Short Synthesis of a Bicyclic Mimic of α-L-Fucose

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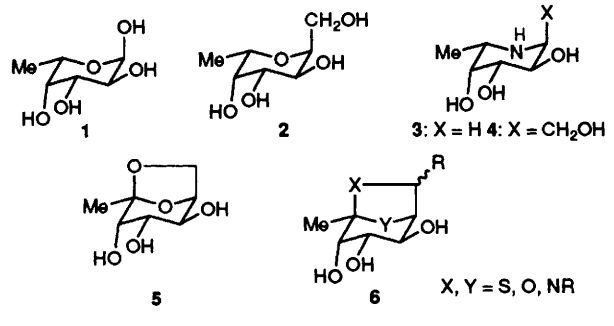
The stability of a 2,7-anhydroheptulose, readily available from L-gulonolactone, may provide clues to a wide range of bicyclic analogues of conformationally fixed α-L-fucose.

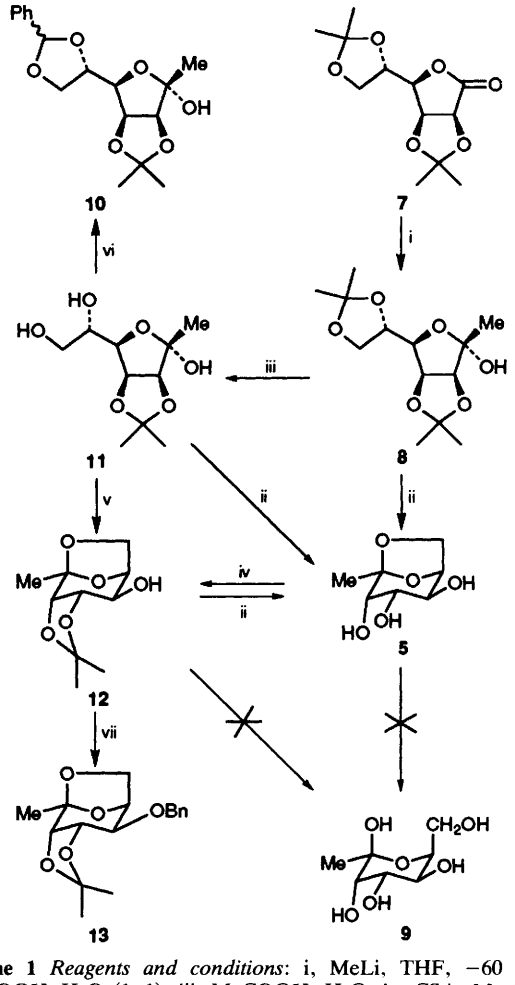
Pyranosides of α-L-fucose **1** play an important role as a major determinant in the interactions of carbohydrates with proteins.[1] Analogues of such materials may provide therapeutic agents for the treatment of inflammation and cancer among other applications; simple fucose mimics have been reported as having potential for such disparate uses as antiviral agents[2] and for increasing the rate of hair growth.[3] It is still unclear in many of these processes what will constitute structures that are both metabolically stable and likely to be recognised either by fucosidases, fucosyl transferases or receptors that apparently recognise fucose epitopes such as sialyl Lewis x. Easy access to divergent intermediates, such as equivalents of α-L-homofucose **2**, would permit the generation of a large library of fucose analogues for screening against a wide range of biological activity.

At present there are a number of good inhibitors of fucosidases, but very little indication of what will constitute general classes of inhibitors of fucosyl transferases or are likely to be ligands for receptors for cell adhesion molecules. Piperidine analogues of sugars, with the same absolute configuration of the secondary hydroxy groups as fucose, are very powerful inhibitors of most fucosidases.[4] Deoxyfuconojirimycin **3**[5] and α-homofuconojirimycin **4**[6] both have K_i of 10^{-8} mol dm^{-3} or less against a number of fucosidases and are the most potent fucosidase inhibitors yet reported. Five-ring pyrrolidine analogues of fucose, although generally less potent inhibitors of fucosidases than the piperidine analogues,[7,8] have been shown to be synergistic inhibitors of α-1,3-fucosyl transferase in the presence of guanosine diphosphate.[9] Both GMP fucose derivatives[10] and a C-fucoside[11] have been investigated as potential fucosyl transferase inhibitors. This paper reports a synthesis, originally intended to provide divergent intermediates for the synthesis of biologically stable non-hydrolysable α-L-homofucose analogues, which leads to a remarkably stable bicyclic framework **5**, indicating that a range of bicyclic α-L-fucose analogues such as **6** should be readily available.

Treatment of the diacetonide of L-gulonolactone **7**[12] with methyllithium gave a single anomeric lactol **8**,† mp 139–141 °C, $[\alpha]_D^{20}$ +4.3 (*c*, 1.0 in $CHCl_3$), in 89% yield. Extensive equilibrium NOE experiments have demonstrated the stereochemistry of the anomeric substituents of **8** and **11** to be as shown (Scheme 1). Hydrolysis of the diacetonide **8** with aqueous trifluoroacetic acid at room temperature caused deprotection, ring isomerisation from the furanose to the pyranose and subsequent dehydration to afford the bicyclic fucose analogue **5**,‡ mp 163.5–164.5 °C, $[\alpha]_D^{20}$ −46.1 (*c*, 1.0 in H_2O), in 96% yield [85% from **7**].

Mild hydrolysis of **8** with aqueous acetic acid gave the monoacetonide **11**, oil, $[\alpha]_D^{20}$ +28.7 (*c*, 1.02 in MeCN), again as a single anomer, in 89% yield. The ring-fused isopropylidene ketal in **11** could not be removed in aqueous acetic acid. All attempts to hydrolyse the remaining isopropylidene protecting group in **11** by stronger acids caused initial dehydration to give **12** followed by subsequent deprotection to **5**; for example, treatment of **11** with aqueous trifluoroacetic acid afforded **5** in 91% yield. The monoisopropylidene derivative **12** could be prepared by reaction of **11** with acid in the absence of water so that camphorsulfonic acid (CSA) in DMF gave **12**, mp 95–97 °C, $[\alpha]_D^{20}$ −46.3 (*c*, 0.94 in $CHCl_3$),





Scheme 1 *Reagents and conditions*: i, MeLi, THF, −60 °C; ii, $CF_3COOH:H_2O$ (1:1); iii, MeCOOH, H_2O; iv, CSA, Me_2CO; v; CSA, DMF; vi, $PhCH(OMe)_2$, CSA, DMF; vii, NaH, $PhCH_2Br$, *n*-$Bu_4N^+I^-$, THF

in 67% yield; **12** was also formed from treatment of **5** with acetone in the presence of CSA. There were some ambiguities in assigning the above bicyclic structures; however, the acetonide **12** on reaction with sodium hydride and benzyl bromide in tetrahydrofuran in the presence of a catalytic amount of tetrabutylammonium iodide gave the highly crystalline benzyl ether **13**, mp 75–77 °C, $[\alpha]_D^{20}$ −19.8 (*c*, 1.05 in $CHCl_3$), in 68% yield; the structure of **13** was firmly established by single crystal X-ray crystallographic analysis.§ Endeavours to give monocyclic homofucose analogues, such as **9**, by ring opening of **5**, **12** or **13** under hydrolytic and reductive conditions were equally unsuccessful. Treatment of **11** with benzaldehyde dimethylacetal in dimethylformamide in the presence of CSA, rather than giving a six-ring pyranoside benzylidene acetal, afforded a mixture of the epimeric five-ring acetals **10** in 83% yield.

The stability of the bicyclic anhydrofucose system in **5** is noteworthy,[13] a related stable nitrogen analogue of the acetonide **12** has been reported recently.[14] Although the anhydrohomofucose derivative **5** did not have any significant effect on the activity of 11 human liver glycosidases, including fucosidase, the stability of the bicyclic framework suggests that a class of structures such as **6** in which the oxygens of the acetal unit might be replaced with nitrogen and/or sulfur would also be stable. Such materials may be useful as probes for the potential biological activity of rigid bicyclic mimics of α-L-fucose.

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Footnotes

† All new compounds in this paper have microanalytical and spectroscopic data consistent with the structures proposed.

‡ Selected data for **5**: δ_H (D_2O; 500 MHz; *J*/Hz) 1.39 (3H, s, Me), 3.60 (1H, d, 3-H, $J_{3,4}$ 4.6), 3.62 (1H, dd, 4-H, $J_{4,5}$ 9.0, $J_{4,3}$ 4.6), 3.65 (1H, dd, 7-H, $J_{7,7'}$ 8.1, $J_{7,6}$ 4.9), 3.72 (1H, dd, 5-H, $J_{5,4}$ 9.0, $J_{5,6}$ 4.1), 3.91 (1H, d, 7′-H, $J_{7',7}$ 8.1), 4.37 (1H, t, 6-H, *J* 4.5); δ_C (D_2O, 50 MHz) 20.5 (q, C-1), 65.4 (t, C-7), 70.0, 70.8, 74.0, 76.8 (4 × d, C-3, C-4, C-5, C-6), 109.3 (s, C-2).

§ Full details of the crystal structure analysis have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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