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Tetrahedron Letters 47 (2006) 5055–5058
Tetrahedron Letters

Procurement of 2-deoxy-2-iodo-D-glucose (2-DIG)

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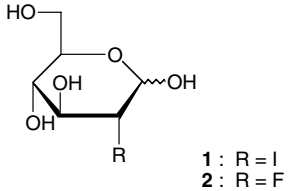
Received 20 April 2006; revised 12 May 2006; accepted 16 May 2006

Dedicated to the memory of Pierre Potier—✠Feb 03, 2006

Abstract—The heretofore elusive 2-deoxy-2-iodo-D-glucose (2-DIG), the iodinated analogue of FDG (2-fluoro-2-deoxy-D-glucose)—a PET imaging agent of glucose cellular uptake—can be obtained from D-glucal and is a stable compound.

The quest for glucose analogues which would be suitable for SPECT (single photon emission computed tomography) medical imaging[1] has resulted in the preparation of a number of carbohydrate iodinated derivatives.[2] Among these, analogues in which an hydroxyl group is replaced by iodine have been obtained: 3-deoxy-3-iodo-D-glucose (3-DIG),[3–7] 4-deoxy-4-iodo-D-glucose (4-DIG),[8] and 6-deoxy-6-iodo-D-glucose (6-DIG)[9,10] with the latter having been shown to be a tracer of glucose transport.[11] However, efforts to get **1**, the analogue in which iodine replaces the 2-OH group of glucose have remained fruitless.[4,12–14] This peculiar interest in 2-deoxy-2-iodo-D-glucose (2-DIG, **1**) stems from the fact that **1** is the iodinated counterpart of 2-fluoro-2-deoxy-D-glucose (FDG, **2**), a PET (positron emission tomography) imaging agent of glucose cellular uptake which has found numerous clinical applications.[15]



1: R = I
2: R = F

The status of 2-DIG has been described in a recent commentary about labeled glucose analogs in the genomic era, as: '2-deoxy-2-iodo-D-glucose is chemically unstable and therefore unsuitable for radiopharmaceutical uses'.[16]

Notwithstanding, it can be asked whether the observed instability of 2-DIG stems from its very structure,[17] or rather from the experimental conditions which were used for attempted preparations (see Scheme 1);[4,12] in the latter case, an approach which would deliver **1** under the mildest possible conditions—ideally as the last step[18]—is desirable.

Towards this goal, the readily available D-glucal (**3**)[19] was selected since substituents can be introduced at C-2 without the need to protect the hydroxyl groups.[20] In particular, the peroxidase-mediated halohydration of some glycals has been shown to yield 2-deoxy-2-halo-glycosides, a reaction that was also carried out non-enzymatically on D-galactal[21] and extended since to various alkenes.[22] Iodohydroxylation of D-glucal (Scheme 2), performed under the very conditions used for D-galactal,[21] led to **4**, the *manno* isomer of 2-DIG, as shown by NMR cross-correlation experiments.[23] This result was secured by peracetylation of **4** to give the known **5**.[24] It can therefore be concluded that the stereochemical outcome of the iodohydroxylation of D-glucal is opposite to that of D-galactal,[21] but although this approach did not afford 2-DIG, iodohydrin **4** was found to be stable which is an encouraging result.

With regard to protected glucal derivatives iodination has been shown to afford predominantly, when not exclusively, compounds of the *manno* configuration;[22,25] however, when bulky substituents are introduced on

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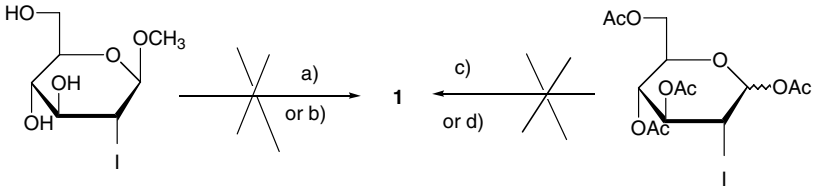
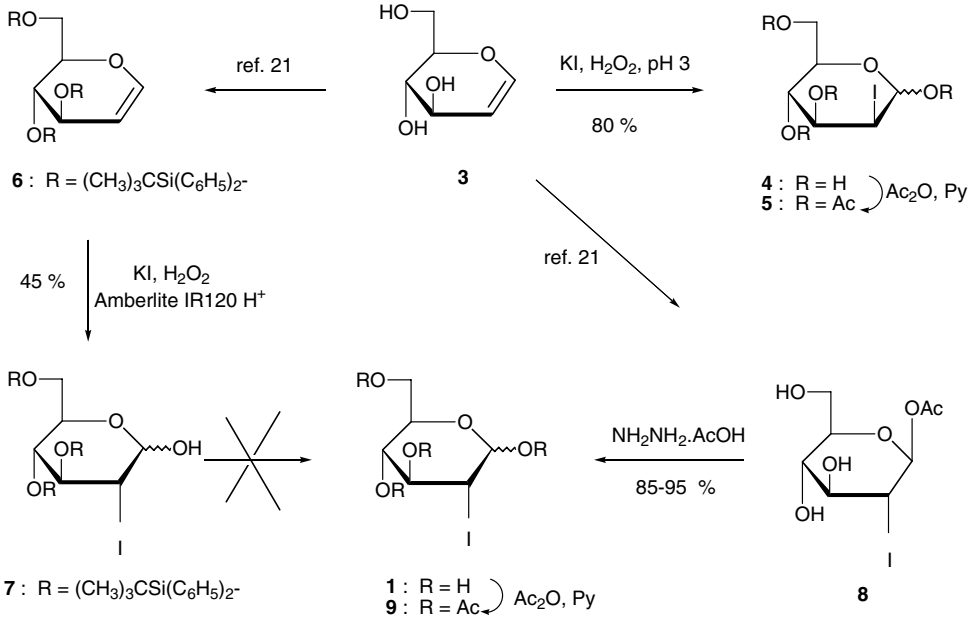
doi:10.1016/j.tetlet.2006.05.091



Scheme 1. Attempted preparations of 2-DIG (see Refs. 4 and 12). Reagents and conditions: (a) 0.1 N H_2SO_4, 100 °C, 2 h; (b) BBr_3, CH_2Cl_2, −80 °C, 10 min; (c) 0.1 N CH_3ONa in CH_3OH; (d) 1 N NH_3 in CH_3OH.



Scheme 2.

oxygens, the predominant conformation becomes half-chair $^5H_4$(D), which has been shown to favor the formation of products of the *gluco* configuration.[26,27]

Therefore, **6**[27] was reacted with hypoiodous acid,[22] (Scheme 2) but although the product is believed to be *gluco* derivative **7**, efforts to deprotect its silyl groups (to get 2-DIG) were vain. Since this drawback could be due to the presence of a free (unprotected) iodohydrin, advantage was taken based on the availability of iodoacetate **8** which is easily obtained from **6**.[27,28] Although removal of the acetyl group of **8** could not be carried out under Zemplen conditions (even at −20 °C), reaction with hydrazine acetate[29] was mild enough to afford the desired iodohydrin.[30] That iodine is equatorial in the product could be inferred from the anomeric protons coupling constant ($J_{1\alpha,2} = 3$ Hz, $J_{1\beta,2} = 8.5$ Hz) that indicates that the configuration is *gluco*; therefore **1** (2-DIG) has been obtained and this could be confirmed by peracetylation of **1**, which gave the known *gluco* derivative **9**[31] (Scheme 2).

As for its 2-epimer **4**, 2-DIG (**1**) was found to be stable; its aqueous solution was left unchanged after >1 week at rt (as shown by ^{1}H NMR) and it can be stored for extended period of times in the cold.[32] The stability and availability of water-soluble 2-DIG now sets the stage for biological evaluation.

Acknowledgements

Julian Garcia is thanked for 500 MHz ^{1}H NMR experiments.

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28. We have found that the intermediate persilylated 1-*O*-acetyl-2-deoxy-2-iodo *gluco* isomer can be easily freed from the (minor) *manno* isomer by fractional crystallization from *n*-hexane. Also, after the silyl ethers deprotection step (Ref. 27) mere washing of the crude organic residue with ether/pentane (1:1) results in pure crystalline **8**.
29. This reagent is usually used for selective deacylation of anomeric acetates in peracetylated carbohydrates: Excoffier, G.; Gagnaire, D.; Utille, J.-P. *Carbohydr. Res.* **1975**,

39, 368–373; in **8**, as a single acetate is to be removed, DMF can advantageously be replaced by methanol, which facilitates isolation of **1**.

30. Under argon, to a 0.1 M solution of **8** in dry methanol was added freshly prepared hydrazine acetate (1.1 equiv). After overnight stirring, the mixture was diluted with thf and put on top of a column of SiO_2. Elution with thf and evaporation of the volatiles gave a residue which was taken up in water, filtered and lyophilized to afford **1** (85–95%). If hydrazine derivatives remain (singlets at ca 1.9–2.0 ppm), **1** can be re-chromatographed (3:1 $CHCl_3$–CH_3OH) on SiO_2. MS (CI NH_3/isobutane) $m/z = 308$ $(M+NH_4)^+$, 290 $(M)^+$. ^1H (500 MHz, D_2O): 5.43 (d, $J = 3$ Hz, H-1α), 5.02 (d, $J = 8.5$ Hz, H-1β), 4.05–3.40, (2nd order systems, H-2 to H-6), ^{13}C NMR (75 MHz, D_2O): 97.0 (C-1β), 93.8 (C-1α), 77.5, 76.4, 70.7 (C-3β, C-4β, C-5β), 73.8, 72.4, C-3α, C-4α, C-5α), 61.0 (C-6β), 60.9 (C-6α), 36.9 (C-2β), 33.4 (C-2α).
31. An authentic sample of β-**9** was prepared according to Binkley, R. W.; Ambrose, M. G.; Hehemann, D. G. *J. Carbohydr. Chem.* **1987**, *6*, 203–219, α-**9:** ^1H NMR (500 MHz, $CDCl_3$): 6.38 (d, $J = 3.3$ Hz, H-1), 5.54 (dd, $J = 11.5$, 9.5 Hz, H-3), 5.10 (t, $J = 9.5$ Hz, H-4), 4.15 (dd, $J = 10.5$, 3.3 Hz, H-2), 4.12–4.00 (m, H-6, H-6′), 3.90 (m, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): 92.1 (C-1), 77.6, 72.8, 70.4 (C-3, C-4, C-5), 61.9 (C-6), 23.7 (C-2).
32. Being an iodinated compound, **1** should be protected from strong light however.