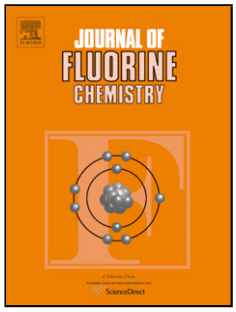

Title: Unprecedented 3-*O*-methyl-3-*C*-trifluoromethyl-D-ribono- (and L-lyxono)-γ-lactones synthesized by nucleophilic trifluoromethylation of D-hexose-derived cyclic ketones

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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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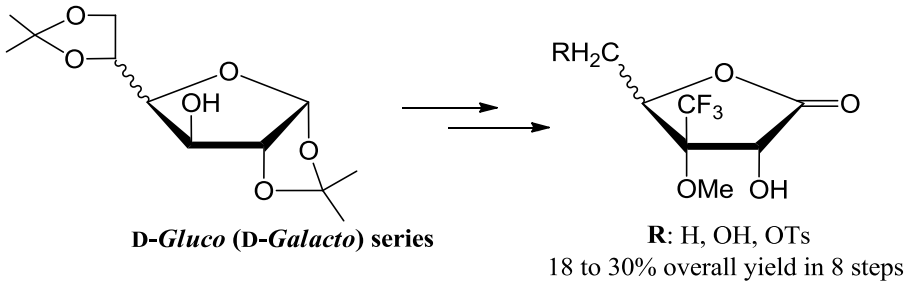
Graphical abstract



D-*Gluco* (D-*Galacto*) series

R: H, OH, OTs
18 to 30% overall yield in 8 steps

Highlights

- Preparation of 3-CF_3 glyconolactones by multi-step routes from D-glucose.
- The introduction of CF_3 group was achieved by nucleophilic trifluoromethylation.
- The nucleophilic trifluoromethylation carried out by using Ruppert-Prakash reagent.

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.

Keywords: Nucleophilic trifluoromethylation/ Lactones/ D-Glucose/ Ketones/ Stereoselectivity

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 analogs 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 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.

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 good yield without isolating the silylated intermediate. Under our conditions, **2b** was readily converted into 1,2:5,6-di-*O*-isopropylidene-3-*C*-trifluoromethyl-α-D-gulofuranose **3b** in 82% yield. The *O*-methylation [22] of **3a,b** and the regioselective acid-catalyzed hydrolysis of the 5,6-*O*-isopropylidene acetals in **4a,b** afforded the precursors **5a,b** in 98 and 90% yields, respectively [23].Their oxidative cleavage in the presence of $NaIO_4$ delivered the alcohols **6a,b** in 72 and 51%, respectively.

In 1D NOE experiments carried out with a $CDCl_3$ solution of **4a** (Figure 1), selective irradiation of the methoxy group increased significantly the resonances of the 4-H proton (0.53%), of the methyl groups in position 1 and 5 (0.31% and 0.28%, respectively) and to a lower extent of the 5-H proton (0.10%). This confirmed that the methoxy group and the 4-H proton were on the same side, which entailed a (*R*) configuration at C-3. Similarly, the 1D NOE experiments carried out for **4b** supported the proposed structure (Figure 1). The nucleophilic attack of the CF_3 group on the less hindered face (*i.e.* to the side opposite to the 1,2-*O*-isopropylidene acetal) was further confirmed by 2D NMR spectroscopy. The structure of **6b**, unambiguously determined by a single crystal X-ray analysis (Figure 2)[24], showed

also that the nucleophilic addition of the CF_3 group occurred from the less hindered face. These observations are consistent with the literature [9].

The benzylation of the compounds **6a,b** afforded the compounds **7a,b** which were subjected to acid-catalyzed hydrolysis to cleave the 1,2-*O*-isopropylidene acetals. Upon treatment by bromine [25], simultaneous debenzylation and regioselective oxidation of the hemiacetals occurred to afford 3-*C*-trifluoromethyl-D-ribono(L-lyxono)-1,4-lactones **8a,b** with free 2-OH and 5-OH groups (Scheme 1). Also, the tosylation of primary alcohol in **6a** with p-toluene sulfonyl chloride afforded the compound **9a** in 98% yield. This latter was subjected to similar modifications at the 1- and 2-positions to afford 3-C-trifluoromethyl-γ-lactone **10a** in 77% yield. Finally, base-catalyzed hydrolysis of 3-*C*-trifluoromethyl-D-ribono-1,4-lactones **8a** and **10a** afforded in good yield 3-*O*-methyl-3-*C*-trifluoromethyl-D-ribonic acid **11a** (Scheme 1).

On the other hand, the substitution of the alcohol function of compound **6a** with iodine (Garegg's conditions) afforded the intermediate **12a** in 85% yield (Scheme 2). When subjected to catalytic hydrogenation in the presence of Pd/C (10%) followed by deprotection of the 1,2-*O*-isopropylidene acetal and oxidation of the anomeric hemiacetalic alcohol, **12a** afforded the 3-*O*-methyl-3-*C*-trifluoromethyl-5-deoxy-D-ribono-1,4-lactone **14a** in 38% yield.

A number of heteronuclear couplings between the fluorine nuclei and the neighbouring hydrogen and carbon atoms can be seen in the NMR spectra of the studied compounds. As expected the CF_3 and C-3 carbon resonances appeared as quartets due to the $^{1}J_{C,F}$ (~285Hz) and $^{2}J_{C,F}$ (~28Hz) couplings. In the ^{1}H and ^{13}C NMR spectra, the OMe group often appeared as a quartet due to weak $^{5}J_{F,H}$ and $^{4}J_{F,C}$ couplings (~1.5Hz). A $^{3}J_{C,F}$ coupling (2.4 Hz) appeared for C-2 in **14a**. A long-range coupling $^{4}J_{C,F}$ (~2.5 Hz) was often detected for the C-5 signal in D-*ribo*-, and L-*lyxo*-configured products, where the CF_3 group and C-are syn-(D-*ribo*) and trans-diaxially (L-*lyxo*) disposed.

Conclusion

In conclusion, starting from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, a cheap derivative of D-glucose, we have developed multi-step syntheses toward four 3-*O*-methyl-3-*C*-trifluoromethyl-D-ribono(L-lyxono)-1,4-lactones and 3-*O*-methyl-3-*C*-trifluoromethyl-D-ribonic acid. The stereoselective introduction of CF_3 group was achieved by nucleophilic trifluoromethylation taking place from the convex less hindered face of ketones. The conversion of γ-lactone with a free 2-OH group into amino-acids being well documented, further developments of this strategy for synthesizing trifluoromethylated unnatural amino acids, now under investigation, will be reported in due course.

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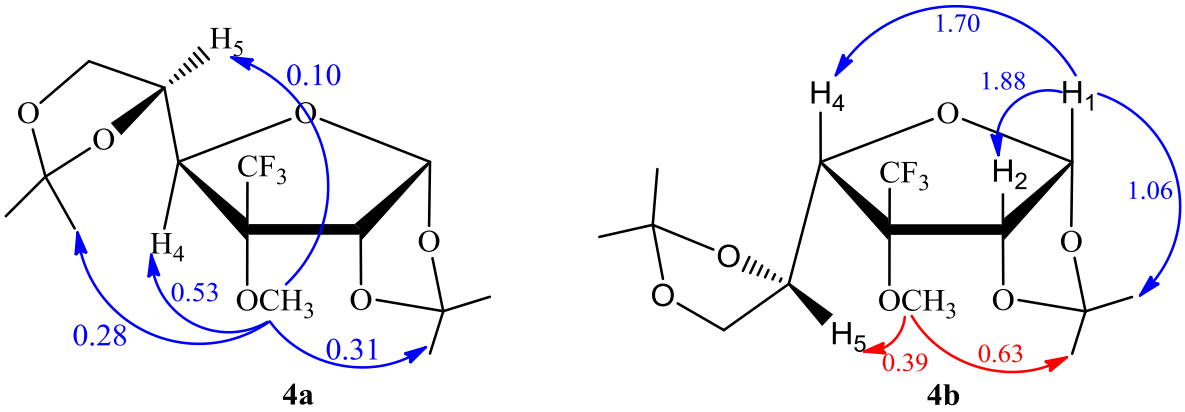


Figure 1. 1D NOE enhancements measured for **4a** (left) and **4b** (right).

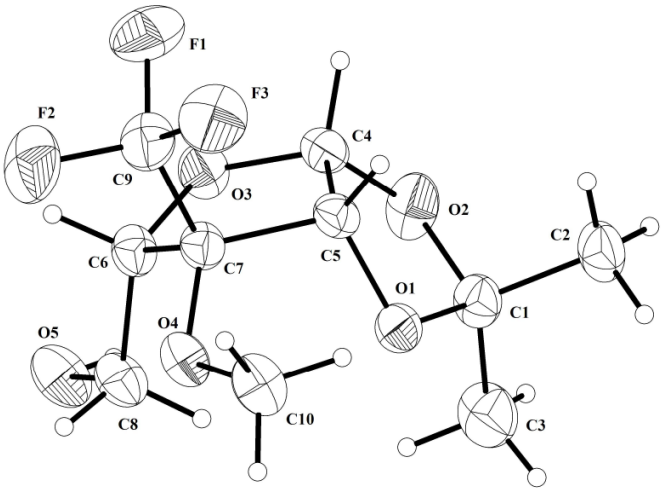
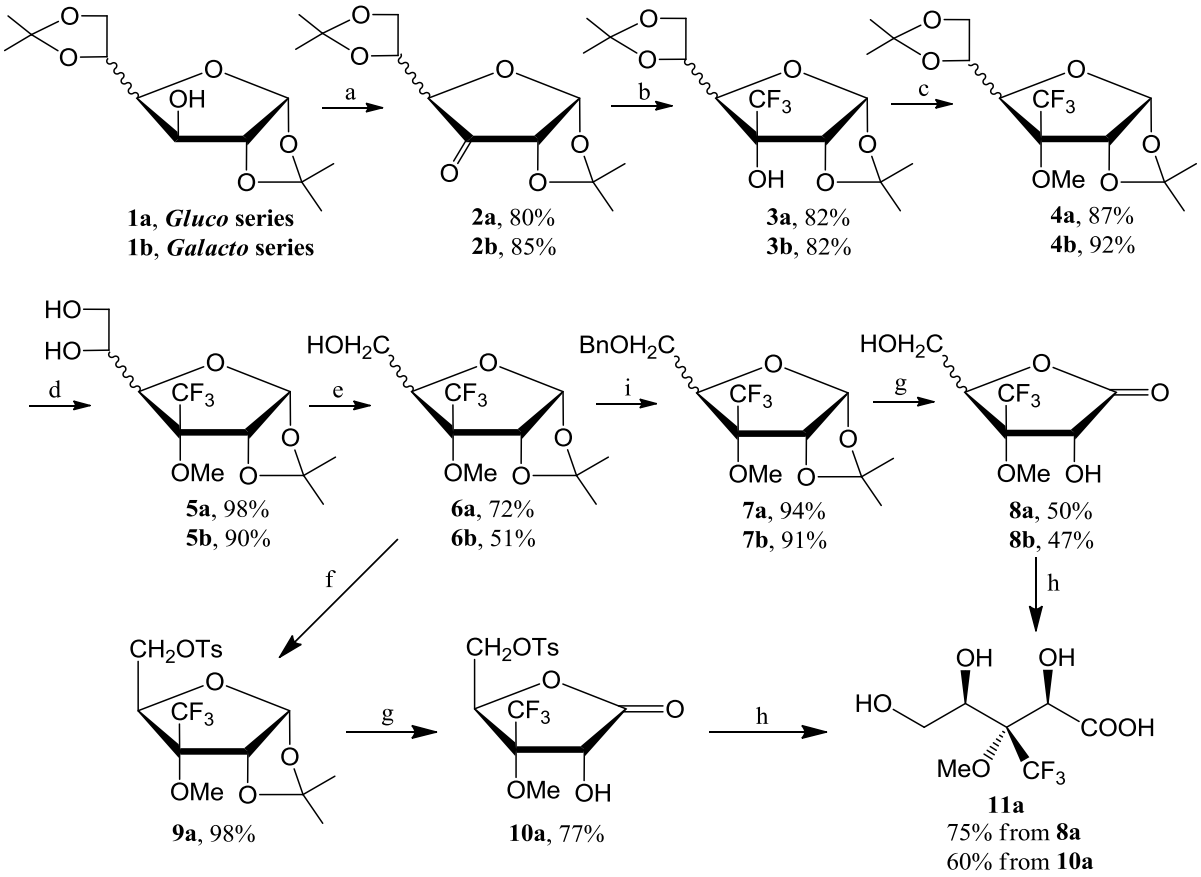
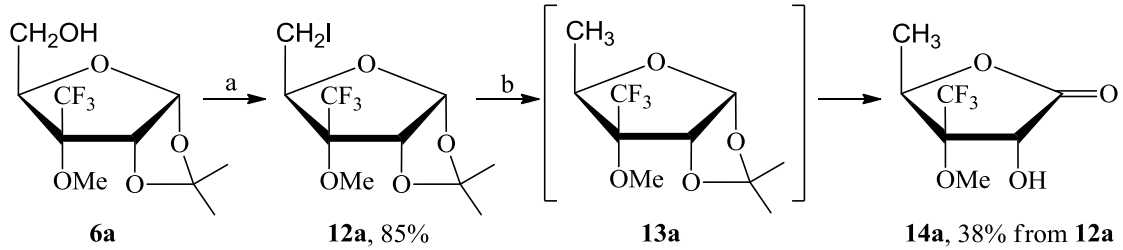


Figure 2.ORTEP representation of the crystal structure of compound **6b** [24].



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, 0ºC; (d) AcOH/H_2O, 60 ºC; (e) 1- $NaIO_4$, H_2O, rt; 2- $NaBH_4$, H_2O, rt; (f) TsCl, pyridine, rt; (g) 1- HCl (1N), 70 ºC; 2- Br_2, $BaCO_3$, dioxan/H_2O, rt; (h) LiOH.H_2O, AcOH, rt; (i) BnBr, NaH, DMF, rt.



6a **12a**, 85% **13a** **14a**, 38% from **12a**

Scheme 2: *Reagents and conditions* (a) I_2, PPh_3, imidazole, toluene, 110 ºC; (b) 1- H_2, Pd-C (10%), MeOH, rt; 2- HCl (1N), 70 ºC; 3- Br_2, $BaCO_3$, dioxan/H_2O, rt.