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Highly Direct α-Selective Glycosylations of 3,4-*O*-Carbonate-Protected 2-Deoxy- and 2,6-Dideoxythioglycosides by Preactivation Protocol

Yin-Suo Lu, Qin Li, Li-He Zhang, and Xin-Shan Ye*

The State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Xue Yuan Rd #38, Beijing 100083, China

xinshan@bjmu.edu.cn

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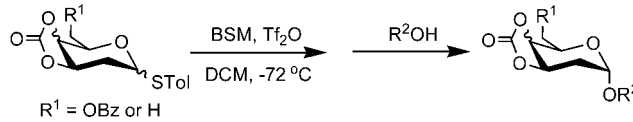
ABSTRACT



A new efficient pre-activation method for the highly α-stereoselective glycosylation of 2-deoxysugars and 2,6-dideoxysugars has been developed using 2-deoxy- and 2,6-dideoxythioglycosides as glycosyl donors. The approach allows a wide range of glycosyl acceptors and donors to be used; the α-selectivity is very good to excellent.

2-Deoxyglycosides containing either α- or *β*-glycosyl linkages are frequently found as integral components of many important natural products, especially antitumor antibiotics.[1] The stereoselective assembly of 2-deoxyglycosyl linkages is more challenging than that of other glycosyl linkages since 2-deoxyglycosyl donors lack a stereodirecting substituent at the C-2 position and the resulting glycosides are more acid labile due to the lack of an electron-withdrawing C-2 substituent. Strategies for the synthesis of 2-deoxyglycosides with good α- or *β*-anomeric selectivities rely heavily on indirect glycosylation. The indirect strategy involves the installation of a directing group at C-2 which is reductively removed after the glycosylation step has been completed.[2] Indirect approaches to 2-deoxyglycosides mainly exploit 1,2-migration,[3] introduce auxiliary groups at the C-2 position,[2] use 2,6-anhydro-2-thio sugars as donors,[4] or cyclize acyclic sulfanyl alkenes.[5] In some cases, glycals are used as donors.[6,7] Most of these methods need a subsequent reduction step which might be not suitable for the construction of some complex natural products. Therefore, a direct strategy for the preparation of 2-deoxyglycopyranosyl linkages that uses 2-deoxyglycopyranosyl donors would be more efficient and practical than the indirect strategies. Although some direct methods such as glycosylation promoted by silver silicate,[8] I_2-Et_3SiH,[9] $AgPF_6$,[10] or polymer-bound iodate(I) com-

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plexes[11] have been used, other approaches have been explored including the conformational assistance approach[12] and the use of *S*-(2-deoxyglycosyl) phosphorodithioates and 2-pyridylthioglycosides as donors.[13] Phosphites, phosphoramidites, and (2-carboxy)benzyl have also been examined as leaving groups in the 2-deoxy systems.[14] Lewis acid- or metal-catalyzed syntheses of 2-deoxyglycosides from glycals[15] have additionally been developed. However, the direct synthesis of 2-deoxyglycopyranosides from 2-deoxyglycosyl donors, with high stereoselectivity, still remains a difficult task. For instance, for the synthesis of 2-deoxy-α-glycopyranosides, good α-selectivity is usually obtained when the galactose-type 2-deoxy sugars are used as glycosyl donors, but the selectivity is not good when the glucose-type 2-deoxy sugars are used. Another weak point of current methods is the relatively narrow window of glycosyl acceptors that perform with good stereoselectivity. Thus, we wanted to develop a direct α-selective glycosylation method for the construction of 2-deoxyglycopyranosides with wide donor and acceptor applicability.

In recent years, "pre-activation" as a new glycosylation approach has generated considerable interest.[16] "Pre-activation" was developed as an effective method for the iterative one-pot synthesis of oligosaccharides in Huang's laboratory as well as in our own group.[17] Very recently, when this protocol was applied to the glycosylation of oxazolidinone-protected glucosamine donors, either α- or *β*-selective glycosyl coupling reactions were realized.[18] Enlightened by this work, we applied the "pre-activation" protocol to the direct synthesis of 2-deoxyglycopyranosides and herein report that high α-selectivity results from the use of carbonate-protected 2-deoxythioglycosides as glycosyl donors.

The "pre-activation" approach was conducted in a manner where the glycosyl donor was completely activated and consumed (by TLC detection) prior to the addition of a glycosyl acceptor. First, the glucose-type 2-deoxysugar donors were examined. Inspired by the results of oxazolidinone-protected glucosamines,[18] we used the carbonate group to mask the hydroxyls at the C-3 and C-4 positions of 2-deoxyglucosides in order to get similar results to those as the conformation-constrained donors.[18,19] The C-6 hydroxyl was protected by a benzoyl group. The combination of benzenesulfinyl morpholine (BSM)[20] and triflic anhydride (Tf_2O) was used as the promoter system in the preactivation operations. Thus, the carbonate-protected thioglycoside **1a** was preactivated at −72 °C in anhydrous dichloromethane using BSM−Tf_2O. After disappearance of donor **1a** (TLC detection in around 5 min) the acceptor **2a** was added to the reaction mixture. Very fortunately, the coupling reaction of **1a** and **2a** exhibited complete α-selectivity and proceeded as shown in Table 1 (entry 1). Next, our investigation was expanded to other glycosyl acceptors **2b**−**g**, and the results are listed in Table 1. As displayed, all the glycosylations proceeded very smoothly in high yields with excellent α-selectivity. The α-anomers were identified by their ^{1}H NMR coupling constants for the anomeric protons or the coupling constants for the axial protons at the C-2 position of deoxysugars ($J_{1,2} = 3.0-4.0$ Hz). It was found that donor **1a** coupled with diverse glycosyl acceptors, including pyranosides as well as furanosides. It was shown that the α-selectivity of acceptor **2b** was better than acceptor **2c** (Table 1, entry 2 vs entry 3); one might therefore conclude that higher reactivity acceptors can improve the stereoselectivity of these glycosylations.[21] The glycosyl acceptors **2e** and **2f**, which differ only in their anomeric configurations, provided the same excellent α-stereoselectivity during the glycosylations (Table 1, entry 5 vs entry 6). On the other hand, when *β*-thioglycoside **1b** was used as the glycosyl donor instead of **1a**, under the same preactivation conditions, the stereochemical outcome of glycosylation was almost the same (Table 1, entry 8 vs entry 4), which means that the anomeric configuration of donors has no influence on the stereoselectivity of these glycosyl coupling reactions.

The α-selectivity of 2-deoxygalactopyranosyl donors has already been recognized in the literature.[12,13b,14b] To extend the scope of our methodology, thiogalactoside donor **1c** was synthesized. Methyl glycosides **2a**, **2b**, **2d**, and **2f**, in which the 6-OH, 4-OH, 3-OH, and 2-OH were exposed, respectively, were again used as the glycosyl acceptors. Under the above-mentioned preactivation glycosylation conditions, all

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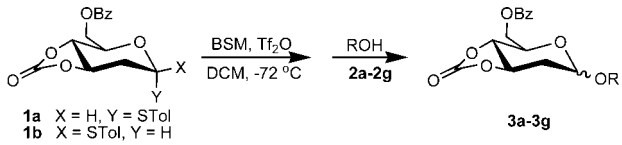
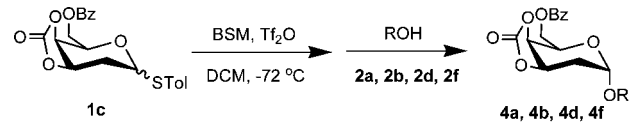
Table 1. Glycosylation of Donors **1a** and **1b** with Various Acceptors by Preactivation



entry	donor	acceptor(ROH)	product	yield[%]	α/β ratio
1	**1a**	**2a**	**3a**	81	α only
2	**1a**	**2b**	**3b**	90	> 20:1
3	**1a**	**2c**	**3c**	90	14:1
4	**1a**	**2d**	**3d**	83	20:1
5	**1a**	**2e**	**3e**	95	α only
6	**1a**	**2f**	**3f**	89	α only
7	**1a**	**2g**	**3g**	80	α only
8	**1b**	**2d**	**3d**	84	α only

Table 2. Glycosylation of Donor **1c** with Various Acceptors by Preactivation



entry	acceptor (ROH)	product	yield [%]	α/β ratio
1	**2a**	**4a**	81	α only
2	**2b**	**4b**	80	α only
3	**2d**	**4d**	83	α only
4	**2f**	**4f**	81	α only

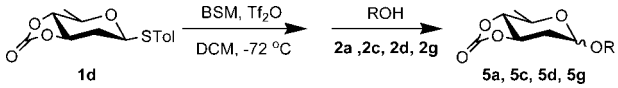
of the coupling reactions proceeded with exclusive α-selectivity and in good yield (Table 2). Therefore, in the 2-deoxygalactose case, our method is at least as good as the reported approaches to 2-deoxygalactosides.

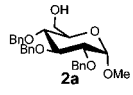
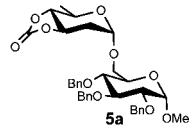
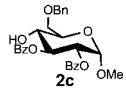
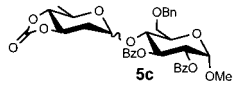
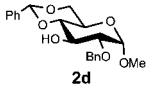
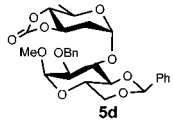
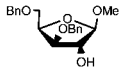
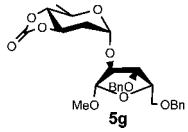
2,6-Dideoxysugars are also found in a plethora of biologically important natural products.[1] To further verify the effectiveness of our method, the construction of 2,6-dideoxyglycosyl linkages was investigated. For this purpose, thioglycoside donor **1d** was synthesized, and monosaccharide building blocks **2a**, **2c**, **2d**, and **2g** were chosen as the glycosyl acceptors. The glycosyl coupling reactions between donor **1d** and acceptors **2a**, **2c**, **2d**, and **2g** by the preactivation protocol were carried out. The results are listed in Table 3. As shown, all of the reactions displayed good to excellent α-selectivity. It appears that the α-selectivity of 2,6-dideoxyglycosyl linkages is almost as good as that of 2-deoxyglycosyl linkages when the preactivation glycosylation approach is used. Although the selectivity is a little lower with the poorly reactive acceptor **2c**, it is still very good (entry 2, Table 3).

In light of the excellent α-selectivity of these glycosylations, it is natural for us to wonder whether it was achieved due to the preactivation strategy. So the comparison experiments were performed. The coupling of donors **1a** and **1d** with high and low reactivity acceptors, promoted by BSM−Tf_2O, under routine glycosylation conditions (non-preactivation operations) was examined (Table 4). It was found that only trace amounts or very small amounts of disaccharide products were gained when donor **1a** reacted with reactive acceptors **2b** and **2d** under routine glycosylation operations (entries 1 and 2, Table 4), whereas **1a** reacted with **2b** and **2d** under the same conditions in preactivation manner providing the corresponding disaccharides **3b** and **3d** in high yields (90% for **3b** and 83% for **3d**, Table 1) and with excellent selectivity (α/β ratio ≥20:1, Table 1). We think that highly reactive acceptors might be unstable in the presence of BSM−Tf_2O. When the highly reactive acceptor **2b** was added to the BSM−Tf_2O mixture in the absence of the donor, the acceptor almost decomposed. Under routine BSM−Tf_2O activation conditions, the coupling reactions of donors **1a** and **1d** with low reactive acceptor **2c** occurred smoothly (entries 3 and 4, Table 4). However, the stereoselectivity was lower than that obtained by preactivation

protocol (in comparison with entry 3, Table 1, and entry 2, Table 3). It was thus demonstrated that preactivation operations can greatly influence the outcomes and stereochemistry of glycosyl coupling reactions.

Table 3. Glycosylation of Donor **1d** with Various Acceptors by Preactivation



entry	acceptor (ROH)	product	yield [%]	α/β ratio
1	 **2a**	 **5a**	87	α only
2	 **2c**	 **5c**	89	10:1
3	 **2d**	 **5d**	89	α only
4	 **2g**	 **5g**	80	α only

The high α-selectivity observed might originate from the species formed as intermediates after preactivation. Once activated, the carbonate protected donor becomes an oxacarbenium ion, which can be trapped by triflate anion to give either α-triflate or *β*-triflate intermediate.[22] As a result of the low reactivity of the cyclocarbonated derivatives,[23] we might assume that the acceptor might prefer to undergo an S_N2-like reaction with the more reactive *β*-triflate intemediate, resulting in the formation of α-glycosides. This process might shift the anomerization equilibrium from the α- to *β*-triflate intermediate. This might also explain how the higher stereoselectivity was achieved when more reactive acceptors were employed.

In conclusion, a new efficient method for highly α-stereoselective glycosylations of 2-deoxysugars and 2,6-dideoxysugars has been uncovered. By comparison with the routine glycosylation approach, the preactivation method may play an important role in the outcomes and stereochemistry of glycosylations of glucose and galactose type donors. The presence of a 3,4-*O*-carbonate group in glycosyl donors appears necessary to enhance α-selectivity; presumably, this occurs by conformational constraint. This approach enjoys a large scope in terms of glycosyl acceptors and donors. The α-stereoselectivity toward glycosyl couplings is very good to excellent. In addition, the carbonate-protected thioglycoside donors are stable and easy to prepare, and the glycosylations are rapid. It is expected that the disclosed protocol might find widespread applications in the synthesis of α-linked 2-deoxyglycopyranose-containing complex structures with important biological functions. Further extension of this protocol to *β*-selective glycosylations is currently under investigation.

(22) See ref 18b and references therein.
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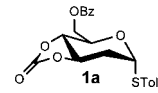
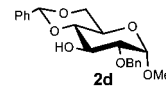
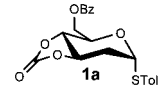
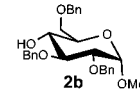
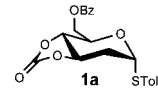
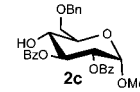
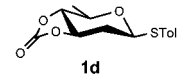
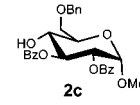
Table 4. Glycosylations Conducted in Routine Operations

entry	donor	acceptor	reaction results
1	 **1a**	 **2d**	Yield < 5% α:β ≈ 1:1
2	 **1a**	 **2b**	trace amount[a]
3	 **1a**	 **2c**	Yield: 90% (90%)[b] α:β = 7.3:1 (14:1)[b]
4	 **1d**	 **2c**	Yield: 95% (89%)[b] α:β = 4.4:1 (10:1)[b]

[a] Detected by TLC. [b] The numbers in the parentheses were obtained in preactivation operations.

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Supporting Information Available: All experimental procedures and data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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