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A convenient synthesis of *C*-galactofuranosylic compounds (*C*-galactofuranosides)

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Dedicated to Professor Derek Horton on the occasion of his 70th birthday

Abstract

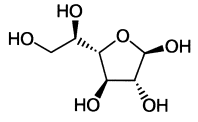
Galactofuranose sugar units are essential for the production of the cell coat of many pathogenic microorganisms. This sugar is not found in mammals, and so compounds that may interfere with the biosynthetic processing of this sugar unit provide interesting targets for drug design. This paper describes the use of a cyanation reaction for the production of a one-carbon extension of a galactofuranosylic unit at C-1, giving 2,5-anhydro-3,4,6,7-tetra-*O*-benzoyl-D-*glycero*-L-*manno*-heptononitrile. A procedure for the efficient hydrolysis of the introduced nitrile group to produce the methyl ester is reported, along with procedures for the synthesis of both the corresponding α,β-unsaturated, and 3-deoxy ester derivatives.

Keywords: Galactofuranose; *C*-Glycosylic compounds; *C*-Glycosides; Cyanation

1. Introduction

Poor socioeconomic conditions in many third-world countries have led to the reoccurrence of many microbacterial diseases that were once thought to be on the decline. One such disease, tuberculosis, is responsible for an estimated three million deaths worldwide every year.[1] Furthermore, incomplete drug treatment of many sufferers has resulted in the emergence of drug-resistant strains of the microorganism, *Mycobacterium tuberculosis*, that causes this disease.[2,3] The significant mortality associated with tuberculosis, as well as appearance of new drug-resistant strains, has resulted in the urgent need for new, cost-effective treatments to combat this disease.

Galactofuranose **1** (Gal*f*) is one of the sugar units which is essential for the production of the peptidoglycan found in the cell coat of many pathogenic microorganisms, including *Mycobacterium tuberculosis*.[4–6] This peptidoglycan layer is essential for viability of the microorganism and provides a tough wall that is responsible, not only for preventing access of many antibacterial compounds, but is also thought to be responsible for the virulence of the organism. Since Gal*f* is not found in mammals, compounds that mimic Gal*f* and interfere with the biosynthetic enzymes that produce and utilise Gal*f* may provide interesting targets for the development of new drug treatments.



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C-Glycosylic compounds (*C*-glycosides) form one class of compounds that have often shown interesting biological properties.[7,8] With regard to *C*-glycosides of Gal*f*, Kovensky et al. reported methods to gain access to α- and β-phosphonic acid derivatives of Gal*f*,

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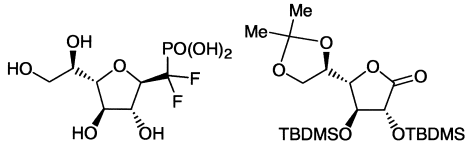
C-glycoside analogues of Gal*f* 1-phosphate.[9] For the synthesis of the β-difluoromethylenephosphonate derivative **2**, introduction of the carbon substituent at C-1 was achieved through olefination of protected galactono-1,4-lactone **3**.[9] Wheatley et al. have described the synthesis of the 1-α-ester derivative of Gal*f* **4**, from a rearrangement of the 2-*O*-trifluoromethanesulfonyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone (**5**) in the presence of acidic methanol.[10] Rearrangement of sugar γ- and δ-lactone 2-triflates in acidic[10] or basic[11] methanol has been applied to the synthesis of a range of C-1 methyl ester derivatives.



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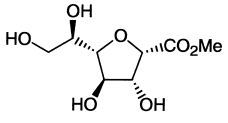

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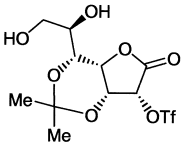

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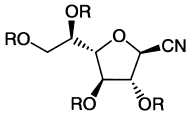
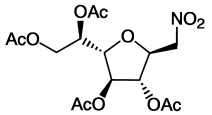
The introduction of a nitrile at C-1, however, offers a useful handle, which can subsequently be manipulated to arrive at a number of interesting *C*-glycosidic analogues.[12–16] Köll et al. have previously accessed the 1-β-cyano derivative **6** of peracetylated Gal*f* by reduction, with phosphorus trichloride, of the corresponding 1-β-nitromethyl Gal*f* derivative **7**.[17] The yield of **6** over three steps from galactose was, however, only 5%, principally due to a low (13%) yield in the preparation of **7** from galactose. Herein we report the use of the cyanation reaction to make the versatile, one-carbon homologated Gal*f* derivative, 2,5-anhydro-3,4,6,7-tetra-*O*-benzoyl-D-*glycero*-L-*manno*-heptononitrile (**9**). In this work, we were initially interested in forming a methyl ester at the C-1 position in order to arrive at a sialic acid–Gal*f*-type hybrid molecule. Thus, we have developed a method that efficiently converts the protected nitrile **9** into the desired, deprotected Gal*f* methyl ester **12**. Further elaboration from nitrile **9** led into the α,β-unsaturated ester **18** and the 3-deoxy derivative **20**.



6 R = Ac
9 R = Bz



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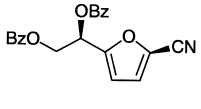
2. Results and discussion

Previous workers have shown that access to one-carbon extensions of sugars is best achieved by a cyanation reaction whereby 1-*O*-acyl sugars react with TMSCN under Lewis acidic conditions to introduce a cyano group into the anomeric position of the sugar.[12,18,19] This reaction when applied to perbenzoylated Gal*f* **8**[20,21] resulted in the production of the desired nitrile **9** in a satisfying 80% yield (Scheme 1). This reaction not unexpectedly furnished the β-isomer exclusively. As our initial goal was to make a methyl ester at the C-1 position, we required a method to hydrolyse the nitrile to the acid, which we could subsequently methylate to produce the desired methyl ester. Unfortunately, under standard acidic or basic hydrolysis conditions, elimination occurred to produce a furan derivative, for example, the benzoylated furan nitrile **13** from attempted acidic hydrolysis. A similar result has previously been reported by Albrecht et al. who had attempted to perform reductive hydrolysis of a C-1 cyano function in ribose.[22] A report by Poonian and Nowoswiat,[23] who had formed the methyl imidate **14** from benzoylated ribosyl cyanide that was then utilised in a heterocyclisation, prompted us to examine the formation of the corresponding methyl imidate of Gal*f* under anhydrous conditions. The methyl imidate should be easily hydrolysed to the desired methyl ester under relatively mild conditions. Reaction of the nitrile **9** with anhydrous sodium methoxide overnight[†] furnished the fully deprotected methyl imidate **10**. This compound could be easily isolated from the reaction by neutralisation, followed by removal of the solvent, or alternatively, it could be hydrolysed *in situ* with a small amount of Dowex 50 (H^+) resin and water to give the crude methyl ester **12**. The deprotected ester **12** was most readily purified and characterised as the corresponding peracetylated derivative. Accordingly, peracetylation of the crude ester yielded the acetylated C-1 ester **11** in a respectable 68% yield (after flash chromatography) from **9** over three steps. O-Deacetylation of **11** gave the desired Gal*f* ester **12**.



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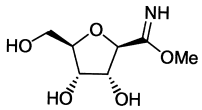

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Having established an efficient route to one of our target compounds, we set about making two further derivatives, namely the corresponding α,β-unsaturated ester derivative **18** and the 3-deoxy derivative **20**. Elimination of the C-3 benzoyl group in **9**, to produce the α,β-unsaturated derivatives, was easily achieved via a simple two-step procedure (Scheme 2). Firstly, reaction of the nitrile **9** with DBU[24] at room temperature for three days, furnished the desired intermediate **15** in virtually

[†] If the reaction was left for only 4 h compared with 20 h, a 1:1 mixture of the desired methyl ester **11** as well as the peracetylated Gal*f* nitrile **6**[17] was subsequently isolated. This result shows that the methyl imidate **10** was slow to form.