which is in line with its lowest nucleophilicity. Hence, $AgBAr^F{}_4$ and $AgCB_{11}H_{12}$ were used as proof

of concept in this study, although weaker nucleophilic anions such as halogenated carboranes[35] may further improve the β-selectivity. In addition, β-thioether **5β** also resulting in excellent β-selectivity (α:β = 1:11) eliminated the possibility of an S_N2 process as such in Au(I) catalyzed glycosylation (**Table 2**, entry 6).[17, 18]

Table 2. Impacts of Weakly Nucleophilic Counter Anion in Glycosylation.

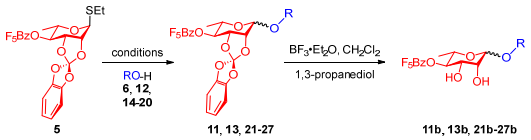


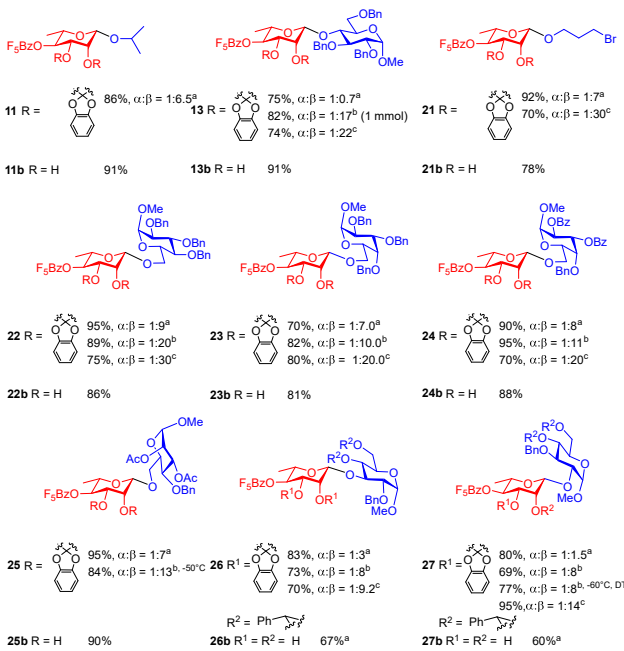
Entry	Donor and conditions	Yield (conv)(%)[a]	α:β [b]
1	**5**, NIS/TfOH	95 (100)	4.7:1
2	**5**, *p*-TolSCl/AgOTf, -78 to 0°C	75 (100)	1.4:1
3	**5**, *p*-TolSCl/$AgSbF_6$, -30 °C	46 (56)	1:3.5
4	**5**, *p*-TolSCl/$AgBAr^F{}_4$, -30 °C	85 (89)	1:4
5	**5**, *p*-TolSCl/$AgBAr^F{}_4$, -78 °C	58 (77)	1:16
6	**5β**, *p*-TolSCl/$AgBAr^F{}_4$, -78 °C	33 (40)	1:11
7	**5**, *p*-TolSCl/$AgCB_{11}H_{12}$, -78 °C	73 (80)	1:22

[a] Isolated yield and conversion. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture.

Subsequently, we investigated the application scope of donor **5** as depicted in **Table 3**. Under the two weakly nucleophilic conditions, particularly the carborane anion, we observed excellent β-selectivities of both primary and secondary acceptors (α:β = 1:9-30, **13**, **21**-**27**, **Table 3**; β isomers: $^1J_{C1\text{-}H1}$ = 156.6-163.8 Hz; α isomers: $^1J_{C1\text{-}H1}$ = 171.0-175.2 Hz, Supporting information). Improved β-selectivities were obtained at lower temperatures, yet similar results observed in the presence or absence of a hindered base (DTBP, **27**[b],

Table 3. β-Rhamnosylation with Donor 5





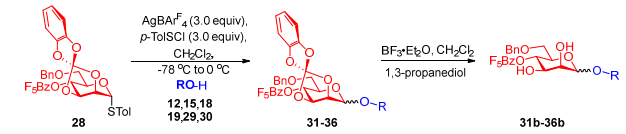
[a] Ag_2O (1.0 equiv), AgOTf (1.0 equiv), *p*-TolSCl (1.1 equiv), CH_2Cl_2/Et_2O (1/3), then ROH, -78 °C gradually to 0 °C. [b] ROH, $AgBAr^F{}_4$ (1.0 equiv), *p*-TolSCl (1.1 equiv), CH_2Cl_2/Et_2O (1/3), -78 °C. [c] ROH, $AgCB_{11}H_{12}$ (1.5 equiv), *p*-TolSCl (1.5 equiv), CH_2Cl_2/Et_2O (1/3), -78 °C. DTBP, 2,6-di-*tert*-butylpyridine.

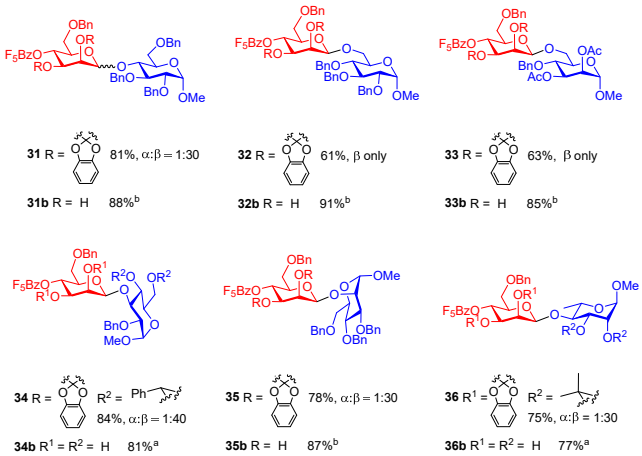
Table 3). In the *p*-TolSCl/AgOTf condition, only primary alcohols exhibited good β-selectivities (α:β = 1:7-14, **21**-**25**, **Table 3**).

The 2,3-O-benzo[1',3']dioxol-2'-ylidene group proved stable toward Brønsted acids, DDQ, or CAN oxidation, but was readily removed by BF_3•Et_2O (3.0 equiv) and 1,3-propanediol (5.0 equiv). We again measured the $^1J_{C1\text{-}H1}$ of **13b**, **21b**-**27b**, and their coupling constants were in the range of 157.8-163.8 Hz, matching that of β-isomers in chair conformation.

With success in β-rhamnosylation, we turned our attention to β-mannosylation. To a 4,6-benzylidene protected thiomannoside **S14**, the 2,3-orthocarbonate was installed, followed by successive reduction of 4,6-benzylidene and installation of the 4-O-acyl group to afford donor **28** (Supporting Information, **Scheme S2**). The mannosylation was conducted by adding 3.0 equiv of *p*-TolSCl/$AgBAr^F_4$ to a solution of **28** and acceptor at -78 ºC, then slowly warming up to 0 ºC. Several typical acceptors were assessed under this condition, including primary alcohols and secondary alcohols. For all acceptors, the β-selectivities were greater than 30:1 (**31**-**36**), with the two primary alcohols displaying exclusive β-selectivity as shown in **Table 4**. The deprotection proceeded smoothly using the same conditions utilized for β-rhamnosides.[36]

Table 4. β-Mannosylation with Donor 28





[a] The reaction was carried out at 0 ºC [b] The reaction was carried out at room temperature.

Since no direct evidence can prove the participation of the *eq*-4-O-acyl group in glycosylation,[12, 25, 27, 37, 38] we identified the necessity of the 4-O-acyl group for this reaction. An armed 4-O-benzyl group (**37**) or a disarmed 4-O-tosyl group (**38**) was installed, respectively, and in both cases, dominating α-selectivities were observed (**Fig. 2a**). These results demonstrate that the 4-O-acyl group is indispensable in the β-selectivity. Whether the 4-O-acyl group could form a bridged bicyclic dioxacarbenium was then explored. We prepared a 4-O-trichloroimidoyl **41**,[25, 38] which was successfully converted into a bridged bicyclic product **42** in an excellent yield (90 %, **Fig. 2b**, including the crystal structure of **42**). Whereas efforts to capture the bridged bicyclic dioxacarbenium intermediate using 4-O-Boc, hemiphthalate, *t*-butyl phthalate, and ortho-(*t*-butoxy)phenylcarbonate were not successful. It is consistent with that the participation of 4-O-ester is a weak interaction and the further study of the stereodirecting mechanism is necessary (**Scheme S3**, Supporting information).[27]

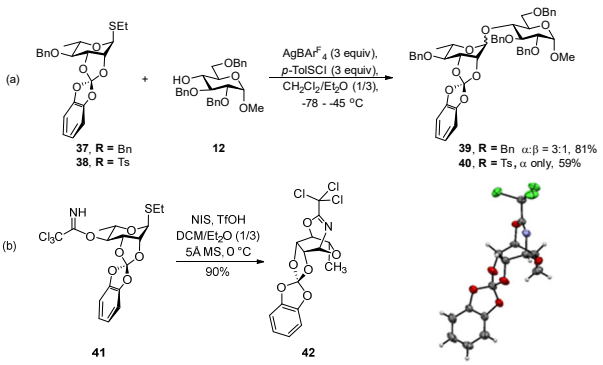


Figure 2. Mechanism Exploration. a) Glycosylation with Various 4-O-Substituents. b) Formation of Bridged Cyclic Product.

In summary, readily prepared, shelf-stable thiorhamnoside and thiomannoside donors with 2,3-*O*-benzo[1,3]-dioxol-2-ylidene and 4-*O*-acyl protections gave excellent β-selectivities with both primary and secondary alcohols. The reaction conditions were critical for the β-selectivity, and weakly coordinating anion from $AgBAr^F_4$ or $AgCB_{11}H_{12}$ in conjunction with *p*-TolSCl could facilitate the directing effect from the 2,3-*O*-orthocarbonate and 4-*O*-acyl group.

Supporting Information

The Supporting Information is available on ChemRxiv website.
General procedure, optimization details, characterization data, crystallographic data, and NMR spectra for all compounds (PDF).
CCDC 2252269 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Corresponding Author

*fcai@sdu.edu.cn

Author Contributions

[+] These authors contributed equally to this work.

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