A Synthesis of 4-Deoxy-4-iodo-D-glucose Suitable for Radiolabelling.

Mehdi Abbadi, Jean-Paul Mathieu (a), Christophe Morin *,

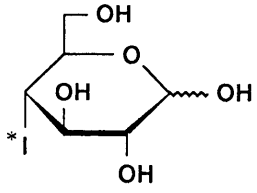
Laboratoire de Chimie (UMR Cnrs 5616), and
(a) Laboratoire d'Etudes des Radiopharmaceutiques (URA Cnrs 1287)
Université de Grenoble, 38402 Grenoble (France)

Summary : A preparation of a D-glucose analogue in which the 4-hydroxyl group can be replaced by radioactive iodine is presented.

Keywords : D-glucose analogues, iodo, deoxy, radiolabelling, SPECT.

As D-Glucose plays a pivotal role in many physiological processes, there has been a continuous search for suitable metabolic tracers of glucose uptake. Among the previously prepared derivatives, 2-deoxy-2-fluoro-D-glucose (FDG) stands in a special position as it is transported, and phosphorylated, in a similar manner to D-glucose (1,2); however, being cyclotron-produced and of short half-life ($t_{1/2}$ = 110 min.) the ^{18}F isotope which is needed for its labelling severely limits its use. Thus, preparation of iodinated analogues of D-glucose for use in Single-Photon Emission Computerized Tomography (SPECT) medical imaging are receiving increasing attention.

The iodo analogue of FDG is notably unstable (3-5). Other derivatives of D-glucose in which one of the hydroxyl groups has been replaced by iodine have been prepared. Such is the case for 4-deoxy-4-iodo-D-glucose **1** (6) but the two preparations



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* E-mail : Christophe.Morin@ujf-grenoble.fr

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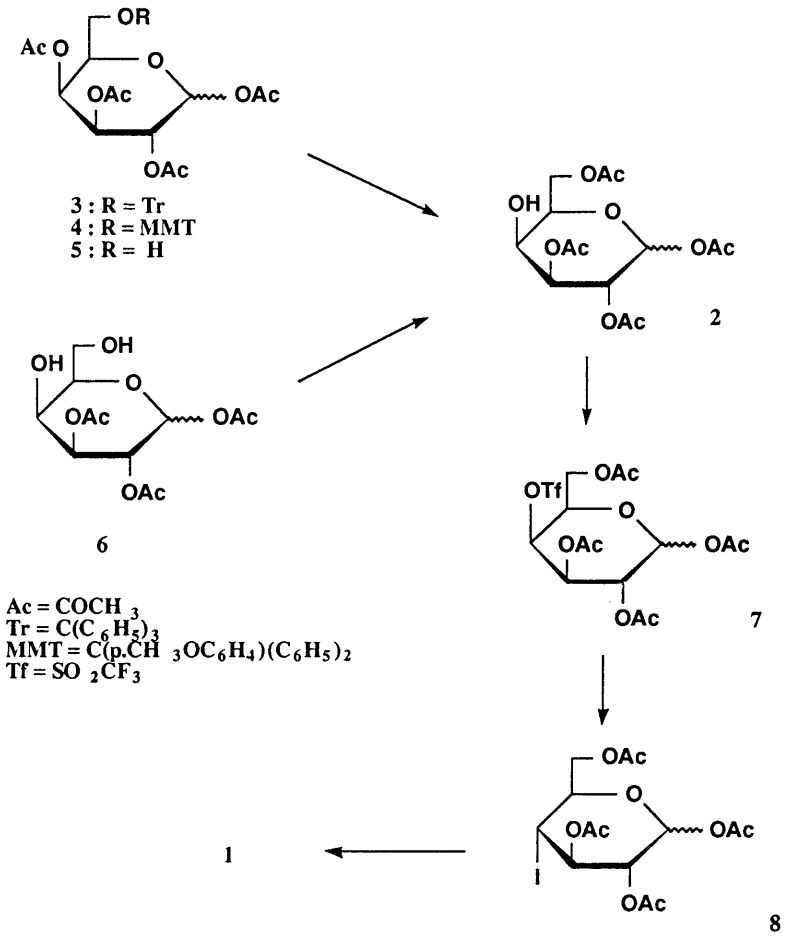
which have been presented do not appear to be of practical value for the introduction of a radioiodine, since a time-consuming two-step final deprotection lies at the end of the synthesis. A scheme which uses a labile and common protecting group for all hydroxyl groups, is now presented, which has allowed the obtaining of radioiodinated **1**.

Acetyl groups were chosen for common hydroxyl group protection, and a polyacetylated galactose derivative such as **2**, having a free hydroxyl group at position -4, appeared to be the required intermediate: indeed, after introduction of a good leaving group at position -4, displacement with iodine would yield the *gluco* series, *i.e.* with inversion of configuration.

1,2,3,6-Tetra-O-acetyl-galactopyranose **2** has been obtained, as a by-product, during cleavage of the trityl group of **3** (7), that is through partial migration of the 4-O-acetyl group during deprotection. For the present work, experimental conditions to achieve this migration in preparative yield were sought and the required precursor, 1,2,3,4-tetra-O-acetyl-D-galactopyranose **5** (7), could be obtained pure, using the more acid-labile 4-monomethoxytrityl ether **4**, with a $FeCl_3$-mediated deprotection (8). However, the acid or base-catalysed (9 -11) selective migration of its 4-acetyl group (from secondary to primary) to give **2**, could not be achieved in acceptable yields. Nevertheless, **2** could be obtained satisfactorily by selective acetylation (12) of the 1,2,3-triacetyl derivative **6**, itself readily available in 3 steps from D-galactose (13).

Compound **2** was then converted to triflate **7**, which was stable enough for full characterisation (see experimental section). Iodide displacement of the triflyl group was then achieved to give **8** in excellent yield. The *gluco* configuration of **8** was proven by determination of the coupling constants of H-4 with H-3 (10 Hz) and H-5 (5 Hz); thus, during introduction of iodine, no significant epimerisation (14) at position -4 takes place, which is presumably due to the excellent nucleofugal properties of the triflyl group. The synthesis was completed by conventional Zemplèn deacylation of **8** to afford **1**.

The short duration and efficiency of the final steps could allow the introduction of radioactive iodine (^{123}I or ^{125}I) and thus give the previously unobtained radiolabelled **1**. Such a practical preparation of **1** (80 % radiochemical yield) will allow its biological evaluation (15,16), which is presently being carried out in our laboratories (17).



Experimental.

Methanol was distilled over magnesium and dichloromethane and pyridine were dried on 4Å molecular sieves before use. After work-up, the volatiles were evaporated under reduced pressure without heating. Standard abbrevations are used for nmr description of spectra which were recorded on a Brucker AM 300 instrument, using built-in software. The residual absorption of the nmr solvent was taken as the internal reference. Microanalyses were performed by the Service d'Analyses du Cnrs (Vernaison - France).

1,2,3,6-Tetra-O-acetyl-β-D-galactopyranose **2**

To a solution of 1,2,3-tri-O-acetyl-β-D-galactopyranose (13) (244 mg - 0.797 mmol) in dry dichloromethane (1.5 mL) were added successively at -78°C and under argon, 2,4,6-collidine (170 μL - 1.275 mmol) and acetyl chloride (86 μL - 0.956 mmol).

The mixture was stirred for 3 hrs at -78°C, and the cooling bath was removed and stirring continued for a further 1 hr. After hydrolysis, the solution was extracted with dichloromethane (3 x 3 mL) and the organic layer washed with water , dried (Na_2SO_4), and the volatiles removed. Crystallisation from diethyl ether of the residue thus obtained gave **2** (173 mg - 62 %).

M.p. 140 - 141°C ; litt = 139 -140°C (ref. 18); 138°C(Ref. 19).^{1}H Nmr (300 MHz , $CDCl_3$) : 5.65 (d, J_{1-2} 7.9 Hz, 1H, H-1); 5.35 (dd, J_{2-1} 7.9 Hz, J_{2-3} 10.3 Hz, 1H, H-2); 5.0 (dd, J_{3-2} 10.3 Hz, J_{3-4} = 3.2 Hz, 1H, H-3); 4.3 (AB part of an ABM... system $J_{6-6'}$ 11.5 Hz, 2H, H-6 and H-6'); 4.05 (M, 1H, H-4); 3.85 (M, 1H, H-5) ; 2.03 (2 peaks); 2.00; 1.97 (4s, 12H, $4COCH_3$). ^{13}C Nmr (75 MHz , $CDCl_3$) :170.9; 170.2; 169.9; 168.9 ($\underline{C}OCH_3$); 92.1 (C-1); 68.0 (C-2); 73.3; 73.1 (C-3; C-5); 66.3 (C-4); 62.4 (C-6); 20.7; 20.4 ($COC\underline{H}_3$)

When conducted on the anomeric mixture (prepared according to ref. 13) a mixture of anomers was obtained, which led to the following nmr assignments for the α anomer.

^{1}H Nmr (300 MHz , $CDCl_3$) : 6.35 (d, J_{1-2} 3.3 Hz, 1H, H-1); 5,4 (dd, J_{2-1} 3.3 Hz, J_{2-3} 11 Hz, 1H, H-2); 5.25 (dd, J_{3-2} 11 Hz, J_{3-4} 2.2 Hz, 1H, H-3); 4.35 (M, 1H, H-5); 4.15 (M, 3H, H-4, H-6, H-6'); 2.03 (2 peaks); 1.98; 1.95 (4s, 12H, $COCH_3$). ^{13}C Nmr (75 MHz , $CDCl_3$) :170.9; 168.9 ($\underline{C}OCH_3$); 89.9 (C-1); 70.1; 69.8 (C-3; C-5); 67.2; 66.7 (C-2; C-4); 62.1 (C-6); 20.7; 20.5 ($COC\underline{H}_3$).

1, 2, 3, 6-Tetra-O-acetyl-4 O-trifluoromethanesulfonyl-β-D-galactopyranose **7**

To a solution of **2** (173 mg - 0.497 mmol) in pyridine (7.8 mL) stirred under argon at -10°C was added dropwise triflic anhydride (260 μL - 1.59 mmol - 3.2 equiv.).After 2 hrs. at room temperature, iced water (5 mL) was added and the solution was extracted with dichloromethane (3 x 5 mL). After washing the organic layer with water and drying (Na_2SO_4) the volatiles were removed. Crystallisation from diethyl ether afforded **7** (147 mg - 62%).

M.p. : 109 - 111°C. Anal. Calcd for $C_{15}H_{19}F_3O_{12}S$: C 37.50; H 3.99. Found : C 37. 66; H 4.05. ^{1}H Nmr (300 MHz , $CDCl_3$) : 5.7 (d, J_{1-2} 8.3 Hz, 1H, H-1); 5.3 (dd, J_{2-1} 8.3 Hz, J_{2-3} 10.0 Hz, 1H, H-2); 5.25 (d, J_{4-3} 3.1 Hz, 1H, H-4); 5.15 (dd, J_{3-2} 10.0 Hz, J_{3-4} 3.1 Hz, 1H, H-3); 4.3 (M, 1H, H-6); 4.05 (M, 2H, H-5, H-6'); 2.11; 2.10; 2.06; 2.04 (4s, 12H, $COCH_3$). ^{13}C Nmr (75 MHz , $CDCl_3$) : 169.9; 169.8; 168.8 ($\underline{C}OCH_3$); 118.3 (q, J_{C-F} 317 Hz, CF_3); 92.0 (C-1); 80.3 (C-4); 71.0; 69.8; 67.1 (C-2; C-3; C-5); 60.4 (C-6); 20.6; 20.4 ($4CO\underline{C}H_3$).

This reaction has been performed on a mixture of anomers which allowed the following nmr assigments for the α anomer :^{1}H Nmr (300 MHz , $CDCl_3$) : 6.38 (d, J_{1-2} 3.3 Hz, 1H, H-1) ; 5.2 - 5.5 (M, 3H, H-2; H-3; H-4); 3.9 - 4.5 (M, 3H, H-5; H-6; H-6'); 2.14; 2.10;

2.06; 2.01 (4s, 12H, $COCH_3$). ^{13}C Nmr (75 MHz , $CDCl_3$) : 170.3; 170.2; 169.2; 169.1 ($\underline{C}OCH_3$); 118.3 (q, J_{C-F} 317 Hz, CF_3); 89.1 (C-1); 81.4 (C-4); 67.9; 66.7; 65.7 (C-2; C-3; C-5); 60.6 (C-6); 21.0; 20.7 ($CO\underline{C}H_3$).

4-Deoxy-4-iodo-1, 2, 3, 6-tetra-O-acetyl-β-D-glucopyranose **8**

To a solution of **7** (19 mg - 40 mmol) in acetone (190 mL) was added sodium iodide (7 mg - 1.2 equiv.) and this was stirred under reflux protected from light overnight. After cooling, the volatiles were removed and the residue taken up in dichloromethane (2 mL). The organic layer was washed with water (3 x 2 mL), dried and concentrated to dryness. The crude residue was column chromatographed on silica gel and elution with CH_3OH : CH_2Cl_2 (5 : 95) afforded **8** as a colorless oil (17 mg - 94%).

^1H Nmr (300 MHz , $CDCl_3$) : 5.7 (d, J_{1-2} 8.4 Hz, 1H, H-1); 5.55 (dd, J_{3-2} 10 Hz, 1H, H-3); 4.95 (dd, J_{2-3} = 3.1 Hz, 1H, H-2); 4.5 (M, 2H, H-6, H-6'); 4.3 (M 1H, H-5); 4.05 (M, J_{4-5} 5 Hz (obtained by irradiation of H-3), J_{4-3} 11 Hz (obtained by irradiation of H-5), 1H, H-4); 2.10; 2.09; 2.00; 1.98 (4s, 12H, $COCH_3$). ^{13}C Nmr (75 MHz , $CDCl_3$) : 170.6; 170.0; 169.7; 169.1 ($4\underline{C}OCH_3$); 92.0 (C-1); 72.1; 71.5; 69.3 (C-2; C-3; C-5); 64.9 (C-6); 30.0 (C-4); 21.2; 21.0; 20.8; 20.7 ($4CO\underline{C}H_3$).

This reaction was also performed on a mixture of anomers and spectroscopic data were identical with those of a sample obtained by acetylation of authentic **1** (prepared according to ref. 6).

4-Deoxy-4-iodo-α,β-D-glucopyranose **1**

To a solution of **8** (17 mg - 37 μmol) in dry methanol (100 μL) was added sodium methoxide (2.9 mL of a 0.05 M dry CH_3OH solution - 148 μmol). After stirring at room temperature for 1-2 hrs, after which time (do not go beyond) there is usually complete disappearance of **8** , water was added (5 mL) and the pH was adjusted to 7.0 (0.001M H_2SO_4). Extraction was performed with dichloromethane (3 x2 mL), the organic layer was washed with water and the aqueous layers were pooled and evaporated to dryness to give pure **1** (10 mg - 93%). Nmr data and optical rotation were in agreement with those of an authentic sample (prepared according to ref. 6).

Preparation of labelled 4-deoxy-4-iodo-α,β-D-glucopyranose **1**.

For radiolabelling, the experimental procedure established for the large scale conversion of triflate **7** to **1** (see above) has been adapted as follows : to a solution of triflate **7** (1.3 mg - 2.7 μmol) in acetone (1 mL) were added $Na^{127}I$ (1 μg) and $Na^{125}I$

(55 MBq) and the mixture heated at 60 °C for 10 hrs. in a closed vessel. After elimination of the volatiles, the residue was dissolved in dry methanol (400 μL) and sodium methoxide (180 μL of a 0.05 M methanol solution) was added (the reaction was followed by hplc : Bondapack C-18 reversed phase column / eluant : water). After 1 hr. the pH was adjusted to 7.0 with 0.001 M sulfuric acid and the reaction mixture chromatographed on an anion-exchange resin (Dowex AG1X8). Labelled-**1** displays 11.7 min. and 13.2 min (for anomers) retention times in hplc (Licrospher RP18 25 cm x 0.4 mm, H_2O flow rate = 0.7 mL/mn). Radiochemical yield : 85 %. When iodine displacement of the triflate was performed at 105 °C for 30 mn., the yield was 78 %.

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REFERENCES

1. Gallagher, B.M., Ansari, A., Hatkins, A., Casella,V., Christman, D.R., Fowler,J.S., Ido, T., Mac Gregor, R.R., Som, P., Wan, C.N. , Wolf, A.P., Kuhl, D.E. and Reivich, M. *J. Nucl. Med.*, 18, 990 (1977).
2. Phelps, M.E., Huang, S.C., Hoffman, E.J., Selin,C., Sokoloff, L. and Kuhl, D.E. *Ann. Neurol.*, 6 371 (1979).
3. Fowler, J.S., Lade, R.E., Mac Gregor, R.R., Shiue, C., Wan, C.-N. and Wolf, A.P. *J. Labelled Compd. Radiopharm.*, 16 7 (1979).
4. Kloster, G., Laufer, P., Wutz, W. and Stöcklin, G. *Eur. J. Nucl. Med.*, 8, 237 (1983) .
5. Kloster, G., Laufer, P. and Stöcklin, G. *J. Labelled Compd. Radiopharm.*, 20 391 (1983).
6. Bignan, G., Morin, C. and Vidal, M. *Tetrahedron Lett.*, 35, 3909 (1994).
7. Kovack, P. and Glaudemans C.P.J. *Carbohydr. Res.* 140, 313 (1985).
8. Igolen,J. and Morin C. *J. Org. Chem.* 45, 4802 (1980).
9. Horton, D. and Lauterbach J.H. *J. Org. Chem.* 34, 86 (1969).
10. Koeppen B.H *Carbohydr. Res.* 24, 154 (1972).
11. Albert,R., Dax, K., Stütz, A.E. and Weidmann H. *J. Carbohydr. Chem.* 2 279 (1983).
12. Ishihara, K., Kurihaera,H. and Yamamoto, H. *J. Org. Chem.* 58 3792 (1993).
13. Gelas, J. and Horton, D. *Carbohydr. Res.* 71 103 (1979).
14. Stevens, C.L.,Taylor,K.G. and Valicenti J.A. *J. Am. Chem. Soc.* 87 4579 (1965).
15. Gatley,S.J. *Nucl. Med. Biol.* 22 829 (1995) .
16. Henry, C., Koumanov, F., Ghezzi, C., Mathieu, J.-P., Hamant,S., De Leiris J. and Comet, M. *Nucl. Med. Biol.* 22 875 (1995) .
17. Bignan, C., Ghezzi, C., Henry, C., Koumanov, F., Morin, C., Ogier,L., and Mauclaire, L. Fr. Patent : 95 95214; PCT/FR/96/ 00655 (Apr. 30, 1996).
18. Libert, H and Schmid, L. *Monatsch. Chem.* 98, 1375 (1967) .
19. Lee, E.E. and O'Brien, E. *Carbohydr. Res.* 41 313 (1975).

