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Synthesis of 4-Iodo-4-deoxy-D-glucose

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Abstract: *Triflation/iodination of appropriately substituted D-galactose derivatives enables the preparation of 4-deoxy-4-iodo-D-glucose without epimerisation.*

Amongst molecules suitable for medical imaging, D-glucose stands with special distinction. Its utilization as an energy source in brain or myocardial tissues is well documented, with abnormal glucose metabolism in cancer cells also calling for D-glucose-based tracers [1, 2]. The use of SPECT (Single Photon Electron Computer Tomography) imaging techniques calls for the introduction of an iodine atom into D-glucose so as to enable the subsequent labelling with a gamma-emmitter iodine isotope (such as ^{123}I or ^{131}I) [3]. 1-Iodo-1-deoxy-D-glucose being notably unstable [4], such efforts have concentrated on the preparation of D-glucose analogues where iodine substitutes the hydroxyl groups at positions -2 [5-7], -3 [8] or -6 [9].

We now report the preparation of the "missing analogue", namely 4-iodo-4-deoxy-D-glucose, **1**, because there is particular incentive to substitute position -4; indeed, structure / activity relationship studies carried out by Barnett *et al*. on a number of analogues [10,11] have shown that entry of D-glucose into the cell through facilitated diffusion [12] was mediated by the "right-side" of the molecule, that is, in a oriented way. Hence, modifications at C-4 (i.e. on the "left side") should minimize unfavorable interactions with the D-glucose transporter protein [13,14].

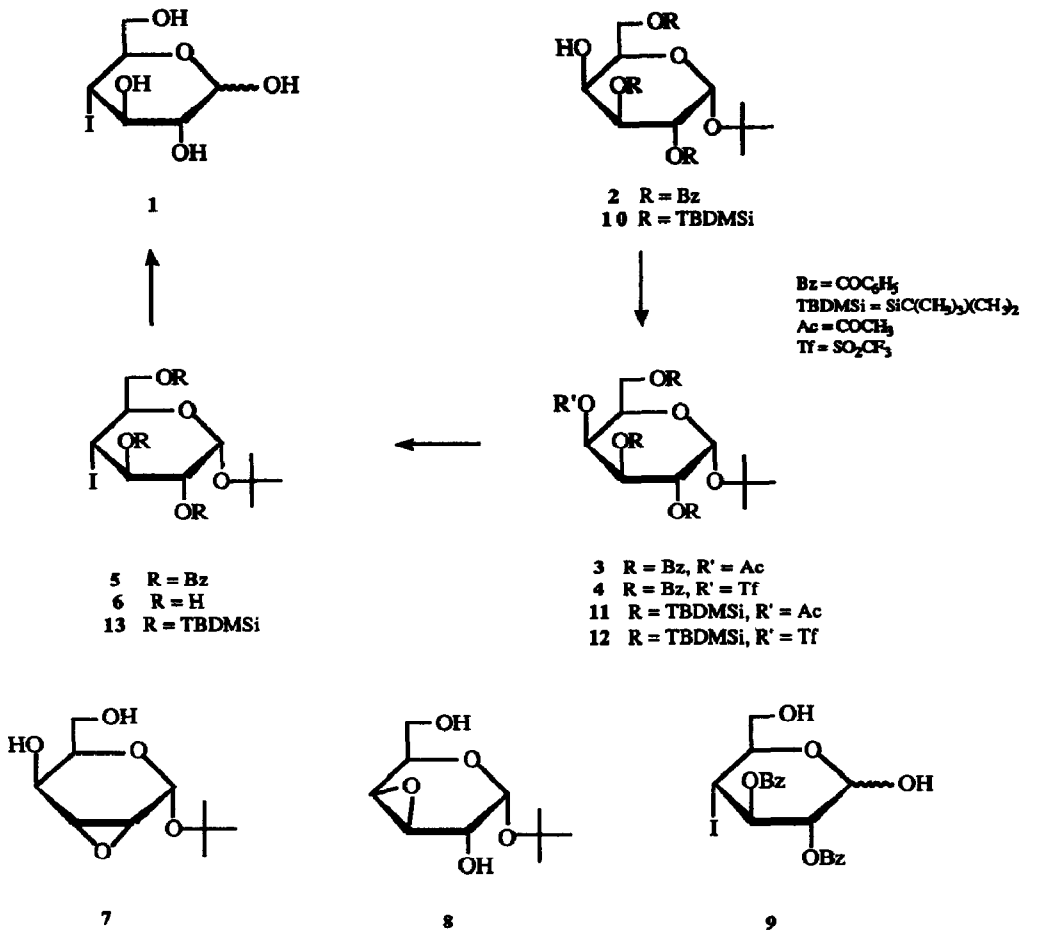
The synthetic scheme calls for the introduction of iodine by an efficient, unambiguous process since epimerization may occur at the iodinated carbon [15-17] during the course of the reaction. This is due to the fact that iodine can act either as a nucleophile or as a nucleofuge and thus guided our decision to displace a triflyl leaving group with an iodide ion. Since this reaction proceeds with inversion of configuration, access to a suitable derivative of D-galactose having a free 4-OH group became necessary.

In t-butyl D-galactoside, the anomeric nature determines the relative reactivities of hydroxyl groups [18]. For the beta anomer the order of reactivity is 6-OH >> 3-OH > 4-OH ~2-OH whereas it is 6-OH >> 3-OH ~ 2-OH > 4-OH for the alpha anomer. This difference in reactivity has been attributed to the axial vs. equatorial

relationships of vicinal substituents [19], hence it is necessary to work with an alpha *galacto* epimer so as to discriminate the hydroxyl group at position -4. Reaction [18] of t-butyl α-D-galactoside with benzoyl chloride gave a tribenzoate in 76 % yield; when recorded in C_6D_6, its ^1H nmr spectrum showed separation of all proton resonances but the low field signal at 4.1 ppm (also coupled with an exchangeable proton) did not however reveal coupling with H-5 which, if corresponding to H-4 of **2**, would imply a particular geometry. This ambiguity was removed using the acetate derivative **3**, a clear double doublet being observed for H-4 (d 5.75 ppm, $J_{4,3}$ = 3.5 Hz; $J_{4,5}$ = 1 Hz). Triflation [20] of **2** then gave a surprisingly stable crystalline triflate **4** isolated in 61 % yield after chromatography. The iodo derivative **5**, obtained in 88 % yield by triflate displacement with sodium iodide [21] was then shown to possess the expected *gluco* configuration ($J_{4,3} \sim J_{4,5}$ = 10.5 Hz), no *galacto* epimer resulting from a double displacement with iodide[15] being observed. Removal of the benzoates was carried out (MeONa cat. - MeOH) to afford **6** in a rather low yield (40 %) since the desired product was always accompanied by an epoxide (tentative structure **7** or **8**) - ester cleavage of **5** by lithium hydroperoxide [22] or potassium cyanide [23] led to no improvement. Final deprotection of the anomeric position was then best accomplished with Amberlite IR 120 (H^+) in refluxing water to give **1** in 80 % yield. It is of interest to note that if anomeric deprotection is attempted directly on **5**, no reaction can be observed with Amberlite, Lewis acids [24] or trifluoracetic acid [25] and even harsher conditions (HCl 2N reflux for 2 days) only resulted in a very low yield of dibenzoate **9**. An alternative choice of protecting groups which would allow <u>simultaneous</u> regeneration of the anomeric position and of the other hydroxyl groups was then considered.

Reacting the alpha anomer of tert-butyl D-galactopyranoside, **2** [18] with a bulky silyl chloride (TBDMSiCl - 4.2 equiv.) [26] gave trisilylated **10** in 62 % isolated yield. That the 4-OH had not been silylated was best proven, as described above, using the acetate derivative **11**. Triflation [27] of **10** was complicated by the fact that, in this case, the triflate **12** was quite fragile [28] and could not be isolated without substantial losses. It was also important to stop triflation before the reaction was complete to avoid the formation of by-products. Iodination [29] was thus carried out on a mixture of **10** and **12** but the desired iodide **13** could nevertheless be obtained in 64 % isolated yield from **10** after chromatography. Exclusive formation of the *gluco* isomer, as shown by the vicinal couplings of H-4 (8 and 11 Hz), was observed here also. Simultaneous acidic deprotection (Amberlite IR 120 (H^+) - 30 equiv.- 80 °C, 3 days - 37 %) of all protecting groups (i.e. the silyl ethers and the t-butyl glycoside) then gave **1** [30], in a straightforward manner, thus avoiding the sequential base/acid treatment previously necessary in the benzoate series.

As a single iodine atom is of less steric hindrance than the iodoallyl group already introduced at position -4 [31,32] **1** brings more similarity to the natural substrate, D-glucose. A short synthetic route to **1**, having now been established, opens up the way for the subsequent synthesis of adequately labelled substrates and their assessment for D-glucose tracers towards SPECT imaging.



1

2 R = Bz
10 R = TBDMSi

3 R = Bz, R' = Ac
4 R = Bz, R' = Tf
11 R = TBDMSi, R' = Ac
12 R = TBDMSi, R' = Tf

5 R = Bz
6 R = H
13 R = TBDMSi

7

8

9

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20. To a 0.1 M pyridine solution of **2** at -10 °C,was added over 5 min. freshly distilled triflic anhydride (2.45 equiv.) After stirring for 60 min. at 4 °C then 45 min. at rt, ice was added and the crude extract obtained after CH_2Cl_2 extraction could be purified (cc on silica gel, eluting with AcOEt:hexane 1 :4) to get **4** (m.p. 109-111 °C; $[\alpha]^{20}_D$ = + 103 (c= 1; CH_2Cl_2).
21. To a 0.01 M acetone solution of **4** in the dark, was added 1.2 equiv. of sodium iodide and the mixture stirred at 50 °C for 16 hrs. After evaporation of the solvent , the crude mixture was examined by nmr then purified by cc on silica gel (eluting with CH_2Cl_2) to afford **5** (m.p. 114 - 115 °C; $[\alpha]^{20}_D$ = + 93 (c= 0.5; CH_2Cl_2).
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27. To a 0.07 M pyridine solution of **10** at -10 °C,was added freshly distilled triflic anhydride (5 equiv.) at a rate so as to avoid the formation of a pasty solid. After stirring for 15 min. at -10 °C, 30 min. at 4 °C and 1.5 hour at rt,the reaction mixture was hydrolyzed by addition of a pH=7.4 phosphate buffer.The iodination step was immediatly performed on the crude reaction mixture obtained after extraction with CH_2Cl_2 and evaporation of the volatiles.
28. Except for the unstable triflate **12**, all new compounds presented analytical and /or spectroscopic data in accord with the proposed structures.
29. To a 0.05 M acetone solution of the mixture of **10** and **12** was added sodium iodide (1.15 equiv. / **12**, the relative ratios of **10** and **12** being determined by ^1H nmr) and the reaction stirred in the dark at 50 °C for 18 hrs. After cooling, filtration and evaporation of the volatiles the crude mixture could be purified by cc on silica gel (eluting with CH_2Cl_2) to afford pure **13** $[\alpha]^{20}_D$ = + 15 (c= 0.5; CH_2Cl_2); the 64 % isolated yield is based on a 60 % conversion, 40 % of **10** being recovered after cc.
30. **1** is obtained in 13-14 % overall yield from t-butyl α - D-galactoside by either route : $[\alpha]^{23}_D$ = -3 (10 minutes) and -12 (70 minutes) (c=0.3 ; MeOH). The following nmr assignments were secured with TOCSY 1D and multiple quanta correlations experiments. ^1H nmr (500MHz, D_2O) : 5.28 (d, 1H, $J_{1,2}$ = 3.7, H-1 α) ; 4.67 (d, 1H, $J_{1,2}$=8.0, H-1β) ; 4.24-4.20 (M, 1H, H-5 α) ; 4.11-4.08 (m, 1H, H-6 β); 4.00-3.98 (m, 2H, H-6 and H-6'α) ; 3.96-3.93 (m, 1H, H-6' β) ; 3.94-3.92 (m, 1H,H-3 α) ;3.90-3.85 (M, 2H, H-4 and H-5 β); 3.88-3.85 (M, 1H, H-4 α); 3.74 (dd, 1H, $J_{3,2}$= 9.1 and $J_{3,4}$=10.3, H-3 β); 3.53 (dd, 1H, $J_{1,2}$ = 3.7 and $J_{2,3}$ = 9.2, H-2 α); 3.23 (dd, 1H, $J_{1,2}$ = 8,0 and $J_{2,3}$ = 9.1, H-2β). ^{13}C nmr (125MHz, D_2O): 95.9 (C-1 β) ; 92.2 (C-1 α) ; 77.2 (C-3 β); 76.8 (C-5 β); 75.15(C-2 β); 73.7 (C-3 α); 72.7 (C-5 α) ;72.1 (C-2 α) ; 63.1, 63.05 (C-6 α and C-6 β) ; 30.3,30.9 (C-4 α and C-4 β).
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