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Synthesis and conformational behavior of the difluoromethylene linked C-glycoside analog of β-galactopyranosyl-(1↔1)-α-mannopyranoside

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Abstract—C-Glycosides in which the pseudoglycosidic substituent is a methylene group have been advertised as hydrolytically stable mimetics of their parent O-glycosides. While this substitution assures greater stability, the lower polarity and increased conformational flexibility in the intersaccharide linker brought about by this change may compromise biological mimicry. In this regard, C-glycosides, in which the pseudoanomeric methylene is replaced with a difluoromethylene group, are interesting because the CF_2 group is more of an isopolar replacement for oxygen than CH_2. In addition, the CF_2 residue is expected to instill conformational bias into the intersaccharide torsions. Herein is described the synthesis and conformational behavior of the difluoromethylene linked C-glycoside of β-D-galactopyranosyl-(1↔1)-α-D-mannopyranoside. The synthesis centers on the formation of the galactose residue via an oxocarbenium ion–enol ether cyclization. Conformational analysis, using a combination of molecular mechanics, dynamics, and NMR spectroscopy, suggests that the difluoro-C-glycoside populates the non-*exo*-Gal/*exo*-Man conformer to a major extent (ca 50%), with a minor contribution (~15%) from the *exo*-Gal/*exo*-Man conformer that corresponds to the ground sate of the parent O-glycoside.

Keywords: Glycomimetic; Oxocarbenium ion; Cyclization; De novo

1. Introduction

The replacement of the glycosidic oxygen in O-glycoside with a methylene substituent leads to an analogue with greater hydrolytic stability than the parent O-glycoside.[1] Such compounds often referred to as exact C-glycosides, may function as biological mimetics of their parent O-glycosides, but the extent of this mimicry could be compromised by the lower polarity and greater flexibility of the intersaccharide linker.[2–5] In this vein, we have been interested in the mimicry of C-glycosides in which the methylene linker is replaced with a CHF or CF_2 residue. The design of these mimetics was guided by two tenets. First, the electronegativity of the fluorine substituents could make the intersaccharide linker more isopolar to the glycosidic oxygen.[6] Second, based on the unusual conformational properties of 2-fluoroethanols and related structures, such fluoro-C-glycosides are expected to have a more well defined conformational bias than the exact C-glycoside with respect to the intersaccharide linker, such that they may more closely mimic the conformational properties of O-glycoside.[7,8] Indeed, the use of CHF and CF_2 as isosteres of oxygen has been examined in other molecules of biological interest, and examples of CF_2 linked C-furanosides have been

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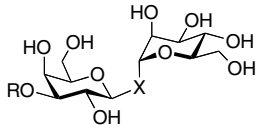


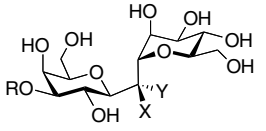


Figure 1. O- and C-disaccharides.

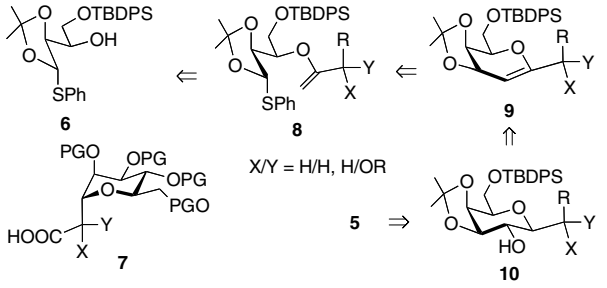
prepared.[9–11] We have previously reported the synthesis and conformational behavior of **2**–**4**,[12,13] the exact and the CHF linked analogues of **1**, a known O-disaccharide mimetic of sialyl Lewis X (Fig. 1).[14] In this series the fluoro-C-glycoside **3** was found to be the closest conformational mimic of **1**. Herein, as an extension of this study, we describe the synthesis and conformational properties of the CF_2 linked analogue **5**.[15]

2. Results and discussion

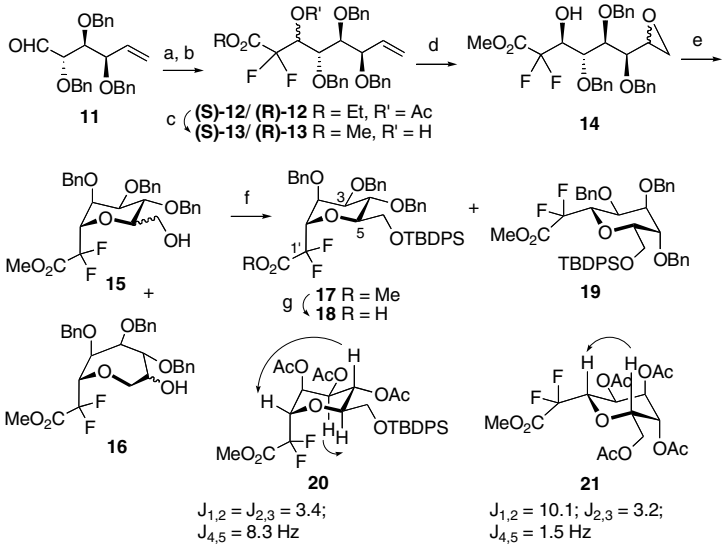
2.1. Synthesis

We have been developing a de novo synthesis of complex C-disaccharides **10**, in which the key step is the formation of a C1 substituted glycal **9** via an enol ether–oxocarbenium ion cyclization.[16] C-Glycoside **10** is then obtained by the stereoselective hydroboration of **9**. Because this method was previously successful for hydroxymethyl linked C-glycosides (e.g., **10**: X/Y = H/OH), we envisaged an initial synthesis of **5** that was based on fluorination of the ketone derived from **10**.[17] Not surprisingly, given the highly substituted nature of this precursor, this strategy was unsuccessful. Therefore, a revised plan in which the CF_2 group was introduced in a less complex precursor (i.e., **7**: X/Y = F/F) was adopted. A key question with this approach was the feasibility of the oxocarbenium ion cyclization on the difluorinated enol ether thioacetal (i.e., **8**, X/Y = F/F) in light of the noted deactivation of related difluorinated enol ethers to electrophilic reagents.[18] In addition, while the thioacetal precursor **5** was available from earlier investigations, a synthesis of an α,α-difluoroacid like **7** had to be devised (Scheme 1).

Initial attempts at the synthesis of α,α-difluoroacid through treatment of an α-ketoester precursor with DAST[17] led to intractable mixture of products. A successful plan originated in the reaction of the Reformatsky-like reagent from methyl bromodifluoroacetate and the known aldehyde **11** (Scheme 2).[19,20] This led to an inseparable mixture of epimeric (*R*)- and (*S*)-alcohols



Scheme 1. Retrosynthesis of the difluoromethylene linked C-disaccharide.



Scheme 2. Synthesis of difluoroacid **18**. Reagents: (a) $BrCF_2CO_2Et$, Zn, THF, reflux then **11**; (b) Ac_2O, DMAP, EtOAc, two steps, 35%; (c) NaOMe, MeOH, 83%; (d) *m*CPBA, CH_2Cl_2, aq NaH_2PO_4/Na_2HPO_4, 74%; (e) (i) NaOMe, MeOH then HCl in ether; (ii) $TMSCHN_2$, MeOH, **15** (52%) + **16** (22%); (f) TBDPSCl, imidazole, DMF, 50 °C, **17** (59%) + **19** (39%); (g) 3 M NaOH, EtOH then 2 M HCl, 94%.