Carbohydrate Research, 233 (1992) C1–C3
Elsevier Science Publishers B.V., Amsterdam

Preliminary communication

A new and extremely fast synthesis of 2-deoxy-2,2-difluoro-D-*arabino*-hexose (2-deoxy-2,2-difluoro-D-glucose)

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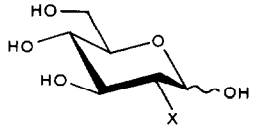
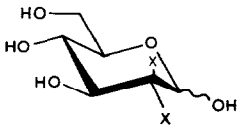
(Received January 27th, 1992; accepted May 13th, 1992)

Fluorinated carbohydrates have been a subject of interest for decades[1] because of their remarkable biological properties. It has been shown, particularly, that 2-deoxy-2-fluoro-D-glucose (**1**) inhibits the biosynthesis of different viruses, promotes the reduction of cellular growing in tumors, and can participate in biochemical pathways[2]. On the other hand, considerable effort has been devoted[3] to improving the synthesis of 2-deoxy-2-[^{18}F]fluoro-D-glucose (**2**). This compound has been used [4] in nuclear medicine for quantitative studies of cerebral D-glucose metabolism. The major synthetic problem with compound **2** is related to the short half-life (110 min) of the positron emitter ^{18}F.



1 X = ^{19}F
2 X = ^{18}F



3 X = ^{19}F
4 X = ^{18}F

It appeared to us that a very rapid synthesis of 2-deoxy-2,2-difluoro-D-*arabino*-hexose (2-deoxy-2,2-difluoro-D-glucose) (**3**) would be of great interest since the corresponding *gem*-fluorine-18 labeled carbohydrate **4** might efficiently replace **2** in cerebral D-glucose metabolism studies. In this communication, we report a very fast synthesis of **3** which appears to be adaptable to the preparation of **4**. The

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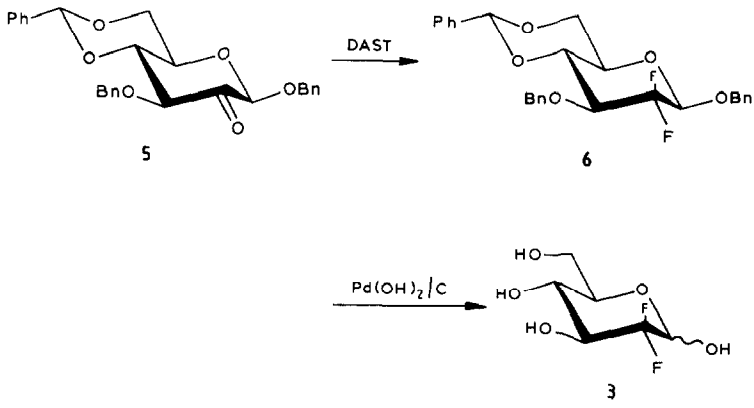

Scheme 1.

synthesis of 2-*gem*-difluorocarbohydrates had not been extensively investigated. Reported methods use the addition of trifluorofluoroxymethane (CF_3OF) to 2-fluoroglycals[5,6] and the Reformatsky reaction of ethyl bromodifluoroacetate[7] or bromodifluoromethylacetylene[8] with acyclic precursors. However, all these methods are inefficient for preparing radioactive fluorine labeled carbohydrates in view of the long time required in the multistep synthetic schemes.

Recently, we have reported[9] that the reaction of 2-uloses with dimethylaminosulfur trifluoride (DAST) was an efficient method of synthesis of 2,2-difluorocarbohydrates if the neighbouring substituents to the carbonyl group both have pseudo-equatorial configuration. Our procedure[9] can be satisfactorily adapted to an extremely fast synthesis of 2-deoxy-2,2-difluoro-D-glucose.

Ulose **5**[10] was selected as the starting material because the benzyl and benzylidene protecting groups can be easily removed in one step under hydrogenolytic conditions. Various solvents and different ulose/ DAST ratios were tested, looking for a clean, rapid, and effective *gem*-difluorination.

We have found that the ulose **5** by reaction with 6 equiv of DAST could be converted, in 5 min in 80% yield, in anhydrous deoxygenated boiling toluene (~ 4 mL/mmol of ulose) into the *gem*-difluorocarbohydrate **6**, mp 101–102°; $[\alpha]_D$ −65° (*c* 0.34, $CHCl_3$); *m/z* 468 (M^+); ^{1}H NMR: δ 7.60 and 7.20 (m, 15 H, 3 Ph), 5.57 (s, 1 H, H-7), 4.98 (d, 1 H, J_{gem} 12.3 Hz, CH_2Ph), 4.89 (d, 1 H, J_{gem} 11.9 Hz, CH_2Ph), 4.83 (d, 1 H, J_{gem} 11.9 Hz, CH_2Ph), 4.73 (d, 1 H, J_{gem} 12.3 Hz, CH_2Ph), 4.56 (d, 1 H, $J_{1,Fax}$ 15 Hz, H-1), 4.38 (dd, 1 H, $J_{6eq,6ax}$ 10.5 Hz, $J_{6eq,5}$ 5 Hz, H-6*eq*), 3.94–3.72 (m, 3 H, H-3,4,6*ax*), 3.42 (dt, 1 H, $J_{5,4}$ 10 Hz, H-5); ^{13}C NMR: δ 138.0–127.0 (3 Ph), 116.1 (t, $J_{C,F}$ 255 Hz, C-2), 101.4 (C-7), 97.4 (dd, $^2J_{C,Fax}$ 28 Hz, $^2J_{C,Feq}$ 20 Hz, C-1), 79.2 (d, $^3J_{C,F}$ 8.7 Hz, C-4), 77.5 (t, $^2J_{C,Fax} = {}^2J_{C,Feq} = 19.3$ Hz, C-3), 74.6 (*C*H$_2$Ph), 71.4 (*C*H$_2$Ph), 68.3 (C-6), 66.5 (C-5); ^{19}F NMR: δ −118.3 (dd, J_{Fgem} 251.5, $^2J_{Feq,H\text{-}3}$ 4.2 Hz, F*eq*), −136.0 (dt, J_{Fgem} 251.5, $^2J_{Fax,H\text{-}1} = {}^2J_{Fax,H\text{-}3} = 15$ Hz, F*ax*).

Anal. Calcd for $C_{27}H_{26}F_2O_5$: C, 69.23; H, 5.55. Found: C, 68.97; H, 5.56.

Removal of the protecting groups of compound **6** was performed in 7 min under a 35-kg pressure of H_2 in the presence of 20% $Pd(OH)_2/C$[11]. The resulting 2-deoxy-2,2-difluoro-D-glucose (**3**) was purified by rapid filtration through a short column of silica gel. The product eluted by ethyl acetate showed physical and spectroscopic properties identical with those published in the literature[5]. From the moment of the use of diethylaminosulfur trifluoride, the total time required for the completion of the synthesis is close to 35 min, resulting in a an overall yield of 65%.

In conclusion, the reaction of the ulose **5** with DAST is an efficient method for obtaining 2-deoxy-2,2-difluoro-D-glucose.

ACKNOWLEDGMENT

Financial suport by DGICYT (Ministerio de Educación y Ciencia, Spain) (PB89-0277-C02) is gratefully acknowledged.

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