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Stereoselective propargylation of glycals with allenyltributyltin(IV) via a Ferrier type reaction

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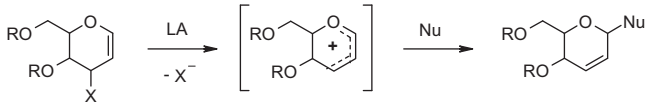
ABSTRACT

Stereoselective introduction of an unsubstituted propargyl group to various glycals was achieved using a Ferrier type reaction with allenyltributyltin(IV). The stereoselectivity was observed based on the conformational preference of glycals as well as steric control of rigid bicyclic systems.

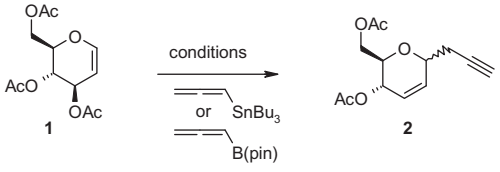
Introduction

In recent years, C-glycosides have attracted significant attention within the scientific community.[1] Various subunits of C-glycosides are found in nature including aloin,[2] anthraquinones,[3] showdomycin, and formycin.[4] In addition, C-glycosides have been used as chiral building blocks[5] for the synthesis of biologically active natural products such as palytoxin, spongistatin, tautomycin, ciguatoxin, okadaic acid, and halichondrin, etc.[6] Furthermore, due to their stable pharmacophore nature, C-glycosides were also studied as potential novel enzyme inhibitors in inflammation pathways, cellobiase, β-D-galactosidase, phosphorylases, immune pathway, and lectin binding.[7] For these reasons, the development of efficient and selective construction of C-glycosidic linkages continues to be an important task. One of the most common methods of constructing a C-glycosidic bond involves an electrophilic substitution reaction where carbon nucleophiles react with an oxocarbenium ion. Due to the facile generation of an oxocarbenium ion intermediate, 2,3-unsaturated glycosides (known as 'glycal') have proven useful for a broad range of applications via a Ferrier type reaction (Scheme 1).[8]

The exceptional synthetic utility of the Ferrier type reaction using glycal systems has been demonstrated by allyl-, alkyl-, aryl-, allenyl-, and alkynylations.[9] However, there are very limited examples of introducing a propargyl group to glycals.[10] Very recently, Panek's group reported stereoselective C-glycosidations with both substituted achiral and enantioenriched allenylsilanes resulting in a substituted propargyl group in the ring.[11] Isobe's group reported that propargylic and acetylenic silyl groups on propyne produced C-glycosidation products with appropriate choice of silyl groups.[12] In the case of unsubstituted propargylation, only one example was shown by Kobayashi's group where they used allenylboronic acid pinacol ester.[13] Herein, we report broad examples of unsubstituted propargylation of glycals using commercial allenyltributyltin via a Ferrier type reaction.



Scheme 1.



Scheme 2. Initial attempts under various conditions. Reagents and conditions: Lewis acid: TMSOTf, TMSI, $BF_3{\cdot}OEt_2$, $InCl_3$, $In(OTf)_3$, $AlMe_3$, AgOTf, I_2; solvent: DCM, CH_3CN, CH_3NO_2, THF, benzene, toluene; temperature: RT to −78°.

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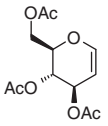
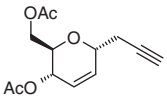
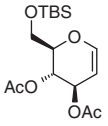
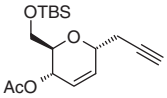
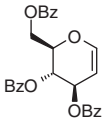
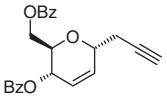
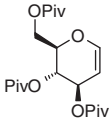
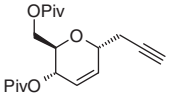
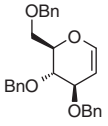
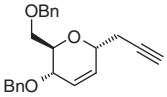
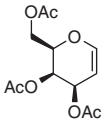
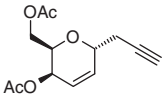
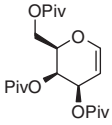
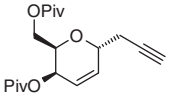
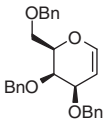
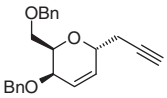
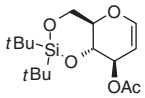
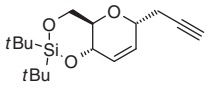
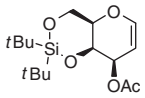
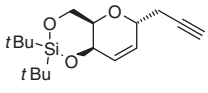
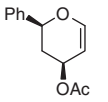
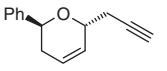
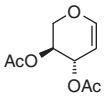
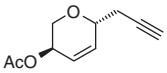
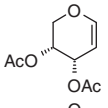
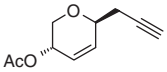
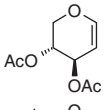
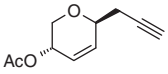
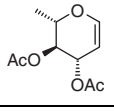
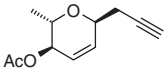
Table 1
$BF_3{\cdot}OEt_2$ mediated propargylation of glycals with allenyltributyltin(IV)

Entry		Glycal		Product	Time (min)	Yield[a] (%)	Ratio[b] α:β
1	**1a**		**2a**		20	>99	2:1
2	**1b**		**2b**		15	93	1.7:1
3	**1c**		**2c**		30	>99	2:1
4	**1d**		**2d**		60	>99	2:1
5	**1e**		**2e**		120	97	3:1
6	**1f**		**2f**		180	89	5:1
7	**1g**		**2g**		240	>99	5:1
8	**1h**		**2h**		120	92	8:1
9	**1i**		**2i**		20	97	8:1
10	**1j**		**2j**		70	96	α only
11	**1k**		**2k**		10	>99	α only
12	**1l**		**2l**		10	91	4:1
13	**1m**		**2m**		10	>99	1:4
14	**1n**		**2n**		10	>99	1:4
15	**1o**		**2o**		10	51	1:1.4

[a] Isolated yield.
[b] Ratio was determined by ^{1}H NMR.

Results and discussion

As shown in Scheme 2, our initial attempts were made by reacting tri-*O*-acetyl-D-glucal with either allenylboronic acid pinacol ester or allenyltributyltin under various Lewis acid conditions and solvents (DCM, THF, actonitrile, toluene, etc.). The use of allenylboronic acid pinacol ester did not give satisfactory results, giving low reaction yields or no reaction. The best result was obtained with allenyltributyltin and $BF_3{\cdot}OEt_2$ as Lewis acid in DCM at rt.[14] The reaction went smoothly to complete conversion within 20 min, producing the desired propargylated C-glycosides quantitatively with $\alpha{:}\beta$ ratio = 2:1. The diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture.

In order to assess the scope of this reaction, the optimal conditions were applied to various glycals producing 2,3-unsaturated C-glycosides efficiently (Table 1). The propargylation of tri-*O*-benzoyl-D-glucal and TBS-protected D-glucal gave a similar result to tri-*O*-acetyl-D-glucal in terms of the reaction yield and the ratio (entries 2 and 3). Changing to bulkier protecting groups such as pivalic ester did not improve the ratio (entries 4 and 7). It is worth mentioning that the reaction with tri-*O*-benzyl-glycals went efficiently, showing a slight improved ratio (entries 5 and 8). Presumably, electron-rich benzyloxy group at C-5 could stabilize the oxocarbenium ion from the β face to form a five-membered ring dioxonium ion intermediate, which would be quenched with allenyltributyltin from the α face (Fig. 1).

Compared to the reactions with D-glucal derivatives, the reaction with tri-*O*-acetyl-D-galactal afforded an improved ratio, $\alpha{:}\beta$ = 5:1 (entry 6). Undoubtedly, the conformation of glycals plays an important role in regard to the stereoselective outcome. As shown in Figure 2, glycals in solution adopt both $^4H_5$ and $^5H_4$ half-chair conformations in equilibrium. There are several known factors influencing the peracetylated glycal conformations. Firstly, the allylic effect dictates the pseudo-axial orientation of the acetoxy group at C-3.[15] Secondly, 1,3-diaxial interactions disfavor the $^5H_4$ conformation when there is a substituent at C-5. Thirdly, the 4-OAc group prefers an axial orientation when the 3-OAc group is oriented pseudo-equatorially. When the two acetoxy groups are oriented equatorially at C-3 and C-4 adjacent to the double bond, the formation of a nearly coplanar structure destabilizes its conformation.[16] Therefore, the $^4H_5$ conformation of tri-*O*-acetyl-D-galactal is more stable than tri-*O*-acetyl-D-glucal (molar fractions in the $^4H_5$ conformation in acetone: 88% and 59%, respectively).[17] Conversely, L-arabinal is known to exist predominantly in the $^5H_4$ conformation, even though the other $^4H_5$ conformation has no 1,3-diaxial interactions. This preferred conformation can be explained by a 'vinylogous anomeric effect (VAE)', a vinylogous hyperconjugative interaction between the lone pair on the oxygen and the oxygen-C3 antibonding orbital.[18] In order to make a favorable overlap between the antibonding σ^*_{CX} orbital with the lone-pair orbital, n_o through the π bond delocalization, a vinylogous C–X bond favors an axial orientation (Fig. 3).

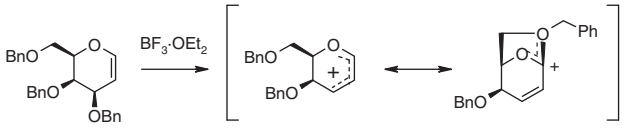


Figure 1. The hypothesis of neighboring group participation.

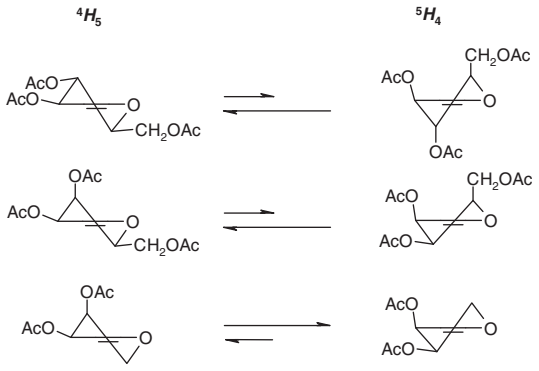


Figure 2. The equilibrium of glycal conformation in solution.

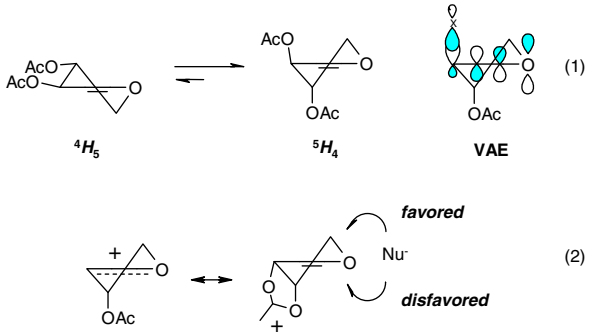


Figure 3. The ground-state conformational preference of 3,4-di-*O*-acetyl-D-xylal due to vinylogous anomeric effect.

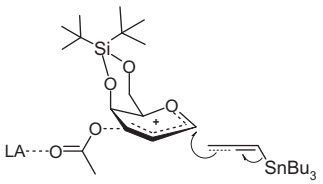


Figure 4. A proposed transition state for highly stereoselective propargylation of glycal **1j**.

Such stereoelectronic interactions also induce C–X bond lengthening and enhanced reactivity in the conformers.[19] The beneficial outcome of VAE can be found in the reaction with all 3,4-di-*O*-acetyl-glycals. It is interesting to see when 3,4-di-*O*-acetyl-L-arabinal was subjected to the reaction conditions, the ratio improved to $\alpha{:}\beta$ = 4:1 (entry 12). A similar reactivity was observed in the reactions with 3,4-di-*O*-acetyl-D-arabinal (entry 13) and 3,4-di-*O*-acetyl-D-xylal (entry 14). As shown in Figure 3, the $^5H_4$ conformational preference of D-xylal over $^4H_5$ resulted in a more favorable nucleophilic attack from the β-face. However, the reaction with 3,4-di-*O*-acetyl-6-deoxy-L-glucal gave almost no stereoselectivity, indicating no conformational preference in solution (entry 15).

Next, we drew our attention to more rigid bicyclic ring systems. Initially, when the PMP-acetal protected glycal was subjected to the reaction conditions, it gave a complex mixture of products. However, when di-*tert*-butylsilyl protection was introduced to the ring, the reaction went smoothly producing the desired products. Noticeably, the sterically bulky di-*tert*-butylsilyl protection not only provides the glycal a more rigid bicyclic conformation, but also efficiently blocks the nucleophile from the β-face producing α-glycosides as the major product (Fig. 4). The most dramatic steric effect was found with di-*tert*-butylsilyl galactal. Only one stereoisomer was observed in the crude reaction mixture (entry 10). A similar effect was observed when a phenyl group was directly introduced into the ring (entry 11).

In conclusion, we have developed a propargylation reaction of glycals using commercial allenyltributyltin via a Ferrier type reaction. The stereoselectivity of the reaction was observed based on the conformational preference of glycals. It is also worth mention-

ing that steric control of a rigid bicyclic system such as di-*tert*-butylsilyl glycal affords exclusively α-glycosides.

Representative procedure

$BF_3{\cdot}OEt_2$ (150 μL, 1.2 mmol) was added to a mixture of tri-*O*-acetyl-D-glucal (272 mg, 1.0 mmol) and allenyltributyltin (495 mg, 1.2 mmol, Alfa Aesar tech. 80%) in CH_2Cl_2 (5 mL) at rt. The mixture was stirred at rt for 20 min and was quenched with aqueous $NaHCO_3$. The phases were separated and the aqueous phase was thoroughly extracted with CH_2Cl_2. The combined organic extracts were washed (brine), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel chromatography with 20% EtOAc/hexanes to give the desired C-glycosides (250 mg, >99% yield)

Acknowledgment

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References and notes

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