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Note

An unexpected rearrangement of pent-4-enofuranosides to cyclopentanones upon hydrogenolysis of the anomeric benzyl group

Shenyou Nie, Xiaoping Chen, Yuyong Ma, Wei Li*, Biao Yu**

State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai, 200032, China

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ABSTRACT

During our synthesis toward the unique nucleoside antibiotic A201A, we were surprised to find that a benzyl arabino-pent-4-enofuranoside underwent a Ferrier II-like rearrangement readily to provide the corresponding cyclopentanone derivative in high yield and stereoselectivity upon hydrogenolysis of the anomeric benzyl group.

1. Introduction

Polyoxygenated cyclopentanoids are the essential scaffolds of many bioactive molecules of pharmaceutical interest, including carbocyclic nucleosides [1], glycosidase inhibitors [2], prostaglandin [3,4], pentenomycin [5], and caryose [6,7]. Over the past few decades, numerous approaches to the construction of the cyclopentanoid skeleton have been developed [2,8–11]. A few of these approaches employ carbohydrates as starting materials to furnish polyoxygenated cyclopentanoids, however, in multiple steps and unsatisfactory efficiency [12–15].

On the other hand, carbohydrates have been extensively used in the construction of polyoxygenated cyclohexanoids [16–22], that could be mainly attributed to the classical Ferrier II rearrangement of hex-5-enopyranosides promoted by a stoichiometric or catalytic amount of Lewis acids such as Hg(II) or Pd(II) salts (Scheme 1) [17,23–28]. This rearrangement involves a cleavage of the acetal bond and a subsequent aldol-like intramolecular cyclization. However, despite its reliable performance and widespread application in synthesizing cyclohexanone derivatives [27,29–35], the Ferrier II rearrangement has rarely been applied successfully in converting pent-4-enofuranosides into the corresponding cyclopentanones [16]. Thus, Gallos et al. reported a nitrile oxide-assisted rearrangement to prepare five-membered carbocycles in two steps, involving a nitrile oxide cycloaddition and subsequent reductive cleavage of the spiroisoxazoline intermediate to promote the key aldol-like cyclization [14,15]. Other examples are limited only on specific substrates, such as spiro dienones [36–38], vinyl alkylidenes [39,40], and γ-enollactones [41]. Rearrangements of pyranosides to construct cyclopentanoids with zirconium, samarium and palladium were also reported [42–47]. It is noteworthy that all the resultant cyclopentanones in these Ferrier II-like reactions remain redundant substituents, which are difficult to remove afterwards.

Very recently, during our synthesis toward a unique nucleoside antibiotic A201A [48], we were surprised to find a cyclopentanone product resulting from the rearrangement of a pent-4-enofuranoside upon hydrogenolysis of the anomeric benzyl group. Herein, we report this unexpected discovery and a brief examination of the reaction scope.

2. Results and discussion

Disaccharide **1** bearing an arabino-pent-4-enofuranoside moiety was envisioned as a key intermediate in our synthetic studies toward nucleoside antibiotic A201A (Scheme 2) [48]. Thus, D-arabinose was converted into 5-aldehyde-furanoside **2** in 9 steps

* Corresponding author.
** Corresponding author.
E-mail addresses: lmwave@mail.sioc.ac.cn (W. Li), byu@mail.sioc.ac.cn (B. Yu).

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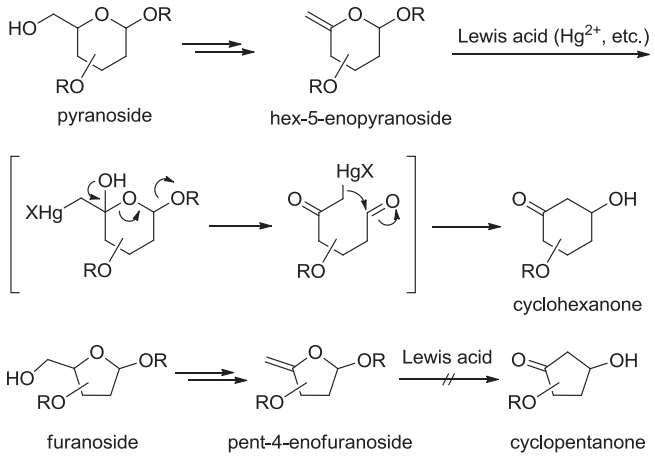
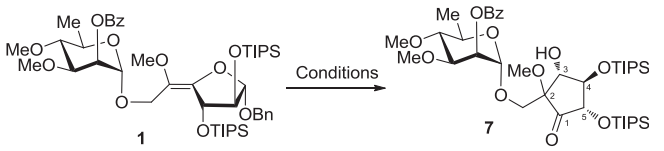
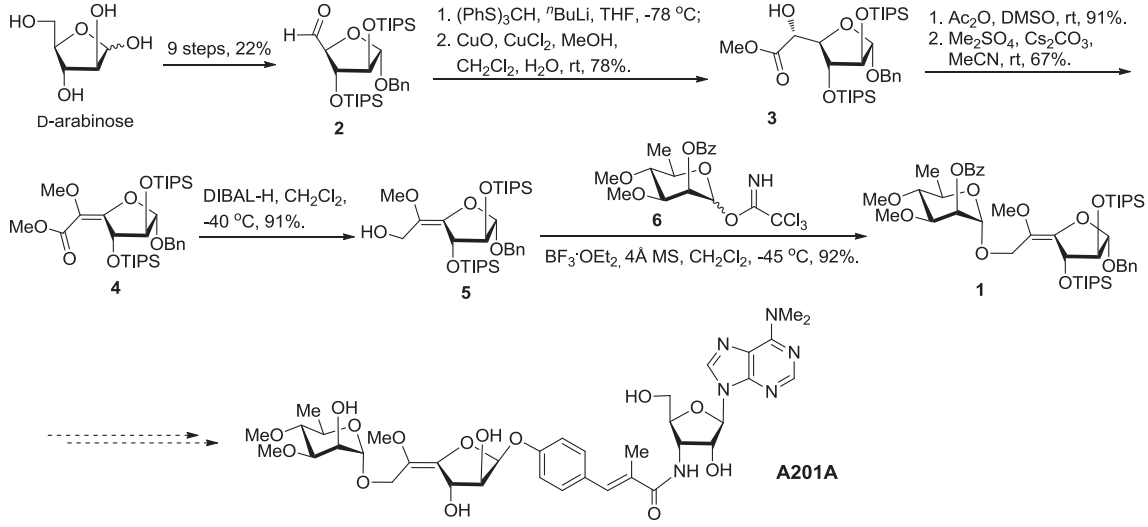


Scheme 1. Ferrier II rearrangement.

Table 1
Attempts to deprotect the benzyl group and the unexpected rearrangement of disaccharide **1**.



Entry	Conditions	Results
1	LDBB, THF, −78 °C.	Complex
2	$FeCl_3$, dry CH_2Cl_2, rt.	Complex
3	Pd/C, H_2(1 atm), ethyl acetate, Et_3N, rt.	No reaction
4	Raney Ni, EtOH, rt.	**7**, 90%

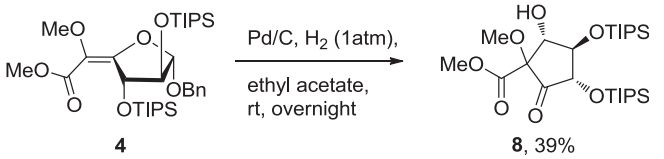


Scheme 2. The preparation of disaccharide **1** toward the synthesis of A201A.

with an overall yield of 22% (see SI for detailed information) [49–52]. Addition of aldehyde **2** with tris-(phenylthio)methyllithium at −78 °C resulted in an unstable phenylthioorthoester, which was treated with CuO and $CuCl_2$ to give α-OH methyl ester **3** in good yield. Oxidation of the nascent α-OH on **3** and subsequent enolization in the presence of Cs_2CO_3 and Me_2SO_4 led to enol methyl ester **4**, which was then reduced with DIBAL-H to give alcohol **5**. Glycosyaltion of **5** with imidate **6** (prepared from D-mannose according to the reported procedure) [48] promoted with $BF_3{\cdot}OEt_2$ at −45 °C furnished the desired disaccharide **1** in 92% yield.

To deprotect the anomeric benzyl group on **1** for further synthetic transformations toward A201A, several debenzylation conditions were examined, wherein the reactive exocyclic enol ether moiety should remain intact. As depicted in Table 1, either Lewis acid $FeCl_3$ or radical reagent LiDBB (lithium di-tert-butylbiphenyl) made disaccharide **1** fully decomposed and led to complex mixtures (entry 1, 2) [53,54]. On the other hand, no reaction was observed in Pd/C-catalyzed hydrogenolysis in the presence of Et_3N (entry 3). Surprisingly, when disaccharide **1** was treated with a catalytic amount of Raney Ni in EtOH at rt, cyclopentanone **7** resulting from a rearrangement was afforded in 90% yield. The structure of cyclopentanone **7** was elaborated with a set of NMR spectra (see SI for more details): The signal at 208 ppm in ^{13}C NMR spectrum revealed the generation of carbonyl group at C1; the nascent 3-OH was confirmed by its active hydrogen signal at 2.61 ppm in ^1H NMR spectrum; the configuration of C3 was presumed by the absence of NOE correlation between H3 (δ 4.03 ppm) and H4 (δ 4.21 ppm). Although the NMR spectra could not provide enough information to determine the configuration of C2, the rearrangement turned out to be highly stereoselective with only trace epimers being observed.

Further study was then conducted on monosaccharide **4** bearing a conjugated exocyclic enol ether which was much less reactive (Scheme 3). As expected, the rearrangement was much slower upon treatment of Raney Ni in EtOH, and most of **4** remained intact



Scheme 3. Rearrangement of conjugated enol ether furanoside **4** under Pd/C-catalyzed hydrogenolysis.