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Synthesis of carbadisaccharide mimics of galactofuranosides

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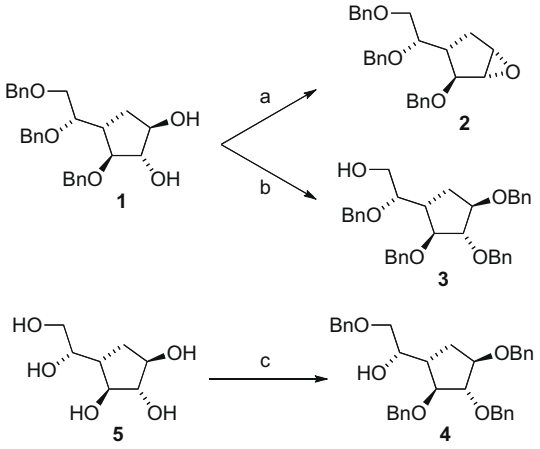
ABSTRACT

A partially protected carbagalactofuranose was converted into a 1,2-anhydro derivative. This epoxide was opened with alcohol nucleophiles under Lewis acid catalysis to give β-carbagalactofuranose pseudodisaccharides with excellent regioselectivity.

Galactose is found in the unusual furanose configuration in bacteria and other lower organisms, some of which are pathogenic, but not in mammals.[1] The arabinogalactan from the cell wall of *Mycobacterium tuberculosis* contains a polymeric region of galactofuranosides with alternating (β1→5)- and (β1→6)-linkages, anchored to the cell-wall peptidoglycan by a (β1→4)-linkage to rhamnose.[2] Hydrolytically stable mimics of fragments of this oligosaccharide may be of interest to investigate the substrate-binding properties of the galactosyltransferases[3–5] that assemble the cell wall polysaccharide and could be interesting targets for inhibition. Carbasugar[6,7] pseudodisaccharides have been previously shown to act as glycosyltransferase substrates.[8]

We recently reported the synthesis of a carbagalactofuranose monomer **5**.[9] For the synthesis of carbasugar-containing pseudodisaccharides mimicking the Gal*f*(β1→5)Gal*f* and Gal*f*(β1→6)Gal*f* linkages of arabinogalactan, the ether linkages should ideally be constructed in a stereocontrolled manner, and we therefore considered S_N2 type processes. A versatile approach would be to use a carbagalactofuranose C-1 electrophile that could be attacked by OH-6 or OH-5 carbasugar nucleophiles, or even other alcohols should it be desirable to synthesise other carbagalactofuranosides. 1,2-Epoxides derived from carbapyranoses have been used as electrophiles for the synthesis of pseudodisaccharides with alcohol nucleophiles under Lewis acidic or basic conditions.[10] In this Letter, we report the extension of this concept to the five-membered ring system, and describe the synthesis of some carbagalactofuranoside-containing pseudodisaccharides.

Diol **1**[9] was converted into the epoxide **2** as follows: treatment with tosyl chloride and pyridine gave the 1-tosylate as the major product (42%) along with minor amounts of 2-tosylate (14%) and 1,2-ditosylate (5%). The orientation of substitution was determined by NMR spectroscopy (coupling between the OH proton and either H-1 or H-2). Treatment of the major regioisomer with sodium hydride eliminated tosylate to give the required α-*galacto* epoxide **2** (87%). The same epoxide **2** was better obtained in one step as a single diastereomer (87%) from the diol **1** under Mitsunobu conditions (Scheme 1).



Scheme 1. Reagents and conditions: (a) DIAD, PPh_3, THF, 0 °C, 86%; (b) (i) BnBr, NaH, DMF, 92%; (ii) $ZnCl_2$, Ac_2O, AcOH, 76%; (iii) NaOMe, MeOH, rt, quant.; (c) (i) acetone, CSA; (ii) BnBr, NaH, DMF; (iii) AcOH, H_2O, 56% (three steps); (iv) Bu_2SnO, MeOH, 60 °C; (v) BnBr, CsF, DMF, 88% (two steps).

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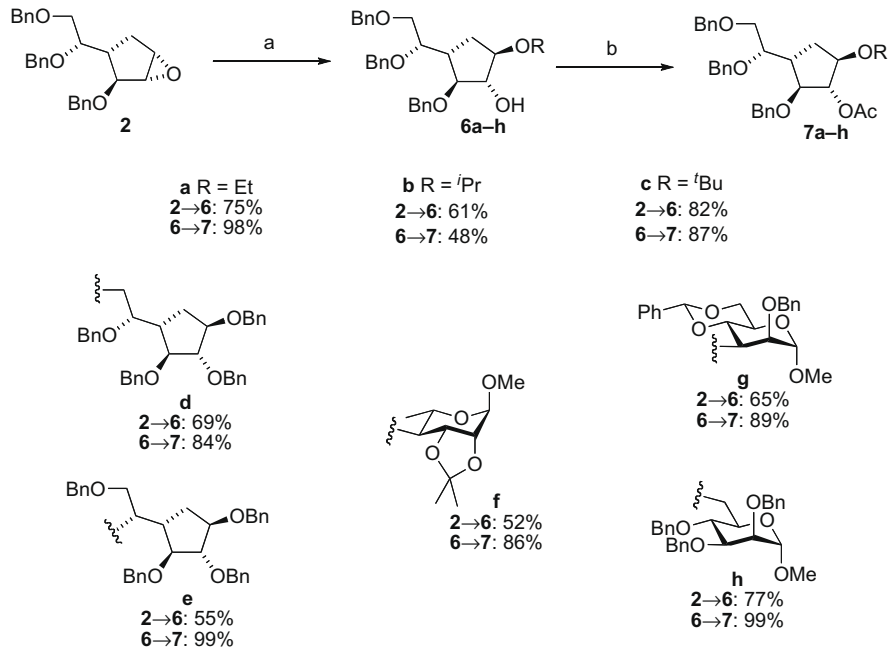


Scheme 2. Reagents and conditions: (a) ROH (equiv: **a–c**, 10; **d**, 3.9; **e**, 3.0; **f**, 3.2; **g**, **h**, 5.0), $BF_3{\cdot}OEt_2$ (0.1 equiv), CH_2Cl_2, rt; (b) Ac_2O, pyridine, DMAP, rt.

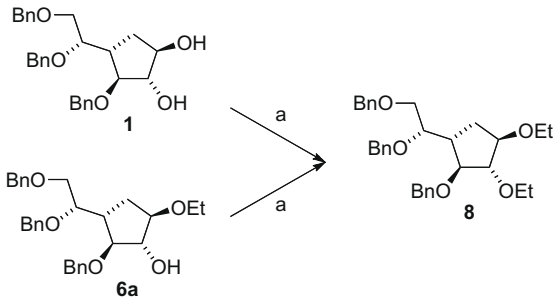
The required OH-6 and OH-5 alcohols (**3** and **4**) were prepared as follows: perbenzylation of the carbasugar **1** was followed by selective acetolysis of the O-6 benzyl ether and deacetylation to give the primary alcohol **3**. From the carbasugar **5**,[9] OH-5 and OH-6 were protected as an isopropylidene acetal. The remaining three hydroxy groups were benzylated, and the isopropylidene protection was removed to give the 5,6-diol, which was selectively protected at C-6 to give the secondary alcohol **4** (Scheme 1).

Next, we attempted the etherification reaction, first using model alcohols to open the epoxide **2** using $BF_3{\cdot}OEt_2$ as promoter. Ethanol, isopropanol and *tert*-butanol (10 equiv) each gave a single regioisomer **6a–c** of the respective ethers in good yield. The regioselectivity of the reaction was confirmed by acetylation of the products to give acetates **7a–c**; OH-2 was acetylated, as was evident from the downfield shift of H-2 in the ^1H NMR spectra (Scheme 2). Our assignment of the stereochemistry of the epoxide **2** (and thence the products of ring-opening **6**) was confirmed by ethylation of both the diol **1** and the alcohol **6a** obtained from opening of the epoxide **2** by ethanol. The two diethyl derivatives **8** obtained were identical with one another (Scheme 3).

The primary and secondary carbasugar alcohols **3** and **4** both opened the epoxide **2** under the same Lewis acid catalysed conditions with essentially complete regioselectivity for attack at C-1 to give bis-carbadisaccharides **6d**, **e** as the only pseudodisaccharide products (Scheme 2).[11] Primary and secondary pyranoid carbohydrate alcohols (Rha O-4,[12] Man O-3[13] and Man O-6[14]) also opened the epoxide with complete regioselectivity to give pseudodisaccharide products **6f–h** resembling substructures of other bacterial polysaccharides. That the sense of regioselectivity was the same for the carbasugar and carbohydrate nucleophiles as for the simple alcohols was confirmed by acetylation. By-products with mass spectral data consistent with the pseudotrisaccharides arising from attack of the product alcohols **6** on the epoxide **2** were also seen.

The explanation of the excellent regioselectivity in the epoxide opening may be both steric and electronic in origin. C-1 is expected to be less hindered than C-2 as the C-4a methylene group (flanking C-1) is smaller than the corresponding benzyl-ether-substituted C-3 (flanking C-2). Attack at C-1 leads to the all *trans* β-*galacto* configuration, while attack at C-2 would give an α-*talo* configuration with a 2,3-*cis* relationship. Under Lewis acid catalysed epoxide opening, attack will usually occur at the carbon most able to stabilise a partial positive charge. The more electron-withdrawing nature of the oxygenated C-3 compared to the methylene C-4a is also expected to favour attack at C-1 over C-2.

To conclude, we have synthesised carbafuranoside pseudodisaccharides for the first time. The regioselective Lewis acid catalysed epoxide opening gives the ether-linked pseudodisaccharides via attack at C-1. Pseudodisaccharide mimics of all three galactofuranoside linkages in mycobacterial arabinogalactan are accessible by this method.



Scheme 3. Reagents and conditions: (a) NaH, EtBr (10 equiv), DMF, rt; 37% from **6a**; 45% from **1**.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.115.

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11. Representative procedure for epoxide-opening; synthesis of **6d**: Epoxide **2** (31 mg, 0.072 mmol) and alcohol **3** (150 mg, 0.28 mmol) were dissolved in CH_2Cl_2 (0.75 mL) under N_2 at rt. $BF_3{\cdot}OEt_2$ (18 μL, 0.14 mmol) was dissolved in CH_2Cl_2 (2.5 mL), and 125 μL (7 μmol) of this solution was added to the reaction mixture, which instantly turned from colourless to pale yellow. After 10 min, TLC (toluene/EtOAc, 5:1) showed complete consumption of epoxide **2** (R_f 0.8), remaining alcohol **3** (R_f 0.4) and the formation of a product (R_f 0.5). The reaction was quenched by addition of Et_3N (0.5 mL) and the mixture was concentrated in vacuo. The crude product was purified by column chromatography on silica gel (toluene/EtOAc, 4:1) to give the pseudodisaccharide **6d** (48 mg, 69%) as a colourless oil.
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