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# *gem*-Difluoro-carbasugars, the cases of mannopyranose and galactopyranose

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**Abstract**—5a-Difluoro-5a-carbamannopyranose (*gem*-difluoro-carbamannopyranose) and 5a-difluoro-5a-carbagalactopyranose (*gem*-difluoro-carbagalactopyranose), close congeners of their respective natural sugars, in which the endocyclic oxygen atom has been replaced by a *gem*-difluoromethylene group, were synthesized from D-mannose and D-galactose, using a rearrangement strategy.
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## 1. Introduction

Carbasugars are strictly defined as sugar analogues in which the endocyclic oxygen atom has been replaced by a methylene group. This family of sugar mimics has found its application as conformational probes of the bound state of carbohydrates linked to proteins.[1] The conversion of the acetal function of the sugar into an ether, making the glycosidic bond stable to hydrolysis, is the underlying principle of this application. However, it is obvious that these compounds, as *C*-glycosyl compounds,[2] show distinct structural features to those present in natural oligosaccharides, especially regarding the stereoelectronic effects at the anomeric centre.[3] Moreover, the interaction of saccharides with receptors requires the presentation of key polar regions to be recognized by the corresponding proteins,[4] in addition to the frequently found sugar–aromatic interaction.[5] To overcome this disadvantage we envisaged the synthesis of fluorinated analogues, which would hopefully induce conformational bias through stereoelectronic effects as well as provide key polar groups for the interaction with potential receptors.[6] We have first synthesized 5a,5a′-difluoro-5a-carbaglucopyranose (*gem*-difluoro-carbaglucose)[7] and we wish to present herein the synthesis of *gem*-difluoro-carbamannopyranose and *gem*-difluoro-carbagalactopyranose (Fig. 1).

Our strategy is based on a Lewis acid induced rearrangement of an enolether possessing an electron-donating group as illustrated in Scheme 1.[8]

We successfully applied this reaction to the synthesis of carbasugars, carbadisaccharides[9] and more recently to *gem*-difluoro-carbaglucose.[7] In this case, we used an original electron-donating group: a cobalt cluster that is conveniently also a precursor of the $CH_2OH$

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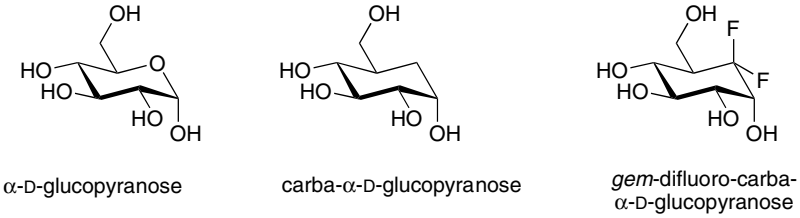
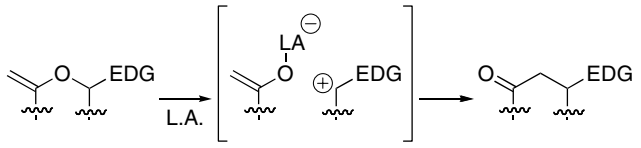



**Figure 1.** α-D-Glucopyranose and its carbocyclic analogues.




**Scheme 1.** General scheme for the Lewis acid induced rearrangement.

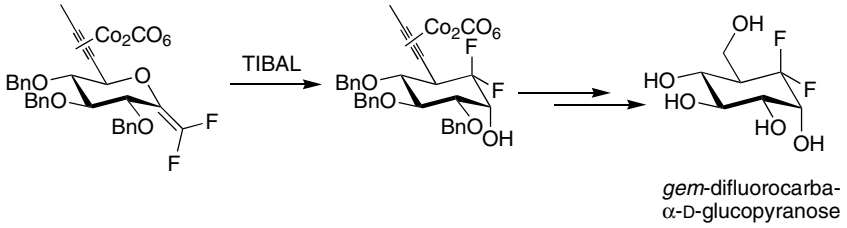
function that will be needed further on in the synthesis. The selected Lewis acid was the triisobutylaluminium (TIBAL), which also conveniently reduces in situ the formed ketone (Scheme 2).

## 2. Results and discussion

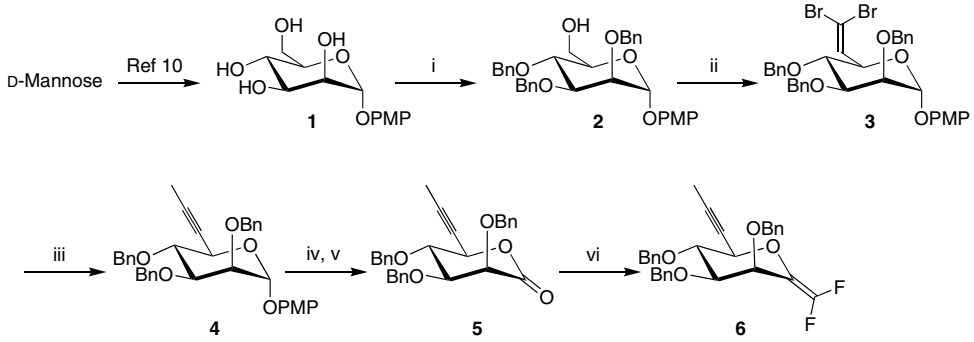
### 2.1. Synthesis of *gem*-difluoro-α-D-carbamannopyranose

Starting from known *para*-methoxyphenyl mannopyranoside **1**,[10] efficiently synthesized from D-mannose, the protected alcohol **2** was prepared in 68% yield, through a selective silylation, benzylation and desilylation sequence. After Swern oxidation of the primary alcohol of **2**, the triple bond was installed via a Corey–Fuchs reaction[11] and methylation of the alkyne afforded **4**. Cleavage of the *para*-methoxyphenyl (PMP) group and subsequent oxidation allowed the formation of lactone **5**, which was then transformed into the key difluoroalkene **6** in 89% yield (Scheme 3).

The key intermediate **6** was next engaged in the rearrangement step through cobalt cluster formation, followed by the addition of TIBAL in the same pot. Removal of the cobalt on the transient carbocyclic cluster afforded 58% of rearranged product as a 3:1 mixture of two isomers, **7** and **8**, respectively. The presence of the axial benzyloxy group induces a lower stereoselectivity of the reduction of the transient ketone compared to that obtained in the *gluco* series (Scheme 4).




**Scheme 2.** Rearrangement-based strategy towards *gem*-difluoro-carbasugars.




**Scheme 3.** Synthesis of difluoroalkene **6**. Reagents and conditions: (i) (1) TBDMSCl, DMAP, pyridine, rt, 150 min; (2) BnBr, NaH, DMF, rt, 16 h; (3) TBAF, THF, rt, 2 h, 68% over three steps; (ii) (1) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −60 °C to rt, 2 h; (2) $CBr_4$, $PPh_3$, $CH_2Cl_2$, rt, 4 h, 68% over 2 steps; (iii) (1) BuLi, THF, −78 °C to −20 °C, 2 h; (2) MeI, HMPA, −78 °C to rt, 17 h, 79%; (iv) CAN, $CH_3CN$–$H_2O$–toluene (1:1:1), 0 °C, 1 h, 70%; (v) PCC, MS 4 Å, $CH_2Cl_2$, rt, 1 h, 83%; (vi) $CBr_2F_2$, HMPT, THF, rt, 89%.

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