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Novel Zinc (II)-Mediated Epimerization of 2′-Carbonylalkyl-α-*C*-glycopyranosides to Their *β*-Anomers

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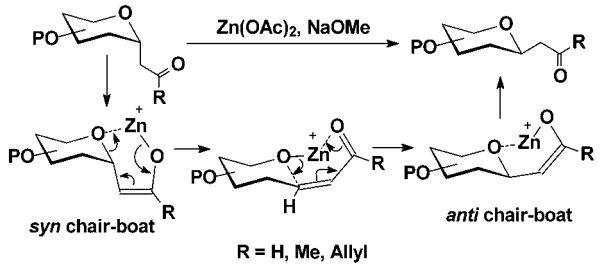
C-glycosides occur as subunits of a variety of biologically important natural products with antitumor, antibacterial, or antiviral activity,[1] and as stable metabolic mimics of their natural *O*- and *N*-counterparts may serve as biological tools and potential therapeutics.[2] The stereoselective synthesis of *C*-glycosides has attracted considerable interest and the synthetic methodology has advanced significantly in the past decade.[1,3] However, most of the methods available are more suited for the synthesis of α-*C*-glycosides. Although stereoselective routes to *β*-*C*-glycosides exist, in practice their use is very limited because of their low yields, poor selectivity, or lack of general applicability due to the complicated procedures involved. Typically, *β*-*C*-glycosides can be made by addition of a nucleophilic reagent to a sugar lactone, giving the corresponding hemiketal or exoglycal, which is then reduced by various reagents,[4] or by a Wittig or Grignard reaction at the anomeric position, forming an unsaturated, open-chain intermediate, followed by an intramolecular cyclization.[5] The stereoselectivity of these reactions are subject to the influence of the neighboring group at 2-*O*-position of the sugar substrates. Consequently, these procedures are limited to selectively preparing *gluco*- and *galacto*-*β*-*C*-glycosides, but are ineffective for the stereoselective preparation of *manno*- and other 2-*deoxy* sugar *β*-*C*-glycosides. Samarium and 1,2-anhydrosugar-based *C*-glycosylation methods for the synthesis of 1,2-*trans*-*C*-glycosides also fail to yield *manno*-*β*-*C*-glycosides.[6] Currently, the best stereoselective syntheses of *manno*-*β*-*C*-glycosides can be achieved (1) by using a tethered approach, which involves placing a silicon-alkynyl group at the 2-*O*-position in combination with activation of C1 by pyridyl sulfone,[7] (2) by a modified Keck reaction,[8] in which glycosyl dihalides are first reacted with allyltin reagents to form halo *C*-allyl glycosides, followed by radical reduction of halide, or (3) by condensation of mannopyranose with a sulfur ylide to an epoxide, followed by intramolecular cyclization.[9]

Obviously, more effective and general methods are needed for the preparation of *β*-*C*-glycosides, especially in the case of *manno*-*β*-*C*-glycosides. Considering the easy accessibility of α-*C*-glycosides a facile transformation of α-*C*-glycosides to *β*-*C*-anomers would be particularly attractive. The strategy could lead to the use of fewer building blocks and create more flexibility in the syntheses of complex structures. Previously, we had attempted a C1 epimerization on α-*C*-2-ulosides with the objective of preparing *β*-anomers without success. Instead, ring-contracted cyclopentenones were obtained.[10] We now report a general procedure, which effectively converts 2′-carbonylalkyl-α-*C*-glycosides (aldehydes and ketones) to their respective *β*-anomers including *manno*-*β*-*C*-glycosides.

Allyl-α-*C*-glucoside was ozonolized and reduced by Zn/HOAc to aldehyde **1**. Without further purification, treatment with $NaBH_4$ in ethanol afforded exclusively, following acetylation (Ac_2O/Py), the *β*-*C*-glucoside (**2**) in good yield, and not the expected α-anomer.[11] We were encouraged by this serendipitous observation to pursue this reaction further, and after careful examination of the reaction conditions a plausible mechanism was hypothesized which is illustrated in Scheme 1. We hypothesized that the epimerization at C1 is initiated by the formation of Zn-enolate and it is known that Zn-enolate adopts exclusively the *Z*-configuration,[12] which can be stabilized by intramolecular chelation to the pyranose ring oxygen to form a *syn* chair-boat structure. Due to the activation generated by the Zn−O coordination, fission of the C1−O bond occurs, leading to opening of the pyranose ring, which is spontaneously followed by a change in conformation. The more stable *anti* chair-boat transition state is favored, and the subsequent hetero-intramolecular Michael addition results in the formation of *β*-*C*-glycoside in a ring-closure step.

Scheme 1



We performed the reaction with such a mechanism in mind. Thus, aldehyde **1** was first converted to Zn-enolate by treatment with $ZnO(Ac)_2$ in NaOMe/MeOH,[13] which led to C1 epimerization. $NaBH_4$ was then added to reduce the aldehyde which followed by acetylation (Ac_2O/py) afforded *β*-*C*-glucoside **2** in 77% yield (see Table 1, entry 1). The structure and the stereochemistry of the anomeric carbon were unambiguously determined by various ^1H NMR experiments. An upfield shift of the H-1 chemical resonance from δ_H 4.25 ppm (α-anomer, $J_{1,2}$ 6.5 Hz) to δ_H 3.37 ppm ($J_{1,2}$ 9.5 Hz) for *β*-*C*-glucoside is observed. In addition, also observed are nOe's among H-1, H-3, and H-5 that confirm the *β*-configuration. Similarly, *galacto*-α-*C*-glycoside **3** was also easily rearranged to its *β*-anomer **4** (entry 2) and to **5** after reduction and acetylation (entry 3).

The ultimate challenge for the method would be the synthesis of *manno*-*β*-*C*-glycosides and to test its applicability to this synthesis two α-*C*-mannosides (**6** and **8**) (entries 4 and 5) were subjected to above conditions. Without difficulty both were converted to *β*-anomers (**7** and **9**) exclusively. Hence, epimerization was successfully performed in *gluco*-, *galacto*-, and *manno*-*C*-glycosides. Unlike other *C*-glycosylation methods[4−7] 2-*O*-substitution and the config-

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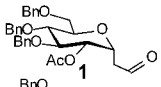
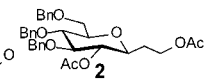
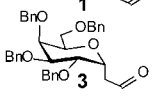
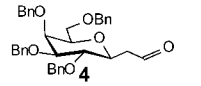
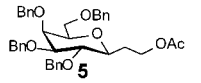
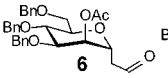
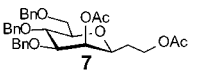
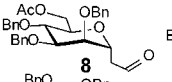
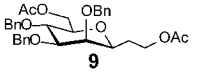
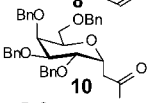
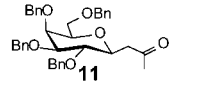
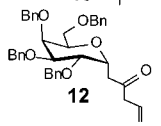
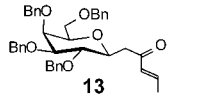
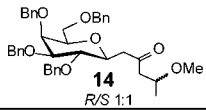
Table 1. Epimerization to β-*C*-glycosides[a]

Entry	α-*C*-glycoside	Product	Yield [b]
1[c]			77% (3 steps)
2			66%
3[c]	**3**		62 % (3 steps)
4[c]			60% (3 steps)
5[c]			67% (3 steps)
6			95%
7			5%
			75%

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[a] Reagents and conditions: 5−10 equiv $Zn(OAc)_2$ in 4% NaOMe/MeOH at rt overnight. [b] Isolated yields with essentially one product based on TLC. [c] Reduced ($NaBH_4$) and acetylated.

uration of the 2-*O*-substituent do not affect the β-stereoselectivity of this epimerization. Thus, this communication describes a novel method for the synthesis of 2′-carbonylmethyl-β-*C*-glycosides, which is particularly useful for the preparation of *manno*-β-*C*-glycosides.

To illustrate the scope of this method, we extended this procedure to 2′-ketones of α-*C*-glycosides. In the presence of $Zn(OAc)_2$ and NaOMe both 2′-ketones (**10** and **12**)[14] were completely epimerized to their β-anomers (entries 6 and 7). The products were isolated without $NaBH_4$ reduction and were consistent with the mechanism as shown in Scheme 1.[15] Although β-*C*-glycoside **13** from epimerization of ketone **12** was isolated, the major product was **14**, which was formed by further Michael addition of MeO^- to **13**. Both diastereomers were formed in this case in the ratio of 1:1 as indicated by ^1H NMR analysis.

The amount of $Zn(OAc)_2$ used in the experiments (entry 4) described above varied from 0.5 to 10 equiv and had no effect on either the yield or stereoselectivity of the epimerization. Therefore, this rearrangement probably proceeds using catalytic amounts of Zn (II). However, the base used has to be strong enough to achieve complete C1 epimerization.

In summary we have discovered a broadly applicable method for the synthesis of 2′-carbonylalkyl-β-*C*-glycosides. This novel zinc (II)-mediated epimerization has been applied to 2′-aldehydes and 2′-ketones of *gluco*-, *galacto*-, and *manno*-β-*C*-glycosides. Obviously, the utility of these functional groups may be further exploited. The procedure described is very simple and reliable without use of toxic and special reagents. This method may also be applied to the epimerization of other pyranose compounds.

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Supporting Information Available: Experimental procedures and ^1H, COSY, NOESY, and ^{13}C NMR spectra of products (**2**, **4**, **5**, **7**, **9**, **11**, **13**, **14**) and α-*C*-glycosides (**10** and **12**) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) We observed that the β-*C*-glucoside **2** was obtained when the reduction of aldehyde **1** was performed with an excess amount of $NaBH_4$ and the reaction was unusually slow (12 h, reflux) probably due to enolation. The reduction was fast (0.5 h at rt) with less $NaBH_4$ used, and only α-*C*-glycoside (δ_H 4.25 ppm, H-1, $J_{1,2}$ 6.5 Hz) was obtained.

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(13) We also treated aldehydes (**1** and **6**) with 5% Zn in 1% NaOEt/EtOH. After reduction ($NaBH_4$) and acetylation (Ac_2O/Py) epimerized products (**2** and **7**) were also obtained in moderate yields (30−50%).

(14) Allyl 2,3,4,6-tetra-*O*-benzyl-α-*C*-galactopyranoside was treated with $Hg(OAc)_2$, the resultant 2′-alcohol was oxidized to ketone (**10**) using DMSO−Ac_2O. Another ketone **12** was synthesized from **3** in two steps: (1) Grignard reaction (allylMgBr) and (2) DMSO−Ac_2O oxidation.

(15) We have no spectroscopic data to support the intermediate structures and stereochemistry illustrated in Scheme 1. However, the similar intermediates have been previously reported (ref 5).

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