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C-GLYCOSIDATION OF UNPROTECTED ALDOPENTOSES WITH KETONES USING PROLINE-TRIETHYLAMINE AS CATALYST

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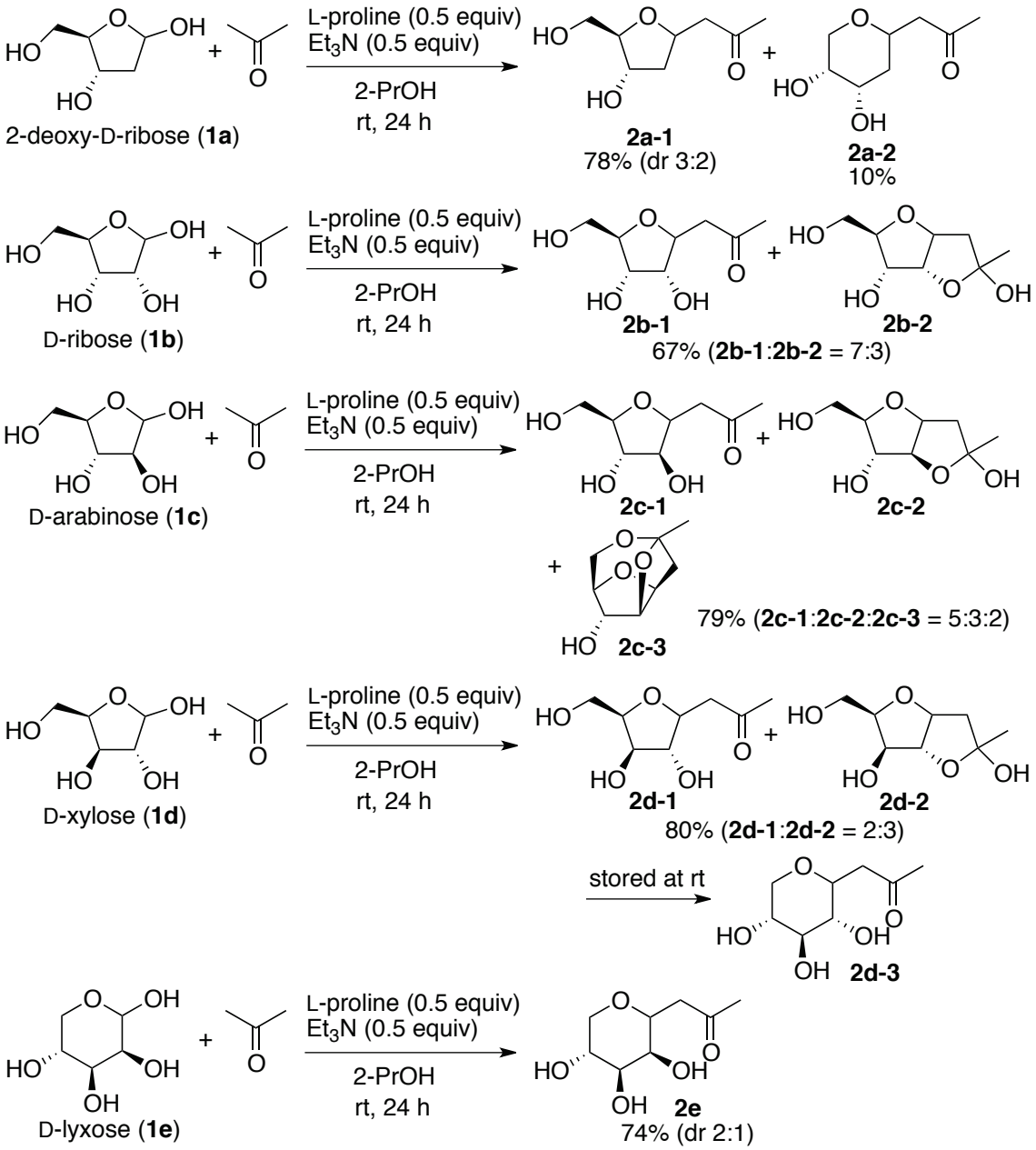
Abstract – Reactions of unprotected aldopentoses with ketones catalyzed by proline and triethylamine that afford C-glycoside derivatives are described.

C-Glycoside derivatives are important as bioactives, probes, and other functional molecules.[1-5] C-Glycosidation reactions have often been performed on preactivated forms of carbohydrates with protected hydroxy groups or on specific precursors bearing functional groups for the bond-formation at the anomeric carbons.[5] Direct C-glycosidation reactions of unprotected carbohydrates without the need for protection of hydroxy groups are more preferable[4] than are reactions that require protection and deprotection steps and/or that require special precursors.[5] Whereas direct C-glycosidation reactions of some aldoses with acetylacetone to provide acetone-derived C-glycosides have been performed since 2000, these reactions require basic conditions and high temperature.[5-10] In these reactions, a deacylation step is needed to afford simple ketone-attached C-glycosides.[6-10] Recently, C-glycosidation reactions of unprotected carbohydrates with ketones other than β-diketones have been developed.[1-4] For example, we have reported direct C-glycosidation reactions of unprotected di- and trisaccharides with ketones that afford functionalized C-glycoside ketones using pyrrolidine-boric acid catalysis under mild conditions.[4] We have also reported C-glycosidation reactions of 2-*N*-acyl-aldohexoses with ketones using amine-based catalyst systems.[3] Despite this progress, the scope of C-glycosidation reactions of unprotected carbohydrates with ketones is limited.[4] Catalysts developed for C-glycosidation of certain types of carbohydrates with ketones do not always catalyze C-glycosidation reactions of other types of carbohydrates.[3,4] Here we report C-glycosidation reactions of unprotected aldopentoses with ketones.

First, catalysts and conditions were evaluated in the reactions of several aldopentoses with acetone to provide C-glycoside products (Supporting Information). Previously published results indicate that carbohydrate stereochemistry, carbon chain length (for example, aldohexose, aldopentose), and

hemiacetal ring size (for example, aldofuranose, aldopyranose) influence reactivities of the carbohydrates and the transition states leading to the products.[1,3,4,8-10] The pyrrolidine-boric acid catalyst system[4] that was useful for C-glycosidation reactions of di- and trisaccharides did not efficiently catalyze the desired C-glycosidation reactions of aldopentoses (Supporting Information). We found that the L-proline-triethylamine catalyst system catalyzed the C-glycosidation reactions of a series of aldopentoses **1** with acetone in 2-propanol and afforded products **2** (Scheme 1).



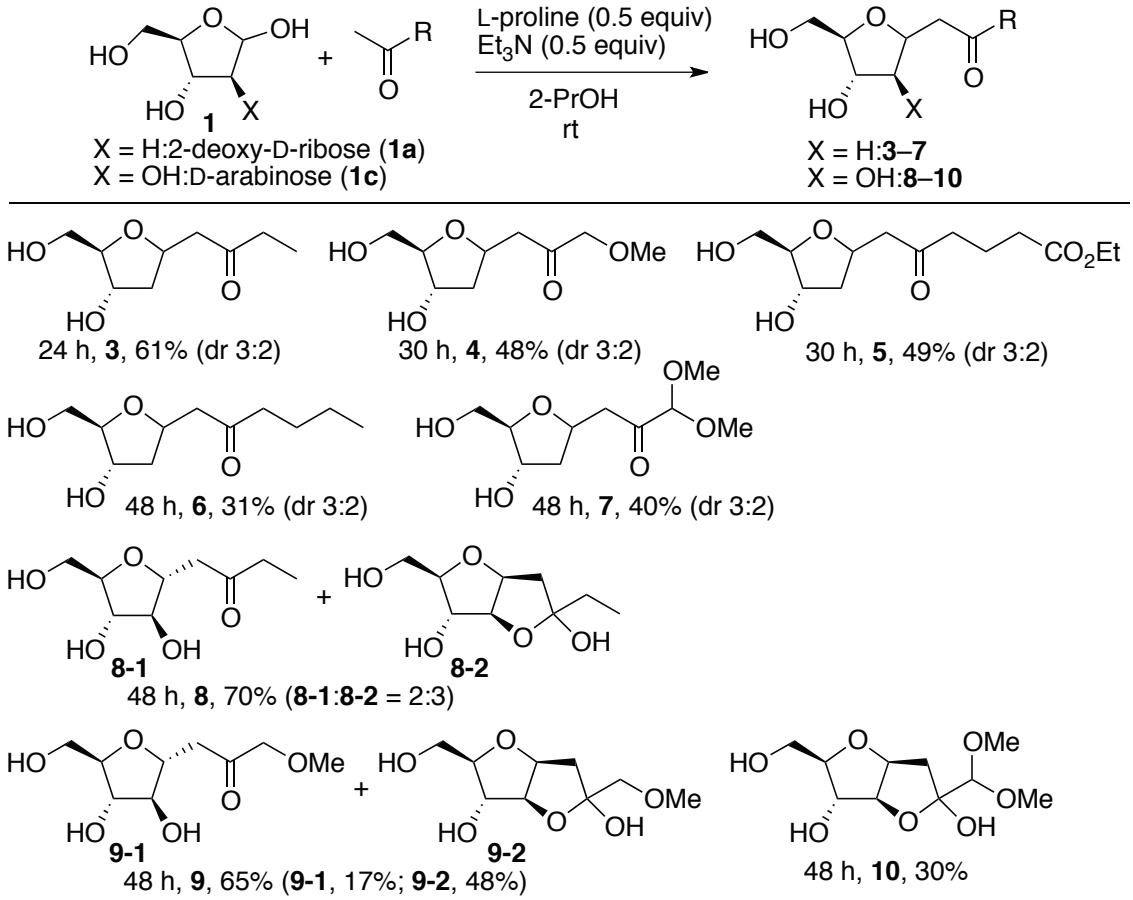
Scheme 1. C-Glycosidation reactions of aldopentoses with acetone using proline-triethylamine catalysis

As we previously reported, in the C-glycosidation reactions of 2-*N*-acyl-aldohexoses, catalyst stereochemistry (such as (*S*)- or (*R*)-configuration of proline) affected the catalytic efficiency and the

reaction rate in the presence of bases (such as diisopropylethylamine) in a manner that depends on carbohydrate and the stereochemistry of the carbohydrate hydroxy groups.[3] For example, in the C-glycosidation reactions of 2-*N*-acyl-aldohexoses, the catalyst enantiomer that was used for the reaction was critical.[3] Depending on the carbohydrate (i.e., depending on the stereochemistry of carbohydrate hydroxy groups), different enantiomer of the catalyst had to be used in order to obtain the product.[3] In contrast, in the reactions of aldopentoses shown in Scheme 1, all tested carbohydrates afforded the C-glycosidation products in the presence of L-proline-triethylamine; there was no need to switch between L- and D-proline depending on the aldopentose structure.

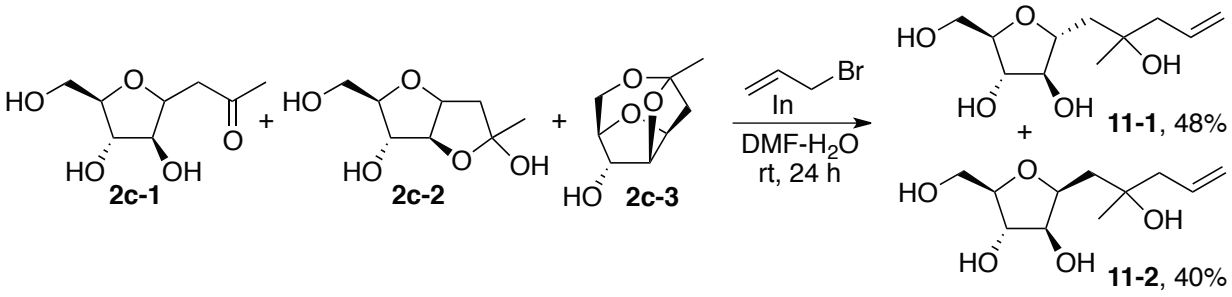
Products **2** were obtained as the ketone form with 5- and/or 6-membered rings and/or their bicyclic hemiacetal forms depending on the presence or absence of the hydroxy group at the 2-position and on the stereochemistries of the hydroxy groups of the carbohydrates. Further, in the products from the reaction of arabinose, polycyclic acetal **2c-3** was also obtained. Certain ketone and hemiacetal forms of product **2** were unstable during storage. For example, 5-membered products **2d-1** and **2d-2** were converted to 6-membered product **2d-3** during storage at room temperature (25 °C).

Table 1. C-Glycosidation reactions of aldopentoses with various methyl ketones



Next, to analyze the scope of the L-proline-triethylamine catalyst system, the C-glycosidation reactions with various ketones were performed using **1a** and **1c** as the starting carbohydrates in the presence of L-proline-triethylamine; the reactions were carried out in 2-propanol at room temperature (25 °C) (Table 1). Various C-glycosides were obtained from the reactions with ketones bearing ester, methoxy, and dimethoxy groups. The C-C bond formation selectively occurred at the methyl group of the ketones. C-Glycosidation reactions of aldopentoses with ketones using the L-proline-triethylamine catalyst system in 2-propanol were generally faster than or comparable to those performed using L-proline-DBU catalyst system in methanol reported by the Mahrwald group.[1] In the L-proline-triethylamine-catalyzed C-glycosidation reactions of unprotected aldopentoses with ketones, the catalyst system may be involved in the formation of enamines of the ketones and in the formation of the iminium ions of the carbohydrates.[3,4,11]

Depending on carbohydrate and ketone, the C-glycosidation products included bicyclic hemiacetals and polycyclic acetals. When a mixture of C-glycosidation products **2c-1**, **2c-2**, and **2c-3** obtained from D-arabinose with acetone was subjected to allylation,[12] allylated products **11** (**11-1** and **11-2**) were obtained (Scheme 2). The combined yield of **11** was high. This result indicated that hemiacetal form **2c-2** equilibrated with ketone form **2c-1** during the allylation reaction and that the ketone group of **2c-1** was allylated. These results suggest that the C-glycoside derivatives obtained under the proline-triethylamine catalysis are useful as mixtures of ketone and hemiacetal forms in further transformations.



Scheme 2. Allylation of C-glycoside derivatives derived from D-arabinose

In summary, we have developed L-proline-triethylamine-catalyzed C-glycosidation reactions of unprotected aldopentoses with ketones that afford C-glycoside ketone derivatives under mild conditions. Various C-glycosides were obtained from unprotected aldopentoses using the developed method.

EXPERIMEMTAL

General Procedure for the Synthesis of 2~10. To a mixture of carbohydrate (1.0 mmol) and ketone (20 mmol) in 2-PrOH (1.0 mL) were added L-proline (0.5 mmol) and Et_3N (0.5 mmol) at room

temperature (25 °C) and the mixture was stirred at the same temperature. Formation of the products was monitored by TLC analyses. The mixture was purified by flash column chromatography (CH_2Cl_2/MeOH) to afford the C-glycosidation product.

Supporting Information Available. Experimental procedures, product characterization, evaluations of catalysts and conditions, and ^{1}H and ^{13}C NMR spectra.

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