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LETTERS

Photobromination of a Bicyclic Mimic of α-L-Fucose; Components for a Combinatorial Library of Rigid Fucose Analogues

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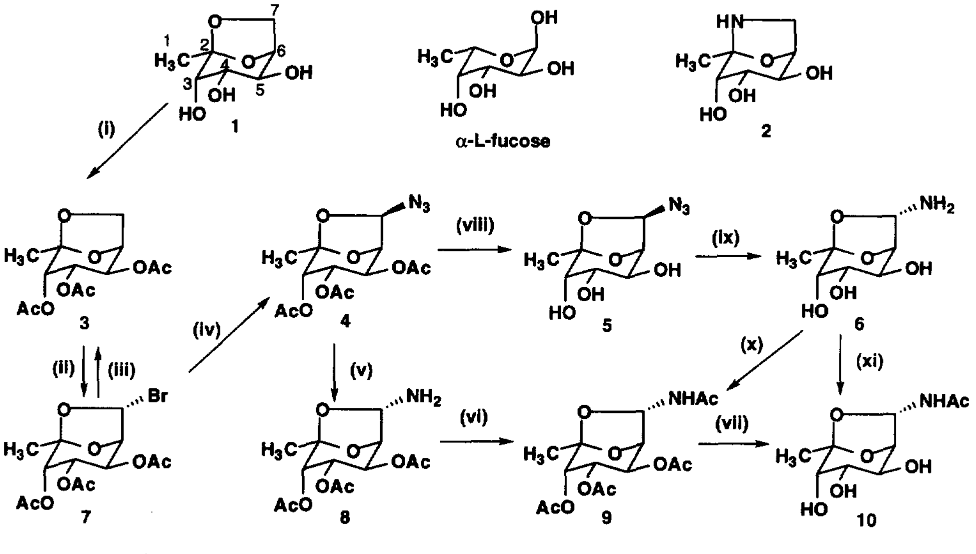
Abstract: Photobromination of a rigid bicyclic α-L-fucose analogue, affords a single crystalline monobromide, the structure of which is confirmed by X-ray crystallography. Displacement of this bromide with azide proceeds with inversion to a single crystalline azide, which on reduction leads to an amine and thence to a range of novel substituted rigid α-L-fucose derivatives. Hydrolysis of the bromide leads to two isomeric alcohols *via* an acetate migration. Both the bromide and amine may prove to be useful intermediates for the generation of libraries of mimics of L-fucose.

Pyranosides of L-fucose play an important role in cell-cell recognition within the body and there is intense interest in inhibition of fucosyl transferases, fucosidases, and in the identification of agonists or antagonists of sialyl Lewis X receptors.[1] The stereochemistry and the conformational environment of the secondary hydroxyl groups in the fucose ring are thought to be important components of the recognition of the fucose moiety. Development of substituted L-fucose analogues based on rigid bicyclic systems may have application as mimics of such naturally occurring oligosaccharides or as inhibitors of the enzymes which catalyse their biosynthesis.[2] We have previously reported the syntheses of two bicyclic analogues of α-L-fucose containing either oxygen **1**[3] or nitrogen **2**[4] in the anhydro bridge; **2** has been shown to be a strong inhibitor of a number of fucosidases and a moderate inhibitor of a fucosyl transferase. This paper reports the radical bromination at C-7 of the protected anhydro bicycle **3** to give the least hindered bromide **7**; subsequent displacement of the bromide in **7** by azide ion in an apparent S_N2 reaction formed the azide **4** which provides access to the amine **6**. Both the bromide **7** and the amine **6** should be convenient intermediates for incorporation into libraries of fucose mimics.



Scheme 1: (i) Ac_2O, pyridine, 99%; (ii) Br_2, $MeCCl_3$, hν, 61%; (iii) H_2, Pd-black, Et_3N, EtOAc, 92%; (iv) NaN_3, DMF, 90°C, 94%; (v) H_2, Pd/C, EtOAc, 66%; (vi) Ac_2O, pyridine, 66%; (vii) Et_3N, MeOH, 88%; (viii) MeONa, MeOH, 91%; (ix) H_2, Pd-black, EtOAc, 70% crude; (x) Ac_2O, pyridine, 76%; (xi) Ac_2O, MeOH, 28%.

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Prior to the bromination, the anhydro bicycle **1** was protected as the known peracetate **3**[3] [Scheme 1]. Radical bromination of anhydro sugars has been shown to proceed both stereo- and regio-selectively at the methylene carbon to afford *exo* monobromides.[5] Irradiation of the triacetate **3** with a 400W bulb in the presence of bromine in 1,1,1-trichloroethane afforded the single monobromide **7**, m.p. 99-100°C, $[\alpha]_D^{23}$ +83.4 (c, 0.97 in $CHCl_3$), presumably the least hindered of the possible epimeric bromides. Hydrogenolysis of the bromide **7** in the presence of palladium on charcoal in ethyl acetate regenerated the unsubstituted bicycle **3**. The stereochemistry of the bromide was determined by consideration of the ^1H NMR spectrum in $CDCl_3$ in which H-7 appeared as a singlet.[6] The absence of coupling between H-7 and H-6 showed the proton to be the *endo* substituent, and hence indicated formation of the *exo* bromide, which is consistent with literature cases.[5] The structure of **7** was firmly established by X-ray crystallographic analysis [Figure 1].[7]

Reaction of the bromide **7** with sodium azide caused an S_N2 displacement with inversion of configuration to give the azide **4**,[8] m.p 86-87°C, $[\alpha]_D^{23}$ -116.4 (c, 0.89 in $CHCl_3$); the appearance of the H-7 resonance as a doublet, $J_{6,7}$ 4.0 Hz, in the ^1H NMR spectrum in *d*-chloroform indicated that the azide substituent was the more hindered *endo*-anomer. The stereochemistry was confirmed by X-ray crystallography [Figure 2].[9] The configuration at C-7 of subsequent derivatives was determined by comparison of their ^1H NMR spectra with those of the bromide **7** and the azide **4**. Hydrogenation of the azido triacetate **4** afforded the least hindered amine **8**, oil, $[\alpha]_D^{23}$ +15.5 (c, 1,01 in $CHCl_3$), as the major product; presumably the initially formed amine epimerises to the more stable and less hindered anomer **8**. The amine **8** is a suitable starting material for the generation of an amide library of rigid L-fucose analogues; thus **8** was acetylated *in situ* to yield the amide **9**, oil, $[\alpha]_D^{21}$ +18.7 (c, 1.24 in $CHCl_3$). Selective removal of the *O*-acetates afforded the L-fucose analogue **10**, m.p. 205-206°C, $[\alpha]_D^{23}$ +44.0 (c, 1.01 in MeOH).[10] The same amido triol **10** could be isolated by deprotection of the azide **4** to give the azido triol **5**, m.p. 158-159°C, $[\alpha]_D^{23}$ -156.6 (c, 0.95 in MeOH),[11] followed by reduction to the amino triol **6**, then selective *N*-acylation with acetic anhydride in methanol; the unprotected amine **6** may also allow access to amide libraries. Acetylation of the unprotected amine **6** gave the protected amide **9**.

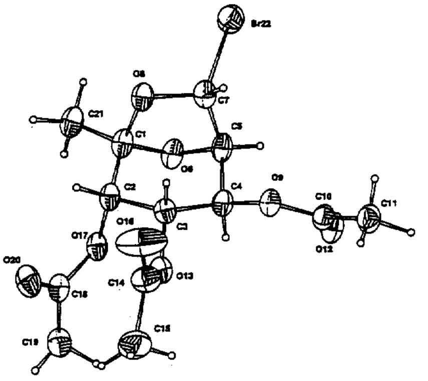


Figure 1: X-Ray structure of 3,4,5-tri-*O*-acetyl-2,7-anhydro-7-bromo-1-deoxy-β-L-*glycero*-L-*gulo*-heptulopyranose **7**

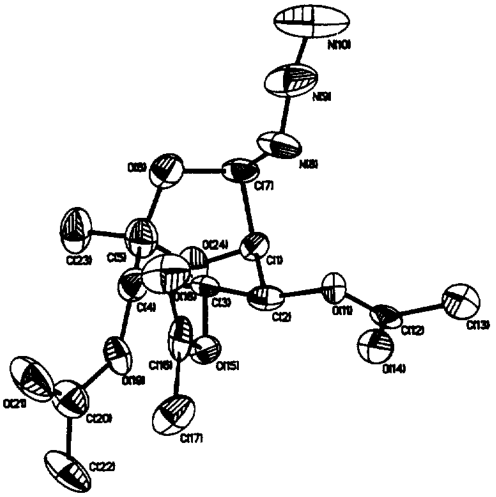
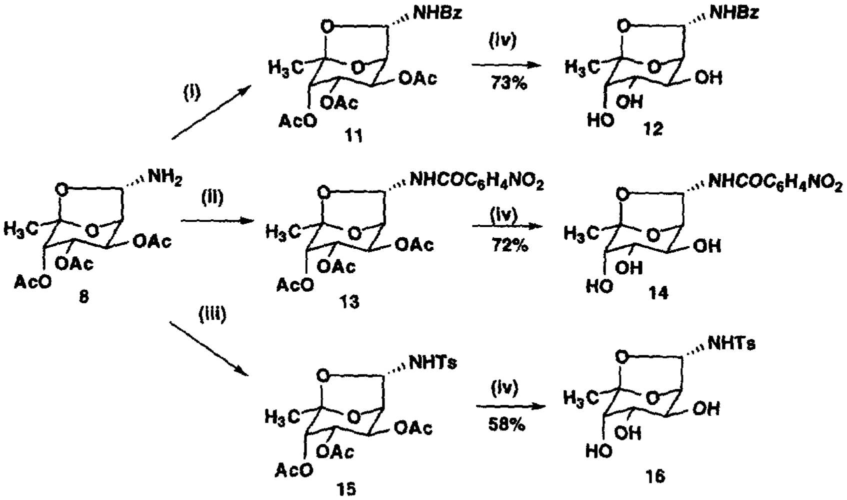


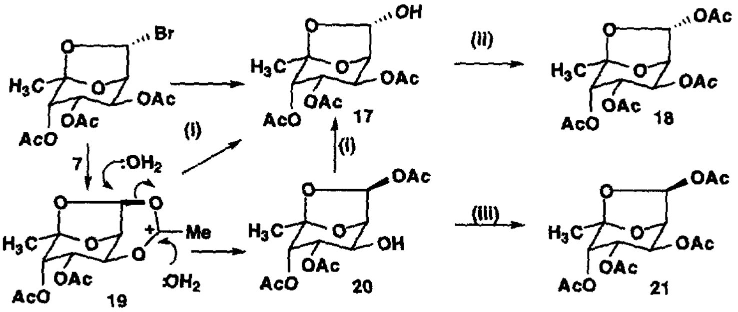
Figure 2: 3,4,5-Tri-*O*-acetyl-2,7-anhydro-7-azido-1-deoxy-β-D-*glycero*-L-*gulo*-heptulopyranose **4**

The value of the amino triacetate **8** as a divergent intermediate for the generation of *N*-linked L-fucose analogues is illustrated in Scheme 2. Treatment with benzoyl chloride afforded the benzylamide **11**, m.p. 64-65°C, $[\alpha]_D^{23}$ +14.1 (c, 0.58 in $CHCl_3$). Deprotection with basic methanol gave the required triol **12**.[12] Analogous reactions with *p*-nitrobenzoyl chloride and tosyl chloride gave the 7-*N*-*p*-nitrobenzoylamide **13**, m.p. 105-106°C, $[\alpha]_D^{20}$ +3.0 (c, 1.03 in CH_3CN) and the 7-*N*-sulphonamide **15**, m.p. 205-206°C, $[\alpha]_D^{21}$ -40.7 (c, 4.2 in $CHCl_3$). Removal of the acetate protecting groups from **13** and **15** gave the L-fucose analogues **14**, m.p. 233-234°C, $[\alpha]_D^{21}$ +22.6 (c, 0.31 in MeOH),[13] and **16**, m.p. 185-186°C, $[\alpha]_D^{21}$ -1.2 (c, 0.33 in MeOH), respectively.[14]



Scheme 2: (i) BzCl, pyridine, 73%; (ii) p-$NO_2C_6H_4COCl$, pyridine, 63%, (iii) TsCl, pyridine, 47%; (iv) MeOH, Et_3N.

Hydrolysis of the bromide with aqueous acetone in the presence of silver carbonate yielded the isomeric alcohols, **17**, oil, $[\alpha]_D^{22}$ +8.2 (c, 1.63 in $CHCl_3$), and **20**, oil, $[\alpha]_D^{22}$ -25.8 (c, 0.52 in $CHCl_3$) [Scheme 3]. The more stable lactol **17** might be formed by S_N1 solvolysis of the bromide **7** in which the cation is trapped from the least hindered side, or by an S_N2 displacement followed by mutarotation from the less to the more stable lactol **17**.



Scheme 3: (i) Acetone, H_2O; 1:1, Ag_2CO_3; (ii) Ac_2O, pyridine, 76%; (iii) Ac_2O, pyridine, 95%

One possible pathway for the formation of **20** is by neighbouring group participation in the departure of the bromide in **7** to give **19**; attack by water on **19** may result in direct formation of the more stable *exo*-lactol **17** directly, or attack on the acylium carbon to afford, after ring opening, the migrated acetate **20**. Further treatment of the *endo* product **20** under the reaction conditions resulted in isolation of only the *exo* alcohol, **17**; presumably the *endo*-anomeric acetate **20** undergoes transesterification to the neighbouring hydroxyl group to give the less stable *endo*-lactol which subsequently epimerises to **17**. The structures were confirmed by acetylation of the alcohols to afford the epimeric tetraacetates, **18**, oil, $[\alpha]_D^{22}$ +17.0 (c, 0.88 in CHCl$_3$), and **21**, m.p. 152-153°C, $[\alpha]_D^{23}$ +47.7 (c, 0.75 in CHCl$_3$).

In summary, this paper indicates a strategy for the generation of rigid bicyclic mimics of L-fucose; further studies on nucleophilic displacement reactions of the bromide are necessary before simple access to library products of displacement of bromide by other nucleophiles is a reality. Bromination of the *N*-bicyclic anhydrofucopyranose **2** to give intermediates for the synthesis of novel 7-substituted bicyclic L-fucose analogues containing a nitrogen bridge is reported in the following paper.[15,16]

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6. Selected data for bromide **7**: δ_H (500 MHz; CDCl$_3$): 1.60 (3H, s, CH$_3$), 1.97, 2.10, 2.16 (3 x 3H, 3 x s, 3 x COCH$_3$), 4.84 (1H, d, H-6, $J_{6,5}$ 3.4 Hz), 5.16-5.21 (3H, m, H-3,4,5), 6.42 (1H, s, H-7).
7. The atomic coordinates for the bromide **7** are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW; the crystallographic numbering system differs from that used elsewhere in the text. Any request should be accompanied by the full literature citation for this paper.
8. Selected data for azide **4**: δ_H (500 MHz; CDCl$_3$): 1.45 (3H, s, CH$_3$), 1.99, 2.11, 2.15 (3 x 3H, 3 x s, 3 x COCH$_3$), 4.57 (1H, dd, H-6, $J_{6,7}$ 4.0 Hz, $J_{6,5}$ 3.6 Hz), 5.20 (1H, dd, H-5, $J_{5,6}$ 3.6 Hz, $J_{5,4}$ 10.6 Hz), 5.32 (1H, d, H-3, $J_{3,4}$ 4.8 Hz), 5.62 (1H, d, H-7, $J_{7,6}$ 4.0 Hz), 5.86 (1H, dd, H-4, $J_{4,5}$ 10.6 Hz, $J_{4,3}$ 4.8 Hz).
9. The atomic coordinates for the azide **4** are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW; the crystallographic numbering system differs from that used elsewhere in the text. Any request should be accompanied by the full literature citation for this paper.
10. Selected data for acetamide triol **10**: δ_H (500 MHz; CD$_3$OD): 1.52 (3H, s, CH$_3$), 1.94 (3H, s, COCH$_3$), 3.55 (1H, d, H-3, $J_{3,4}$ 4.4 Hz), 3.66 (1H, dd, H-4, $J_{4,5}$ 9.2 Hz, $J_{4,3}$ 4.4 Hz), 3.69 (1H, dd, H-5, $J_{5,6}$ 4.0 Hz, $J_{5,4}$ 9.2 Hz), 4.08 (1H, d, H-6, $J_{6,5}$ 4.0 Hz), 5.75 (1H, s, H-7).
11. Selected data for azido triol **5**: δ_H (500 MHz; CD$_3$OD): 1.48 (3H, s, CH$_3$), 3.67 (1H, d, H-3, $J_{3,4}$ 4.9 Hz), 3.77 (1H, dd, H-5, $J_{5,6}$ 3.9 Hz, $J_{5,4}$ 9.8 Hz), 4.20 (1H, dd, H-4, $J_{4,5}$ 9.8 Hz, $J_{4,3}$ 4.9 Hz), 4.28 (1H, dd, H-6, $J_{6,7}$ 4.2 Hz, $J_{6,5}$ 3.9 Hz), 5.61 (1H, d, H-7, $J_{7,6}$ 4.2 Hz).
12. Selected data for benzylamide triol **12**: M.p. 209-210°C (ethyl acetate / methanol); $[\alpha]_D^{23}$ +22.3 (*c*, 0.31 in CH$_3$OH); υ_{max} (KBr): 3400 (br., NH/OH), 1649 (C=O), 1528 (N-C=O) cm^{-1}; δ_H (500 MHz; CD$_3$OD); 1.55 (s, 3H, 3 x H-1), 3.60 (1H, d, H-3, $J_{3,4}$ 4.0 Hz), 3.72-3.74 (2H, m, H-4, H-5), 4.29 (1H, d, H-6, $J_{6,5}$ 3.4Hz), 5.98 (1H, s, H-7), 7.44-7.47 (2H, m, 2 x CH(Ar)), 7.54 (1H, t, CH(Ar), *J* 7.4 Hz), 7.83 (2H, d, 2 x CH(Ar), *J* 7.3 Hz).
13. Selected data for nitrobenzylamide triol **13**: M.p. 233-234°C (ethyl acetate); $[\alpha]_D^{21}$ +22.6 (*c*, 0.31 in CH$_3$OH); υ_{max} (KBr): 3392 (br., NH/OH), 1657 (C=O), 1602 (C-C(Ar)), 1530 (H-NC=O) cm^{-1}; δ_H (500 MHz; CD$_3$OD); 1.56 (s, 3H, 3 x H-1), 3.61 (1H, d, H-3, $J_{3,4}$ 4.2 Hz), 3.73 (1H, dd, H-4, $J_{4,5}$ 9.1 Hz, $J_{4,3}$ 4.2 Hz), 3.76 (1H, dd, H-5, $J_{5,6}$ 3.9 Hz, $J_{5,4}$ 9.1 Hz), 4.30 (1H, d, H-6, $J_{6,5}$ 3.9 Hz), 5.97 (s, 1H, H-7), 8.03, 8.32 (2 x 2H, 2 x d, 4 x CH(Ar), *J* 8.8 Hz).
14. Selected data for sulphonamide triol **15**: M.p. 185-186°C (MeOH / EtOAc); $[\alpha]_D^{21}$ -1.2 (*c*, 0.33 in CH$_3$OH); υ_{max} (KBr): 3447 (br. NH) cm^{-1}; δ_H (200 MHz; CD$_3$OD); 1.24 (s, 3H, 3 x H-1), 2.42 (3H, s, CH$_3$Ar), 3.41 (1H, d, H-3, $J_{3,4}$ 4.5 Hz), 3.52 (1H, dd, H-4, $J_{4,5}$ 9.0 Hz, $J_{4,3}$ 4.5 Hz), 3.65 (1H, dd, H-5, $J_{5,6}$ 4.2 Hz, $J_{5,4}$ 9.0 Hz), 4.08 (1H, d, H-6, $J_{6,5}$ 4.2 Hz), 5.35 (s, 1H, H-7), 7.33, 7.76 (2 x 2H, 2 x d, Ar, *J* 8.2 Hz).
15. Smelt, KH; Harrison, AJ; Biggadike, K; Muller, M; Prout, CK; Watkin DJ; Fleet, GWJ following paper
16. This work was supported by a GlaxoWellcome studentship to KHS. All new compounds in this paper have microanalytical and spectroscopic data consistent with the structures proposed except for the amines **8** and **6**, which have been characterised on the basis of spectroscopic evidence only.