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 \(\beta\)-carbagalactofuranose pseudodisaccharides with excellent regioselectivity.

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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 (\(\beta1\sim5\)) and (\(\beta1\sim6\))-linkages, anchored to the cell-wall peptidoglycan by a (\(\beta1\sim4\))-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 Galf(\(\beta1\sim5\))Galf and Galf(\(\beta1\sim6\))Galf 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 carbagalactofuranose-side-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 \(\alpha\)-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\(_2\), ACO\(_2\), AcOH, 76%; (iii) NaOMe, MeOH, rt, quant.; (c) (i) acetone, CSA; (ii) BnBr, NaH, DMF; (iii) AcOH, H\(_2\)O, 56% (three steps); (iv) Bu\(_2\)SnO, MeOH, 60 °C; (v) BnBr, CsF, DMF, 88% (two steps).
The required OH-6 and OH-5 alcohols (3 and 4) were prepared as follows: perbenzylation of the carbasugar 1 was followed by selective acetylation of the O-6 benzyl ether and deacetylation to give the primary alcohol 3. From the carbasugar 5, 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 BF₃·OEt₂ as promoter. Ethanol, isopropanol and tert-butanol (10 equiv) each gave a single regiosomer 6a–c of the respective ethers in good yield. The regioselectivity of the reaction was confirmed by acetylation of the products to give acetates 6a–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 opening was confirmed by acetylation of the respective ethers in good yield. The regioselectivity was the same for the carbasugar and carbohydrate nucleophiles as for the simple alcohols 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-2) 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 carba-furanoside 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.

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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.
References and Notes


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\(_2\)Cl\(_2\) (0.75 mL) under N\(_2\) at rt. BF\(_3\)/C\(\text{OEt}_2\) (18 \(\mu\)L, 0.14 mmol) was dissolved in CH\(_2\)Cl\(_2\) (2.5 mL), and 125 \(\mu\)L (7 \(\mu\)mol) 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\(_3\)N (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.