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Short communication

Unprecedented 3-*O*-methyl-3-*C*-trifluoromethyl-D-ribono- (and L-lyxono)-γ-lactones synthesized by nucleophilic trifluoromethylation of D-hexose-derived cyclic ketones

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ABSTRACT

3-*O*-Methyl-3-*C*-trifluoromethyl-D-ribono-(and L-lyxono)-γ-lactones have been prepared from protected D-hexoses (*gluco*,*galacto*) by multi-step routes from D-glucose. The synthetic strategy includes the following steps: regioselective oxidation, nucleophilic trifluoromethylation with the Ruppert-Prakash reagent of 3-keto hexofuranose derivatives attacked stereoselectively from the less hindered face, protective group manipulations, and regioselective oxidation of a hemiacetalic hydroxyl. Base-catalyzed hydrolysis of two related D-ribonolactones afforded 3-*O*-Me-3-*C*-CF_3-D-ribonic acid.

1. Introduction

Glyconolactones which typically display several hydroxyl groups bound to chiral centers constitute a valuable family of synthons suitable for diverse chemical modifications and they have found broad applications as building blocks for the synthesis of various derivatives, such as *C*-glycosyl compounds, aza-, thio-, and carbasugars (sugar analogues with a N-, S-, or C-atom in the ring), L-sugars, natural products, surfactants and related polymers [1]. For example, α-glucosidase inhibitors 1-deoxynojirimycin (DNJ) and 1-deoxymannojirimycin (DMJ) are significant bioactive natural products synthesized from L-gulono-1,4-lactone and D-mannono-1,4-lactone, respectively [2].

We reported previously a multi-step approach from D-glucose toward analogues of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine, a naturally occurring insulinotropic amino acid [3]. For this purpose, and as previously shown by Fleet et *al*. when exploring the synthesis of sugar-derived amino acids [4], glyconolactones with a free 2-OH were key intermediates which were converted to the corresponding triflates. Upon treatment with NaN_3, they afforded the corresponding azido derivatives stereospecifically through S_N2 displacement [4]. Subsequent catalytic reduction followed by base-catalyzed hydrolysis delivered the desired amino acids.

We reasoned that the synthetic potential of glyconolactones could be enhanced further by modifying their C-3 carbon atom. A common mean to achieve this goal involves the nucleophilic attack of a keto group installed at C-3 [5]. Although this synthetic approach allowed for the introduction of various groups (for example: methyl [6], dichloromethyl [7], nitromethyl [8], trifluoromethyl [9a,b], and other [10]), 3-trifluoromethylated glyconolactones appear to be unprecedented to date. A synthesis of 3-trifluoromethylated γ-lactones with four asymmetric centers via sequential [3,3]-Ireland-Claisen rearrangement and iodolactonisation has been reported [11]. Related multi-step routes giving access to α-trifluoromethyl-γ-lactones have been developed [12].

Owing to its unique properties, the CF_3 functionality (high electronegativity, higher energy of C—F bond, low polarizability combined with a high ionization potential) if present in organic molecules convey metabolic stability, enhanced binding interactions, lipophilicity, changes in physical properties with a profound effect on its bioactivity and bioavailability [13]. Found in many bioactive molecules and commercial drugs/specialities, the CF_3 group is a privileged structural motif in medicinal chemistry and other fields [14,15], so that many strategies toward trifluoromethyl-containing molecules are being developed nowadays [16]. Actually, trifluoromethylated amino acids have found

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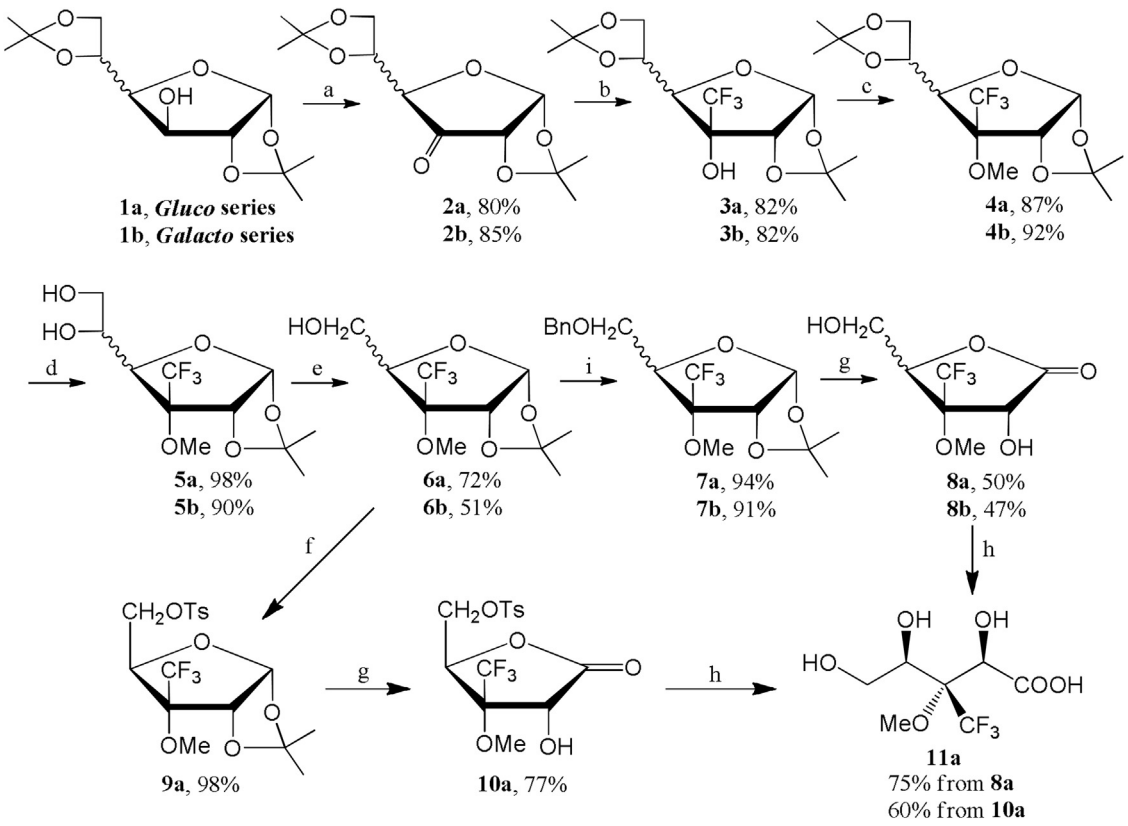

Scheme 1. *Reagents and conditions* (a) PDC, Ac_2O, CH_2Cl_2; (b) CF_3SiMe_3, THF, TBAF, rt; (c) 1- CH_3I, KOH, $Bu_4N^+Br^-$, acetone, 0 °C; (d) AcOH/H_2O, 60 °C; (e) 1- $NaIO_4$, H_2O, rt; 2- $NaBH_4$, H_2O, rt; (f) TsCl, pyridine, rt; (g) 1- HCl (1N), 70 °C; 2- Br_2, $BaCO_3$, dioxan/H_2O, rt; (h) LiOH·H_2O, AcOH, rt; (i) BnBr, NaH, DMF, rt.

innovative and valuable applications in biochemistry and medicinal chemistry [17]. Because of the hydrophobicity of fluorocarbon chains, they have the capacity to enhance helical protein stability, increasing the protein–protein interaction's (PPIs) selectivity in peptide and protein designs [18]. Fluorinated amino acids also play an important role in the control of blood pressure, allergies and tumor growth [19].

We herein describe the synthesis of unprecedented 3-*O*-methyl-3-*C*-trifluoromethyl-D-ribono(and L-lyxono)-1,4-lactones and (2*R*,3*R*,4*R*)-3-*O*-methyl-3-*C*-trifluoromethyl-D-ribonic acid from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose that might be of interest as precursors of trifluoromethylated unnatural amino acids.

2. Result and discussion

As depicted in Scheme 1, our syntheses started from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (diacetone glucose), a cheap commercially available substrate amenable to regioselective oxidation to afford the 3-oxo derivative **2a** [20]. Diacetone glucose was converted into its D-*galacto*-configured analog using a known procedure [21]. It has been reported that nucleophilic trifluoromethylation carried out with CF_3SiMe_3 (Ruppert-Prakash reagent) and catalytic TBAF in anhydrous THF occurred stereoselectively on the convex face of the ketone **2a** to afford 1,2:5,6-di-*O*-isopropylidene-3-*C*-trifluoromethyl-3-*O*-trimethylsilyl-α-D-allofuranose [9a]. In our case, we used 0.5 eq of TBAF (1.0 M solution in THF) to access directly to the 3-*O*-unprotected **3a** in

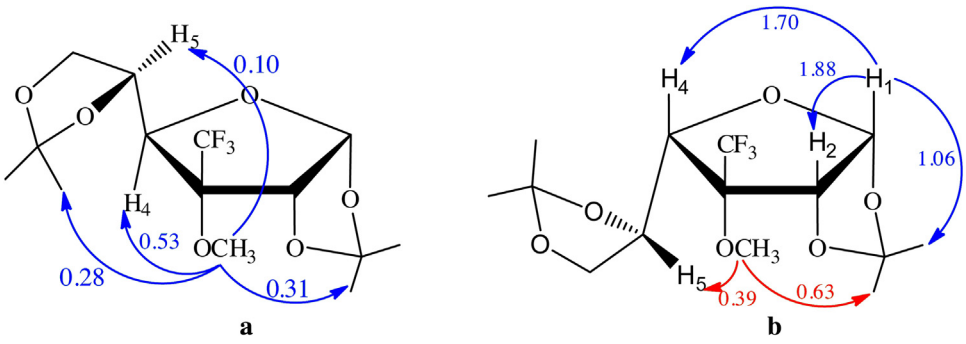

Fig. 1. 1D NOE enhancements measured for **4a** (left) and **4b** (right).