Synthesis of Pseudo-α-L-fucopyranose from Toluene

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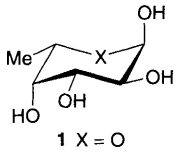
Microbial oxidation of toluene by *Pseudomonas putida* provides the chiral cyclohexadienediol **3**, used as the key intermediate in a five-step synthesis of pseudo-α-L-fucopyranose **2**.

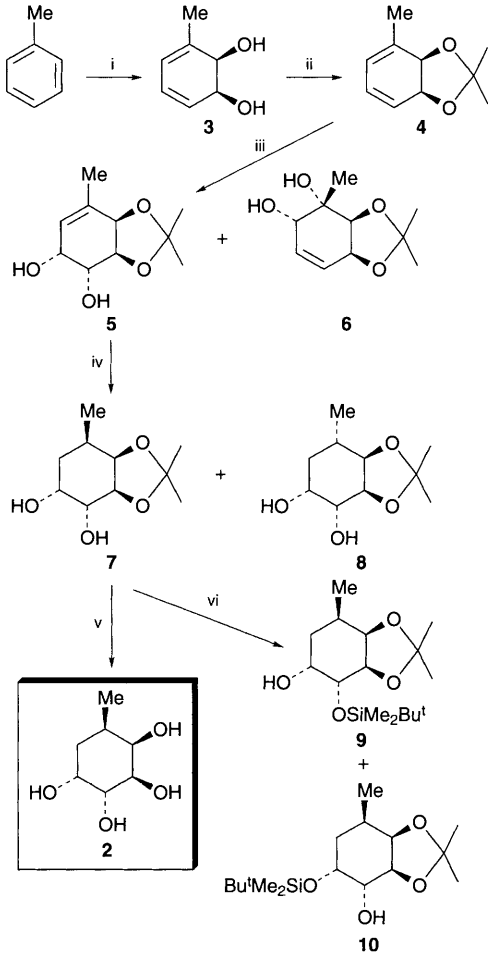
There is considerable current activity in the synthesis of the pseudo-sugars[1,2] in view of the ability of these compounds to mimic the shape and polarity of natural sugar rings, whilst lacking the hydrolytic reactivity that sugars have towards glycosidases. L-Fucose, shown in its α-pyranose form **1**, is a biologically important 6-deoxysugar involved in the immunological response. It forms a constant α-pyranose unit of the tri- and tetra-saccharides which act as the blood group antigenic determinants.[3] Fucose is transferred during the terminal glycosylation of oligosaccharide portions of glycoconjugates, and its processing can thus be an essential part of the changes which occur during cell maturation or malignancy.[4] Much attention is therefore being paid to the search for potential inhibitors of fucosyltransferases.[5] Interest in this area has been heightened by the discovery that the L-fucose-containing tetrasaccharide sialyl Lewis X acts as a ligand for the selectins (*e.g.* endothelial leukocyte adhesion molecule-1, ELAM-1 or E-selectin) and controls the binding of leukocytes in zones of inflammation.[6] Recent attempts to exploit this recognition have resulted in the publication of several syntheses of fucose-containing sialyl Lewis X analogues.[7]

There have been two recent syntheses of pseudo-L-fucopyranose **2**. Redlich's group[8] have reported **2**, isolated *via* the major product (36%) of free radical cyclisation of a 7-deoxy-7-iodohept-1-enitol, in turn available in five steps from a D-mannofuranose derivative. Toyokuni and coworkers[9] have synthesised **2** in 11 steps from L-fucose, *via* an unsaturated inosose. We now describe a direct route to pseudo-α-L-fucopyranose, capable of providing both the pseudo-sugar and suitably protected derivatives having the C-1 or C-2 hydroxy group free.† Our method exploits the *cis*-cyclohexadienediol **3**, available in enantiopure (1*S*,2*R*) form by microbial oxidation of toluene using *Pseudomonas putida* mutants.[10,11]

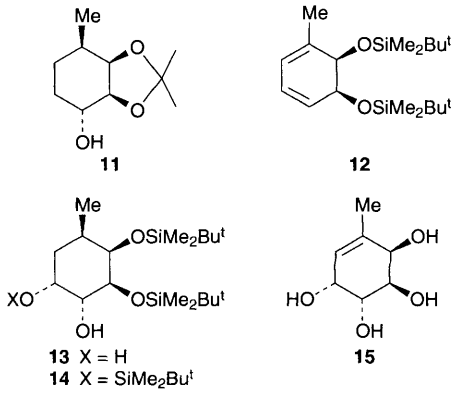
As shown in Scheme 1, isopropylidenation of **3** gave the protected diene **4** in good yield.[11a] Catalytic osmylation of **4** using 1.2 equiv. of *N*-methylmorpholine-*N*-oxide led to the two diols **5** and **6**, readily separable by chromatography on silica gel (isolated in yields of 30 and 47% respectively). Tetrahydroxylation of the conjugated diene system was not competitive in this instance,[12] and the two diol isomers can be seen as arising from attack *anti* to the isopropylidene group, at the di- and tri-substituted double bonds respectively. Hydrogenation of the double bond in **5** was most effectively carried out using platinum as catalyst, resulting in the pseudo-α-L-fucopyranose derivative **7** and the 6-deoxy-pseudo-β-D-altropyranose **8** (5 : 1).‡ Acid hydrolysis of **7** gave pseudo-α-L-fucopyranose **2**, having spectral data in good agreement with the literature.[8,9]§ Alternatively, mono-silylation of diol **7** gave the partially protected pseudo-fucose isomers **9** and **10**, which were separated by chromatography. The position of silylation was confirmed by acetylation of **9** or **10**, which led to characteristic downfield ^{1}H NMR shifts of the respective α-protons of these alcohols. The alcohols **9** and **10** may find use in the synthesis of novel fucosidase inhibitors because they have C-1 or C-2



1 X = O
2 X = CH_2



Scheme 1 *Reagents and conditions*: i, *Pseudomonas putida*; ii, Me_2CO/$Me_2C(OMe)_2$, CF_3CO_2H, 86%; iii, Me_2CO/H_2O, 4 : 1, NMO (1.2 equiv.), OsO_4 (**5**, 30%; **6**, 47%); iv, PtO_2, H_2 (20 psi), 0.5 h (**7**, 58%; **8**, 12%); v, AcOH/H_2O, 1 : 9, 100 °C, 0.5 h, 96%; vi, Bu^tMe_2SiCl (1 equiv.), imidazole, DMF (**9**, 35%; **10**, 42%)



11 **12**

13 X = H
14 X = $SiMe_2Bu^t$

15

(fucose numbering) hydroxy groups free for coupling to other saccharide or epoxide units.[13]

A reaction sequence similar to **4** → **5** → **7** was carried out on the disilylated diene **12**. In this route, hydrogenation (using platinum) occurred stereospecifically to yield the diol **13**, which was then deprotected (Bu_4NF, THF) to give pseudo-sugar **2**. Further monosilylation of **13** was regiospecific for this example, to afford the 1,3,4-trisilylated pseudo-fucose derivative **14**.

The action of glycosidases is thought to involve the formation of a flattened glycosyl cation,[14] and it is therefore worth noting that hydrolysis of **5** gave an extremely expedient synthesis of the unsaturated analogue of carba-α-L-fucopyranose **15**.[9]

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Footnotes

† Fucose numbering.

‡ In contrast, hydrogenation using 10% palladium on carbon gave **7**:**8** = 1:2.7 in addition to hydrogenolysis (14%) to afford the deoxy analogue **11**

§ Compound **2**: $[\alpha]_D^{20}$ −58 (*c* 0.4, MeOH); lit,[8] $[\alpha]_D^{20}$ −58 (*c* 1, MeOH).

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