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Stable D-Xylose Ditriflates in a New, Divergent Synthesis of Dihydroxyprolines and Pyrrolidines †

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Abstract: Carbohydrates constitute an abundant source of useful scaffolds for the synthesis of highly functionalized carbo- and heterocycles. They provide the stereogenic centers bearing their OH substituents and a proper functionality for the generation of the two C-C or the two C-heteroatom bonds involved in the generation of the carbo- or heterocyclic ring. Two approaches have been developed for these purposes. Sugar triflates showed to be more suitable for these purposes, due to their easy preparation and their high reactivity, that facilitates the easy and efficient formation of the new ring by intramolecular nucleophilic displacements both prior or after the opening of the sugar ring. The alternative of using sugar dimesylates or sugar ditriflates for the simultaneous formation of the two key bonds leading to the new ring is particularly attractive, but has some limitations. In fact, for the formation of ditriflates from diols, it is necessary the absence of a neighboring hydroxyl group that could lead to intramolecular cyclization, particularly to a five membered ring. The synthesis of carbocycles and heterocycles from sugar ditriflates is at present practically limited to several synthesis of azetidines. This article reports further chemistry on in this field. It includes new divergent synthesis of iminocyclopentitols anad 3,4-dihydroxyprolines

Keywords: sugars, sugar ditriflates, iminosugars, prolines, stereoselective synthesis

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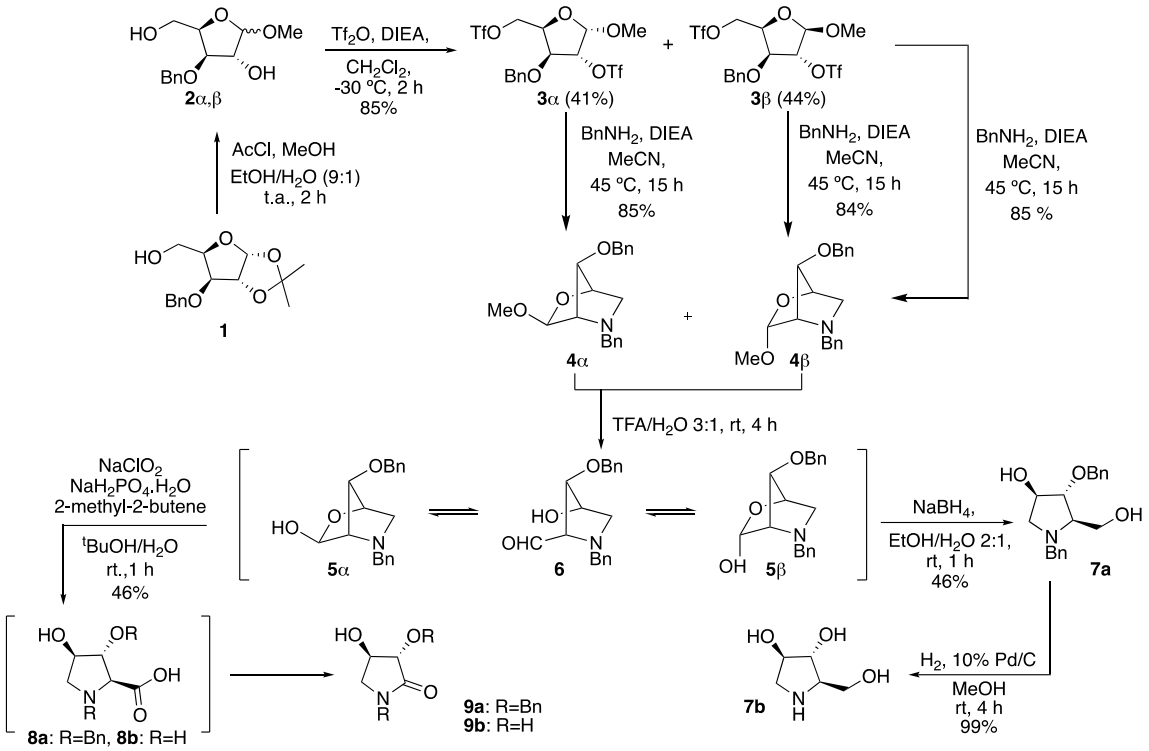
1. Introduction

Iminosugars are natural and synthetic polyhydroxylated azacyclicle compounds that can be considered sugar mimetics resulting from the replacement of oxygen ring by nitrogen [1]. Their great interest is due to their ability to act as potent inhibitors of both glycosidases and glycoxyltransferases [2], a property related to their potential for the treatment of a wide range of diseases [3], such as diabetes, viral infection, tumor metastasis, hepatitis and lysosomal storage disorders [4]. In particular, a representative example of polyhydroxylated pyrrolidines is l,4-dideoxy-l,4-imino-D-arabinitol (**7b,** DAB), a natural product that has shown to be an efficient inhibitor of α-glucosidases [5], Moreover, structurally related 3,4-dihydroxyprolines may similarly result from the replacement of the endocyclic oxygen of uronic acids by nitrogen. Some hydroxyprolines and dihydroxyprolines also exhibit glycosidase inhibitory activity, anti-HIV activity or immunostimulating properties. In fact, (2*S*,3*R*,4*R*)-3,4-dihydroxyproline (**8b**), a constituent amino acid of virotoxin in *Amantia virosa mushrooms*, has been shown to be a potent inhibitor against β-D-glucuronidase [6].

Among the strategies developed for the synthesis of iminosugars, those using carbohydrates as synthetic source are the most suitable, since they provide the stereogenic centers carrying their OH substituents and a suitable functionality for the sequential or

simultaneous generation of the two C-N bonds involving the endocyclic nitrogen atom. An attractive, recent approach involves the simultaneous generation of the two C-N bonds by reaction of stable sugar ditriflates with amines. This approach was firstly applied to an efficient synthesis of azetidines [7], and more recently to a divergent synthesis of iminocyclopentitols and 3,4-dihydroxyprolines [8]. This paper reports a new synthesis of DAB (**7b**) from a D-xylose ditriflates **3α** and **3β**, together an attempt for synthesize the corresponding dihydroxylated proline **8b** (Scheme 1).



Scheme 1. Synthesis of the iminosugar DAB (**7b**).

2. Results and Discussion

Reaction of the D-xylose derivative **1** with acetyl chloride and methanol provided an anomeric mixture of the methyl xylofuranoside derivatives **2αβ**, as a result of the removal of the isopropylidene protecting group and methylation of the anomeric hydroxy group of the resulting compound. Treatment of this mixture **2αβ** with triflic anhydride under basic conditions (DIEA) resulted in the formation of a c.a. 1:1 anomeric mixture **3αβ**, from which the key ditriflates **3α** (41%) and **3β** (44%) were isolated by column chromatography. The configuration of their anomeric centers were easily established from their respective ^{1}H NMR spectra. The anomeric proton of **3α** shows a doublet at 5.13 ppm (J = 4.3 Hz). This data indicates that protons the H_1 and H_2 adopt *cis* arrangement. On the other hand, the anomeric proton of **3β** shows a singlet at 5.2 ppm, in agreement with a *trans* disposition of protons H_1 and H_2.

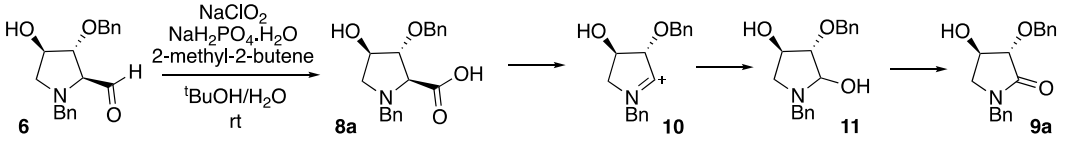
The key reaction of ditriflates **3α** and **3β** with benzyl amine resulted in an efficient double displacement of the triflates at C-2 and C-5 positions, affording the *exo* azabyciclic glycoside **4α** (85% yield) and the *endo* azabyciclic glycoside **4β** (84% yield), respectively. On the other hand, when this reaction was carried out with the anomeric mixture **3αβ**, a 1:1 anomeric mixture **4αβ** resulted (85% yield). The presence of the *N*-Bn group in **4α** was easily established from its ^{1}H NMR, which includes a multiplet at 7.20-7.42 ppm, due to the ten aromatic protons of the *N*-Bn and *O*-Bn groups, along with two quartets at 4.00 ppm (J = 13.5 Hz) and 4.59 ppm (J = 11.7 Hz), corresponding to the benzylic protons of the *N*-Bn and *O*-Bn groups, respectively. Similar signals were present i

n the ^{1}H NMR of **4β**, at 7.20-7.42, 4.16 (*J* = 14.0 Hz) and 4.56 (*J* = 11.7 Hz) ppm. As for the stereochemistry at the anomeric center, the *exo* arrangement of the OMe group of **4α** was deduced from a singlet at 4.80 ppm due to the H_3 proton, while the *endo* disposition of the OMe group in **4β** agrees with a doublet at 4.95 ppm (*J* = 1.5 Hz), due to the coupling of protons at H_3 and H_4.

According to our plan, acid hydrolysis of the glycoside moieties of this mixture **4αβ** with aqueous trifluoroacetic acid afforded the tricomponent mixture **5α** + **6** + **5β**, which was reduced to the dibenzylated iminosugar **7a**, after treatment with sodium borohydride. Finally, removal of the benzyl protecting groups of **7a** by catalytic hydrogenation provided the known iminocyclopentitol DAB (**7b**).

On the other hand, the mixture **5α** + **6** + **5β** was directly subjected to the oxidative reaction conditions indicated in Scheme 1, in order to obtain the corresponding proline **8a**. But the result was the formation of lactam **9a**, a debenzylated derivative of the commercial compound **9b**, a member of a family of sugar lactam HIV integrase inhibitors [9]. The molecular formula of **9a** was established by HRMS ($C_{18}H_{19}NaNO_3$, $[M + Na]^+$, m/z: 320.1262) and its structure was deduced from its spectroscopic data, mainly from the presence in its ^{13}C NMR of signals from only two CH carbons at 71.7 and 82.9 ppm and from the presence band in its IR spectrum of an amide carbonyl at 1685 cm^{-1}.

The formation of this lactam **9a** could occur as shown in Scheme 2. Oxidation of carbaldehyde **6** should give the expected proline **8a**, but this compound probably underwent spontaneous decarboxylation giving rise to the iminium derivative **10**. Hydration of this compound could give the carbinol amine **11**, which should readily oxidize to **9a** [10].



Scheme 2. Mechanism for the transformation of **8** into **9a.**

In conclusion, we have developed a new synthesis of the iminosugar DAB (**7b**) from D-xylose that is shorter and more efficient than our two previous syntheses of this iminosugar from this pentose.

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Conflicts of Interest:.

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