Tetrahedron Letters 50 (2009) 5142–5144

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of carbadisaccharide mimics of galactofuranosides

Jens Frigell, Ian Cumpstey *

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, 106 91 Stockholm, Sweden

ARTICLE INFO

Article history:
Received 20 May 2009
Revised 17 June 2009
Accepted 26 June 2009
Available online 1 July 2009

Keywords:
Carbasugars
Galactofuranose
Pseudodisaccharides
Ethers

ABSTRACT

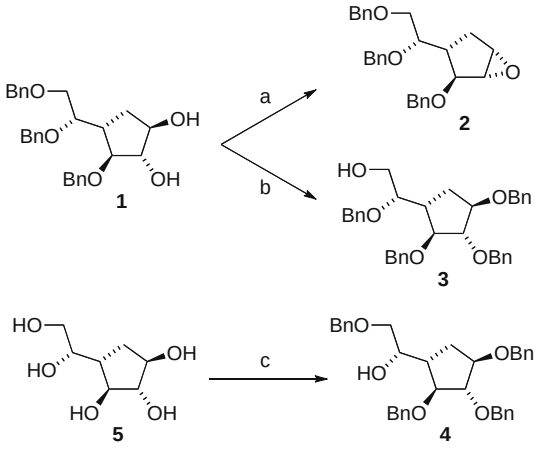
A partially protected carbagalactofuranose was converted into a 1,2-anhydro derivative. This epoxide was opened with alcohol nucleophiles under Lewis acid catalysis to give β-carbagalactofuranose pseudodisaccharides with excellent regioselectivity.

© 2009 Elsevier Ltd. All rights reserved.

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.

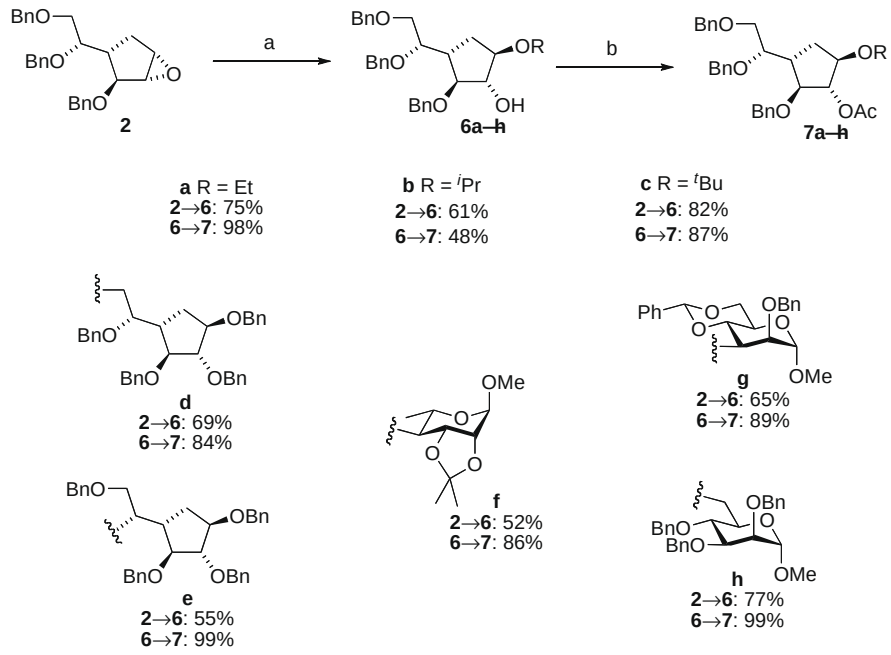
Diol **1**[9] was converted into the epoxide **2** as follows: treatment with tosyl chloride and pyridine gave the 1-tosylate as the major product (42%) along with minor amounts of 2-tosylate (14%) and 1,2-ditosylate (5%). The orientation of substitution was determined by NMR spectroscopy (coupling between 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).

* Corresponding author. Tel.: +46 0 8 16 2481; fax: +46 0 8 15 4908.
E-mail address: cumpstey@organ.su.se (I. Cumpstey).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.06.115



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.

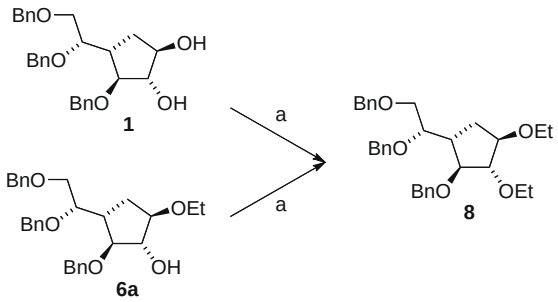
The required OH-6 and OH-5 alcohols (**3** and **4**) were prepared as follows: perbenzylation of the carbasugar **1** was followed by selective acetolysis of the O-6 benzyl ether and deacetylation to give the primary alcohol **3**. From the carbasugar **5**,[9] OH-5 and OH-6 were protected as an isopropylidene 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

We gratefully acknowledge financial support from the Swedish Research Council (Vetenskapsrådet) and an Ivar Bendixson grant.

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

1. Peltier, P.; Euzen, R.; Daniellou, R.; Nugier-Chauvin, C.; Ferrieres, V. *Carbohydr. Res.* **2008**, *343*, 1897.
2. Mahapatra, S.; Basu, J.; Brennan, P. J.; Crick, D. C. In *Tuberculosis and the Tubercle Bacillus*; Cole, S. T., Eisenach, K. D., McMurray, D. N., Jacobs, W. R., Jr., Eds.; American Society for Microbiology: Washington, DC, 2005; p 275.
3. Belanova, M.; Dianiskova, P.; Brennan, P. J.; Completo, G. C.; Rose, N. L.; Lowary, T. L.; Mikusova, K. *J. Bacteriol.* **2008**, *190*, 1141.
4. Completo, G. C.; Lowary, T. L. *J. Org. Chem.* **2008**, *73*, 4513.
5. Rose, N. L.; Completo, G. C.; Lin, S.-J.; McNeil, M.; Palcic, M. M.; Lowary, T. L. *J. Am. Chem. Soc.* **2006**, *128*, 6721.
6. McCasland, G. E.; Furuta, S.; Durham, L. J. *J. Org. Chem.* **1966**, *31*, 1516.
7. Ogawa, S. *Trends Glycosci. Glyc.* **2004**, *16*, 33.
8. Ogawa, S.; Matsunaga, N.; Palcic, M. *Carbohydr. Lett.* **1997**, *2*, 299.
9. Frigell, J.; Cumpstey, I. *Tetrahedron Lett.* **2007**, *48*, 9073.
10. Ogawa, S.; Sasaki, S.-I.; Tsunoda, H. *Chem. Lett.* **1993**, 1587.
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.
12. Liptak, A.; Imre, J.; Nanasi, P. *Carbohydr. Res.* **1981**, *92*, 154.
13. Ennis, S. C.; Cumpstey, I.; Fairbanks, A. J.; Butters, T. D.; Mackeen, M.; Wormald, M. R. *Tetrahedron* **2002**, *58*, 9403.
14. Ruiz Contreras, R.; Kamerling, J. P.; Vliegenthart, J. F. G. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 85.