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•Special topic•

Anomeric configuration-dependence of the Lattrell-Dax epimerization from D-glucose to synthetically useful D-allose derivatives

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[ABSTRACT] D-Allose and its derivatives play important roles in the field of health care and food nutrition. Pure and well-defined D-allose derivatives can facilitate the elucidation of their structure-activity relationship as an essential step for drug design. The Lattrell-Dax epimerization, refers to the triflate inversion using nitrite reagent, is known as valuable method for the synthesis of rare D-allose derivatives. Here, the influence of protecting group patterns on the transformation efficiency of D-glucose derivatives into synthetically useful D-alloses and D-allosamines *via* the Lattrell-Dax epimerization was studied. For C3 epimerization of D-glucose derivatives bearing *O*2-acyl group, an anomeric configuration-dependent acyl migration from *O*2 to *O*3 was found. In addition, a neighbouring group participation effect-mediated S_N1 nucleophilic substitution of the D-glucosamine bearing C2 trichloroacetamido (TCA) group in the Lattrell-Dax epimerization was dependent upon anomeric configuration. Thus, the effect of anomeric configuration on the Lattrell-Dax epimerization of D-glucose suggests that *β*-D-glucosides with low steric hindrance at C2 should be better substrates for the synthesis of D-allose derivatives. Significantly, the efficient synthesis of the orthogonally protected D-allose **13** and D-allosamine **18** will serve well for further assembly of complex glycans.

[KEY WORDS] D-allose; D-allosamine; Epimerization; Anomeric configuration; Acyl migration
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Introduction

D-Allose is a rare aldohexose that plays important roles in the field of food and nutrition [1]. This rare sugar has been known as one of the best low calorie supplements and nonnutritive sweetener because of its 80% relative sweetness and ultra-low calorie [2]. In addition, D-allose and its derivatives have drawn much attention in health care field for its pharmaceutical activities, including anti-carcinogenic, anti-inflammatory and anti-oxidative activities [3]. As a potential anti-carcinogenic agent, D-allose shows high capability in inducing the tumor suppressor gene thioredoxin interacting protein (TXNIP). Moreover, combinations of D-allose with radiation [2] or with 5-fluorouracil [4], have markedly enhanced the efficacy of cancer therapy. Besides, there has been increasing awareness of the fact that allose derivatives are key intermediates for developing a variety of important pharmaceuticals [5], or valuable analogues to identify the mechanisms of pharmaceutical activities [6, 7].

Notably, pure and well-defined D-allose derivatives can facilitate the elucidation of their structure-activity relationship as an essential step for drug design. In addition, as a C3 epimer of D-glucose, D-allose and its derivatives are valuable intermediates in the carbohydrate chemistry research [8–11]. Thus, development of efficient chemical methods to access orthogonally protected allose building blocks has received considerable attention [12]. Mehta and coworkers developed a synthetic route to D-*β*-allose with the commercially available cyclooctatetraene as starting material in 18 steps [13]. Significantly, C3 epimerization of D-glucose, the most accessible monosaccharide, has been known as an efficient approach to synthesizing D-allose [14]. Minnaard and coworkers found that Pd/neocuproine catalyst can distinguish between the various hydroxy groups on the sugar ring

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and selectively oxidizes the one at C3. A combination of the catalytic, regioselective oxidation with borohydride reduction achieved the efficient, protecting group-free synthesis of D-allose from D-glucose in two steps [15]. Notably, the Lattrell-Dax epimerization, refers to the triflate inversion using nitrite reagent, has been widely used to establish expedient and facile protocols to synthesize rare sugars that can be used in the assembly of complex glycans [12, 14, 16-17]. Yadav and coworkers have developed a facile synthetic route to orthogonally protected D-allosamine thioglycoside *via* the Lattrell-Dax epimerization at C3 of the D-glucosamine substrate [14]. In our previous synthesis of an aminoglycoside trisaccharide from *Plesiomonas shigelloides* O51, C3 epimerization of a D-glucosamine derivative *via* the Lattrell-Dax epimerization afforded a D-allosamine intermediate, that was transformed to synthetically useful 2, 3-diamino-D-glucose building block *via* nucleophilic substitution [11]. However, a 3-nitro-D-glucosamine byproduct was formed in the Lattrell-Dax epimerization of 3-triflate-D-glucosamine that gave the desired D-allosamine in moderate yield (72%), indicating that the efficient C3 epimerization of D-glucose derivatives remains challenging. Here, we report a study on the influence of protecting group patterns on the transformation efficiency of D-glucose derivatives into synthetically useful D-alloses and D-allosamines via the Lattrell-Dax epimerization.

Result and Discussion

Preparation of orthogonally protected D-glucose derivatives

Focusing on synthesis of synthetically useful D-allose derivatives, a series of orthogonally protected D-glucose substrates were designed (Fig. 1). The benzylidene acetal, which can be easily removed or regioselective reductive ring opening, was chosen as protecting group of C4 and C6 hydroxy groups of D-glucose derivatives. The anomeric oxygens of D-glucose derivatives were protected by the allyl group that has excellent chemical stability and could be selectively removed for further assembly. Considering the possible influence of protecting group patterns of neighbouring C2 hydroxy group on C3 epimerization, levulinoyl (Lev) and benzoyl groups known as participating groups, *tert*-butyldimethylsilyl (TBS) group known as non-participating group were placed at C2 of D-glucose derivatives **1**, **3**, **4** and **2**, respectively. Significantly, levulinoyl (Lev) and benzoyl groups are valuable for the stereoselective formation of the 1, 2-trans-glycosidic bond in further glycosylation reactions. The C2 amino groups of D-glucosamine **5** and **6** were masked by the trichloroacetyl (TCA) group that will facilitate the synthesis of 1, 2-trans-glycosides and can be easily transformed to acetyl group [11]. Moreover, the D-glucose anomeric isomers **3** and **4**, and the D-glucosamine anomeric isomers **5** and **6** would be beneficial for understanding whether the anomeric configuration will influence the outcome of Lattrell-Dax epimerization at C3.

The synthesis of the D-glucose derivatives **1**, **2** and **3** started from commercial diacetone-D-glucose (Scheme 1). Glucose intermediate **7** was synthesized by *O*3-naphthylmethylation, acid-catalyzed hydrolysis of isopropylidene acetals and installation of *O*1-allyl group, and 4, 6-*O*-benzylidene acetal formation in 42% overall yield. Levulinoylation of compound **7** delivered 2-*O*-Lev derivative which was transformed to D-glucose derivative **1** by removal of *O*3-Nap with DDQ [18] in 88% overall yield. Introduction of *tert*-butyldimethylsilyl (TBS) group and subsequent removal of *O*3-Nap converted **7** to D-glucose derivative **2** in 72% overall yield. Compound **3** was synthesized from **7** by *O*2 benzoylation and subsequent *O*3 deprotection in 73% overall yield. In addition, a *β*-glucopyranoside **4** bearing *O*2-Bz was synthesized from *β*-isomer of compound **7** (see Supplementary Material).

Lattrell-Dax epimerization of D-glucoses to D-alloses

Treatment of triflate product of compound **1** with potassium nitrite at 50 °C, the common reaction temperature of the Lattrell-Dax epimerization, converted a small amount of starting material (Scheme 2). Increasing the reaction temperature to 80 °C, the triflate compound was completely consumed and transformed to D-allose product in 38% overall yield from compound **1**. Notably, in addition to desired 2-*O*-Lev-D-allose **8**, 3-*O*-Lev-D-allose **9** was the major product obtained from the C3 epimerization of compound **1**. Triflate compound derived from 2-*O*-TBS-D-glucose **2** was also not completely consumed until increasing the Lattrell-Dax reaction temperature from 50 to 80 °C. Unfortunately, only a C3 amine D-allose derivative **10** was obtained in 22% overall yield from compound **2**. It is presumed that the electron-donating *O*2-TBS decreased the eletrophilicity of 3-carbon, which is not suitable for *O*-attack by nitrite, an essential part

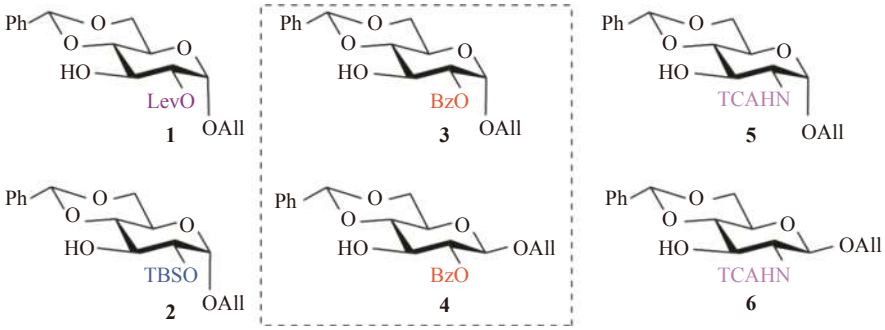
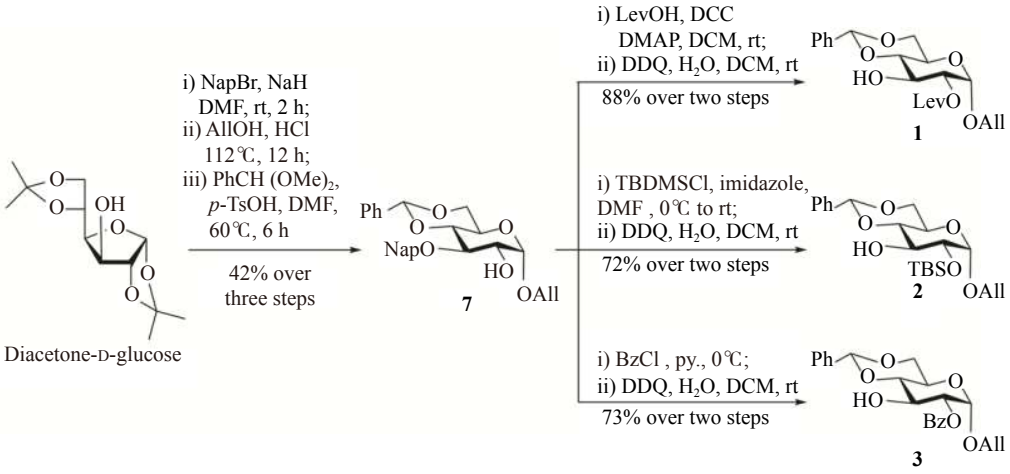
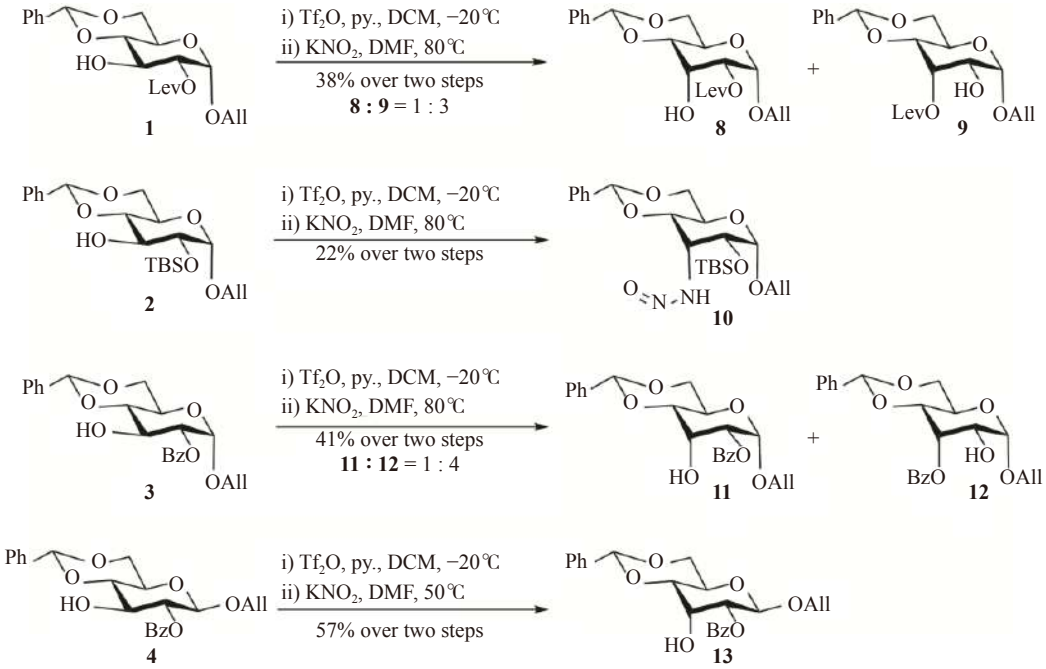


Fig. 1 Glucose and glucosamine derivatives designed as substrates for C3 epimerization



Scheme 1 Synthesis of C3-OH glucose derivatives 1, 2 and 3



Scheme 2 C3 epimerization of glucose derivatives

of the Lattrell-Dax epimerization. Thus, an *N*-attack of the 3-carbon by nitrite and subsequent transformation happened in this reaction condition to afford the byproduct **10**. However, the exact formation mechanism of this rare compound is unknown. The C3 epimerization of compound **3** showed a similar result as compound **1**, delivering desired 2-*O*-Bz-D-allose **11** and byproduct 3-*O*-Bz-D-allose **12** in a ratio of 1 : 4. In addition, the *β*-glycoside **4** was transformed to triflate compound which was smoothly converted to desired D-allose product **13** at 50 °C in 57% overall yield. Notably, no byproduct was observed when compound **4** was employed as starting material, indicating that the side reaction was correlated to anomeric configuration.

The formation of epimerized and acyl migrated product from triflate compound has been reported as a neighbouring group participation effect-mediated epimerization, which was relied on the presence of water for conversion of acyloxonium to orthoester (Fig. 2A) [17, 19]. However, since the Lattrell-Dax epimerization of triflate product were proceeded under anhydrous condition, the D-allose derivatives **9** and **12** should not be formed through this water-mediated epimerization. Considering the base condition of the Lattrell-Dax epimerization, the *O*3-acyl products **9** and **12** could be formed by base-mediated acyl migration of the desired C3 epimerized product (Fig. 2B). Moreover, the anomeric configuration-dependence of the acyl migration from *O*2 to *O*3 indicated that the steric effect may play a key role in formation of acyl migrated product.

C3 epimerization of D-glucosamines to D-allosamines

The C3 epimerization of the 3-triflate-*α*-D-glucosamine

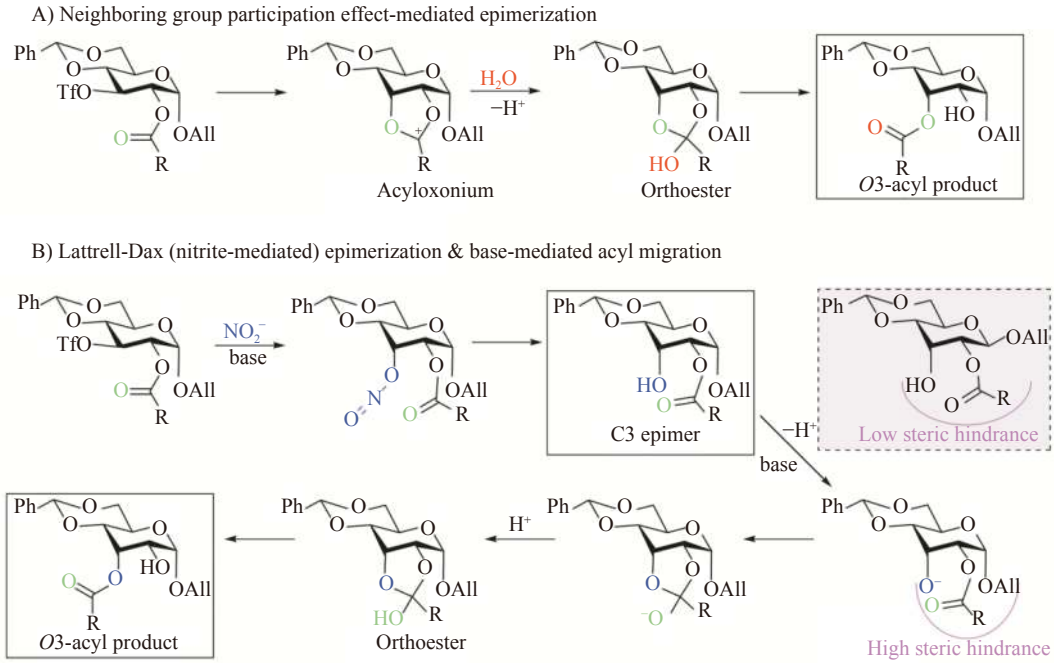
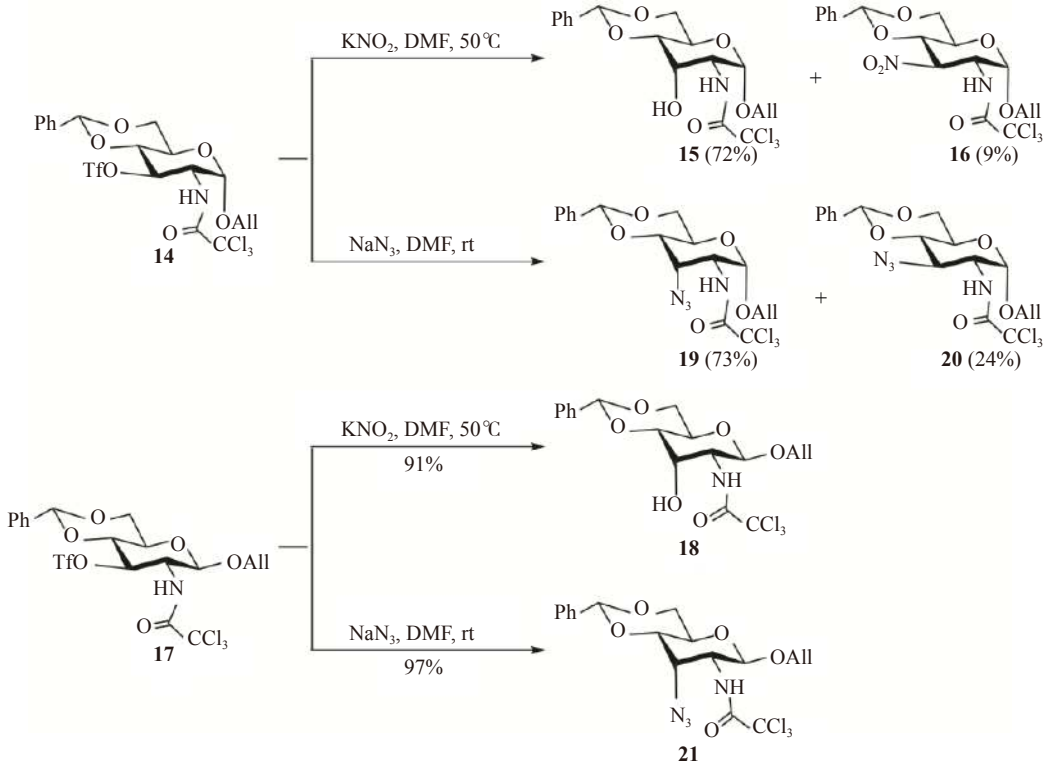


Fig. 2 Proposed mechanism of acyl migration during the Lattrell-Dax epimerization for D-allose synthesis

14 [11] with potassium nitrite at 50 °C afforded the desired allosamine **15** in 72% yield and the 3-nitro-D-glucosamine **16** in 9% yield (Scheme 3). Conversely, the Lattrell-Dax epimerization of 3-triflate-*β*-D-glucosamine **17** [20] delivered the corresponding allosamine **18** in 91% yield without any detectable byproduct. Focusing on the effect of the anomeric configuration on nucleophilic substitution of 3-triflate-D-glucosamine, **14** and **17** were treated with sodium azide at room temperature. Notably, *α*-D-glucosamine **14** was transformed to 3-azide D-allosamine **19** and 3-azide D-glucosamine **20**, while 3-azide D-allosamine **21** was the only detectable product from *β*-D-glucosamine **17**. It is proposed that the 3-



Scheme 3 C3 epimerization of D-glucosamine derivatives

nitro-D-glucosamine **16** and 3-azide-D-glucosamine **20** were formed through a neighbouring group participation effect-mediated S_N1 nucleophilic substitution, instead of S_N2 nucleophilic substitution (Fig. 3). The formation of 3-nitro product **16** suggests that the eletrophilicity of 3-carbon in oxazoline intermediate is suitable for *N*-attack by nitrite. In addition, the anomeric configuration-dependence of the formation of oxazoline intermediate may attribute to the steric effect of C2.

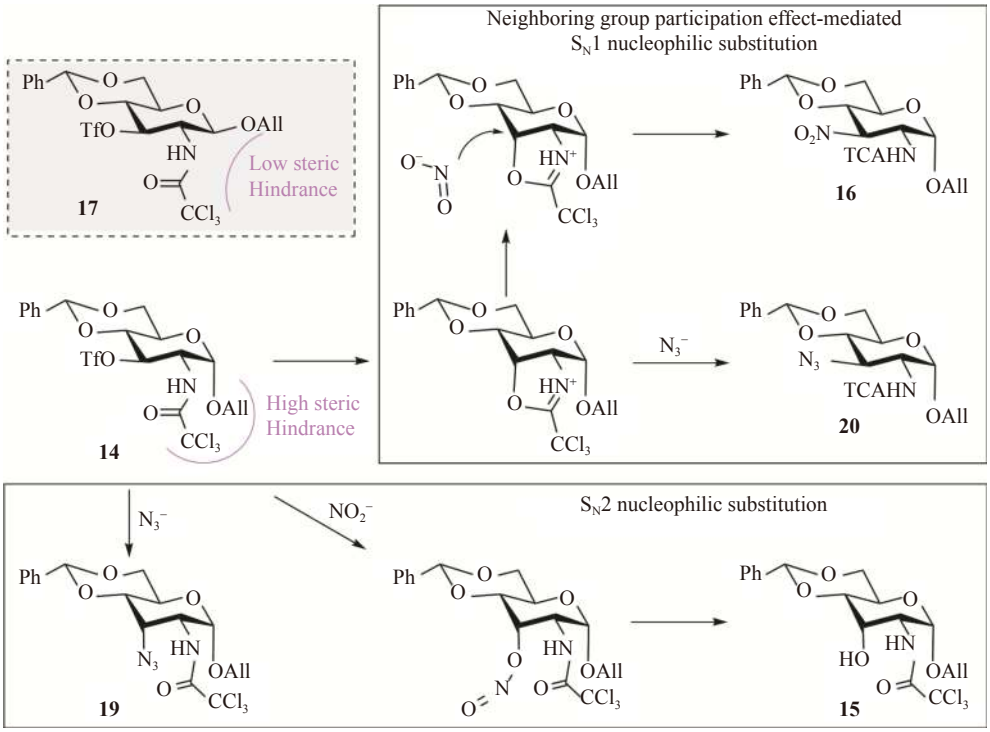


Fig. 3 Proposed mechanism of side reaction during the Lattrell-Dax epimerization for D-allosamine synthesis

Conclusion

In the purpose of access to synthetically useful D-allose and D-allosamine derivatives, the C3 epimerization of orthogonally protected D-glucose and D-glucosamine substrates via the Lattrell-Dax epimerization was performed. For C3 epimerization of D-glucose derivatives bearing *O*2-acyl group, an anomeric configuration-dependent acyl migration from *O*2 to *O*3 suggested that the *β*-glycoside with low steric hindrance at C2 should be chosen to devoid the acyl migration. In addition, transformation efficiency of the D-glucosamine bearing C2 trichloroacetamido (TCA) group in the Lattrell-Dax epimerization was dependent upon anomeric configuration, highlighting that the *β*-glycoside with low steric hindrance at C2 was better substrate for D-allosamine synthesis. Significantly, the efficient synthesis of the orthogonally protected D-allose **13** and D-allosamine **18** will serve well for further assembly of complex glycans. Moreover, understanding the effect of anomeric configuration on the Lattrell-Dax epimerization of D-glucose will be valuable for synthesis of other D-allose derivatives.

Experimental and Supporting Information

All detailed experimental data and supporting information were provided in supplementary material, and can be requested by sending E-mail to the corresponding author.

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