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A Short Synthesis of L-Fucose and Analogs from D-Mannose

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Abstract: *A new efficient synthesis of L-fucose (and 6-alkyl analogs) in only six steps from D-mannose is described. This transformation is based on addition of an organometallic reagent to the bis-acetonide of D-mannose followed by selective glycol cleavage with sodium periodate. Efficient separation of diastereomeric dibenzoates and formation of 2,5-di-O-benzyl(or benzoyl)-L-fucofuranose derivatives are also noteworthy.*

L-fucose **1a** is a naturally occurring sugar which is part of oligosaccharides of biological importance such as glycolipids, blood-group antigens or complex polysaccharides of plant or bacterial origin.[1] L-Fucose is a rather expensive sugar usually prepared by hydrolysis of the *Fucus* species of seaweed.[2] Several total syntheses have been reported from common carbohydrates such as L-arabinose,[3] L-rhamnose,[4] D-galactose,[5] D-mannose[6] or D-glucose.[7]

2-Deoxy-L-fucose (easily prepared from **1a**) is also present in some important trisaccharide antitumor anthracyclines such as aclacinomycin A[8] and the replacement of L-daunosamine by this sugar (which formally results in the replacement of the primary amino group at C-3 by a hydroxyl group) in monosaccharide anthracyclines such as daunorubicin affords potent analogs.[9]

As part of a study aimed at the development of new semi-synthetic anthracyclines, the preparation of 2-deoxy-L-fucose glycosides bearing either a modified side chain (alkyl instead of methyl) or specifically derivatized at O-3 or O-4 was considered. Indeed the preparation of L-fucose analogs having an ethyl or benzyl side chain as potential antimetabolites of L-fucose has already been reported by Sartorelli et al.,[10] starting from the rare L-Galactose.

This paper describes a short and efficient synthesis of L-fucose in only 6 steps from D-mannose which also allows the preparation of such higher alkyl analogs through the intermediacy of L-fucofuranose derivatives selectively protected at positions 2 and 5.

Retrosynthetic analysis shows that diastereoselective chain extension at C-1 of D-mannose followed by selective cleavage of the terminal glycol unit should give L-fucose and analogs. The first step implies condensation of an organometallic species with the readily available bis-acetonide **2**.[11] This reaction was first studied by Buchanan[12] who has shown that addition of ethylmagnesium bromide in THF affords predominantly (in a 7/3 ratio as judged by NMR) the expected 6S diol **3b**[13] resulting from a chelation

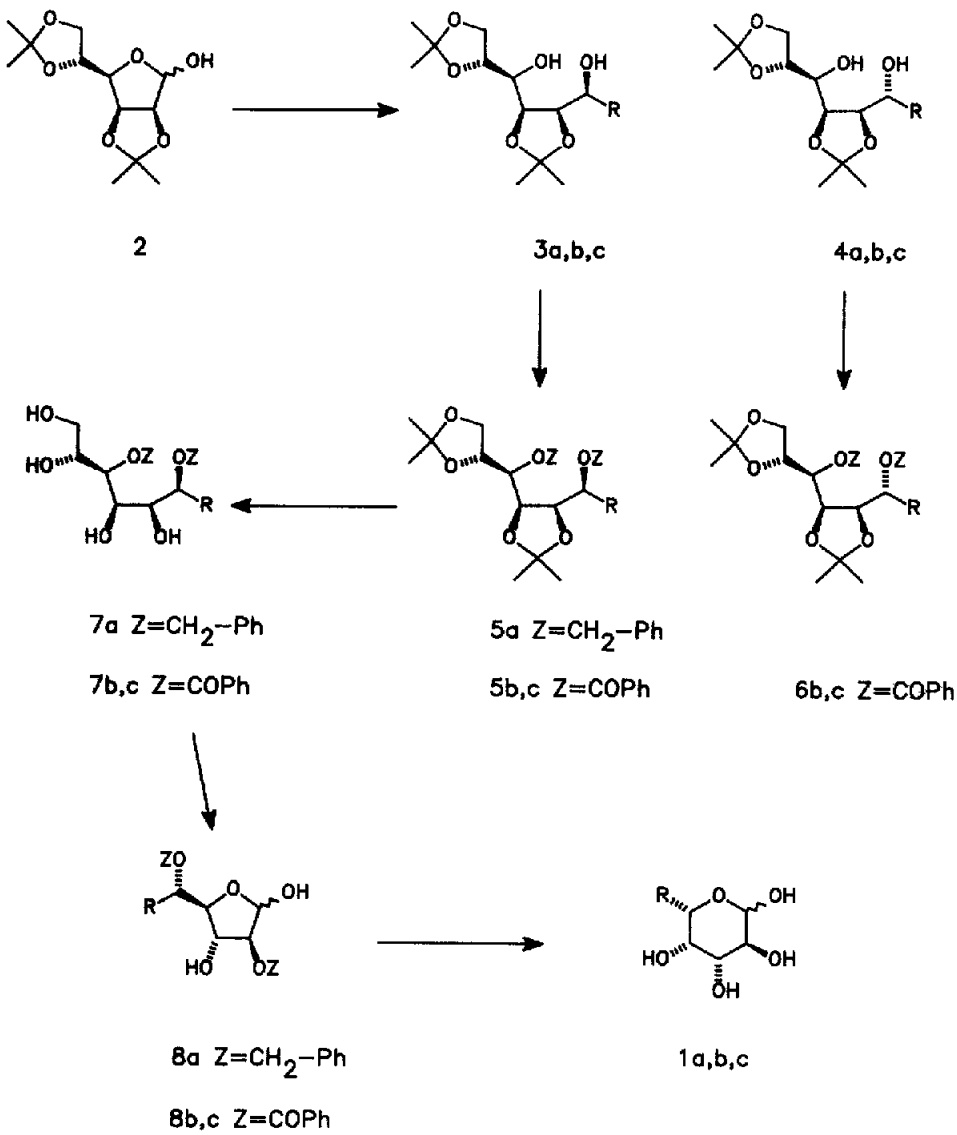
controlled *syn* addition (36% isolated yield after selective recrystallization). More recently Corey[14] has shown that addition of MeLi in ether is *syn* stereoselective, giving **3a**. A recent report by Singh[15] on the diastereoselectivity of the addition of organometallic species (Mg, Li) to 2,3-O-isopropylidene derivatives of carbohydrates has confirmed that *syn* addition is observed with **2** and lithium reagents (MeLi or PhLi) in THF. However *anti* addition is observed with Grignard reagents (MeMgCl or PhMgBr) in the same solvent. The discrepancy between the Buchanan and Singh results suggests that reaction conditions (solvent, halide used, possible presence of magnesium dihalide salts,...) are crucial and that any prediction should be done with great care.

Condensation of **2** in THF at -40°C with methyllithium in hexane afforded similarly only **3a** in 95% yield which was then benzylated to **5a** (75%), $[\alpha]_D$ -3 (c 1, $CHCl_3$).[16] Because an attempted cleavage of the less hindered acetonide was not completely selective, the total hydrolysis to **7a**,[16] mp 108°C, $[\alpha]_D$ +22 (c 0.6, $CHCl_3$), was done in 92% yield using acetic acid-water. Since the reactivity of glycols toward sodium periodate oxidation is known to depend on glycol substitution and stereochemistry,[17] it is expected that the terminal less hindered glycol should be cleaved faster than the erythro. This assumption was fully confirmed since treatment of **7a** with 1 eq. of sodium periodate afforded quantitatively a mixture of 2,5-di-O-benzyl-L-*fuco*furanose **8a** (in about a 1.5/1 ratio of α and β anomers as judged by the relative intensities of the signals in ^1H NMR at δ 5.41 and 5.26 ppm).[16] Catalytic debenzylation (H_2-Pd/C, MeOH) then gave L-fucose **1a** (91%) as a 2/1 mixture of α and β pyranose anomers, mp 152-153°C (from ethanol), $[\alpha]_D$eq -80 (c 0.35, water), Lit.[2] : mp 140-141°C, $[\alpha]_D$eq -76 (c 2, water). The observed ^{13}C NMR chemical shifts were identical to those reported for α and β anomers of L-fucose in the literature.[16,18]

Extension of the above process to prepare higher alkyl analogs failed because addition of either ethyl or butyllithium gives complex mixtures resulting apparently from partial cleavage, even at low temperature, of one (or both) of the ketal functions. Therefore addition of the less selective Grignard reagent ethyl (or butyl)magnesium bromide was carried out following the procedure of Buchanan to give a mixture of 6S diol **3b** and 6R diol **4b** (or **3c** and **4c**). Instead of using a tedious recristallization to separate these diols as done by Buchanan[12], this mixture was converted (PhCOCl, pyridine) to dibenzoates **5b/6b** (or **5c/6c**) and then triturated with petroleum ether to give the unsoluble crystalline dibenzoate **6b**[16] (20%), mp 170°C, $[\alpha]_D$ +2 (c 0.5, $CHCl_3$) and the soluble oily dibenzoate **5b**[16] (52%), $[\alpha]_D$ -14.5 (c 0.5,$CHCl_3$). Similar results have been obtained for **5c**,[16] mp 164°C, $[\alpha]_D$ -43 (c 1, $CHCl_3$) and **6c**,[16] oil, $[\alpha]_D$ -5 (c 1.3, $CHCl_3$).[19] The structures of the major isomers, **5b,c**, were confirmed after glycol cleavage.

Subsequent hydrolysis (75%) to tetrol **7b**,[16] mp 135°C, $[\alpha]_D$ -3 (c 0.85, $CHCl_3$) or **7c**,[16] mp 138°C, $[\alpha]_D$ -27 (c 1, $CHCl_3$) followed by sodium periodate oxidation gave 2,5-di-O-benzoyl-6,7-dideoxy-L-*galacto*-hepto-1,5-furanose **8b** or **8c**[16] which was finally treated with a catalytic amount of MeONa in MeOH to give 6-methyl-L-fucose **1b** , mp 130°C, $[\alpha]_D$eq -33 (c 1.2, water), Lit.[10] syrup, $[\alpha]_D$eq -26.2° (c 1, pyridine) or 6-propyl-L-fucose **1c**, mp 140°C (dec.), $[\alpha]_D$eq -30 (c 1, water). The structure of **1b** was fully confirmed by peracetylation to the corresponding 1,2,3,4-tetra-O-acetyl pyranoside derivatives from which the pure β anomer could be isolated as an oil, $[\alpha]_D$ -32.4 (c 1.1, $CHCl_3$), and characterized by ^1H NMR.

In conclusion, the conversion of the readily available D-mannose to L-*fuco*furanose derivatives has been completed in a few steps. This method may also be applied to *anti* addition compounds such as **4** to give access to 6-deoxy-D-altrose and analogs (and hence to D-digitoxose).



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16. All new compounds have been characterized by IR, ^{1}H NMR, MS, HRMS or elemental analysis. Selected NMR ($CDCl_3$, TMS as internal standard, J in Hz) data of new compounds are given below. **5a**: δ 1.18 (d, 3H, J= 7, H-7), 1.32 (s, 3H), 1.38 (s, 6H), 1.56 (s, 3H), 4.54 and 4.63 (ABq, 2H, J= 12), 7.1-7.4 (m, 10H arom.) ppm. **7a**: δ 1.31 (d, 3H, J= 7, H-7), 1.67 (s, 2H, OH),2.59 (s, 1H, OH), 3.40 (s, 1H, OH), 4.48 and 4.66 (ABq, 2H, J= 14), 4.69 (s, 2H), 7.30 (s, 10H arom.) ppm. **8a**: δ 1.20 (d, 3H, J= 6, H-6), 5.26 (d, 0.4H, J= 3, H-1 β anomer), 5.41 (s, 0.6H, H-1 α anomer), 7.29 (s, 10H arom.) ppm. **1a**: α anomer: δ 92.35 (C-1), 71.95 (C-4), 69.5 (C-2), 68.3 (C-3), 66.3 (C-5), 15.6 (C-6) ppm; β anomer: δ 96.30 (C-1), 73.2 (C-3), 71.95 (C-2), 71.6 (C-4), 70.9 (C-5), 15.6 (C-6) ppm. **5b**: δ 0.99 (t, 3H, J= 7, H-8), 1.36 (s, 6H), 1.38 (s, 3H), 1.56 (s, 3H), 1.77 (p, 2H, J= 7, H-7), 4.05 (m, 2H, H-1), 5.36 (q, 1H, J= 7, H-6), 5.51 (dd, J= 7 and 4.5 , H-3) ppm. **6b**: δ 0.86 (t, 3H, J= 7, H-8), 1.13 (s, 3H), 1.41 (s, 3H), 1.60 (s, 3H), 4.03 (d, 2H, J= 7, H-1), 4.34 (q, 1H, J= 7, H-2), 4.47 (t, 1H, J= 7, H-5), 4.58 (d, 1H, J= 7, H-4), 5.07 (broad s, 1H, H-6), 5.52 (broad d, 1H, H-3) ppm. **7b**: δ 1.00 (t, 3H, J= 7, H-8), 2.04 (m, 1H, H-7), 3.54 (d, 1H, J= 9.8, H-5 or H-4), 3.66 (qd, 2H, J= 11 and 3.8, H-1), 3.87 (d, 1H, J= 9.8, H-4 or H-5), 4.16 (m, 1H, H-2), 5.40 (m, 2H, H-3 and H-6) ppm. **8b**: δ (major isomer) 0.96 (t, 3H, J= 7, H-7), 1.85 (m, 2H, H-6), 4.18 (m, 1H, H-3), 4.43 (t, 1H, J= 5.4, H-4), 5.12 (broad s, 1H, H-2), 5.33 (q, J= 5.4 , H-5), 5.61 (broad s, 1H, H-1) ppm.
   Compounds **5c**, **6c**, **7c** and **8c** exhibit similar NMR data.
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19. This difference in physical properties appears to be general even with aryl, aralkyl and long chain alkyl groups (unpublished results).

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