Synthesis of 3-Deoxy-3-fluoro-D-fructose

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3-Deoxy-3-fluoro-D-fructose has been synthesized using a new method for making ketoses involving hydroxyalkylation of 2-deoxy-2-fluoro-D-arabinono-1,4-lactone using (benzyloxymethyl)tributylstannane–n-butyllithium.

Fluorinated carbohydrates are important probes in the study of transport, metabolism and enzymology of sugars.[1] Numerous deoxyfluoro analogues of sugars have been synthesised including all of the monofluoro analogues of the common monosaccharides involved in metabolism.[2] A notable exception has been 3-deoxy-3-fluoro-D-fructose **1**, although several attempts have been made to synthesise it by chemical methods.[3,4] Evidence has been presented that **1** is an important metabolite of 3-deoxy-3-fluoro-D-glucose,[5,6] and there is great interest in studying the metabolism of **1**, one possible exploitation being chemotherapy.[4] We here report the synthesis of **1** using a new method of preparing ketoses.

Attempts at substituting sulfonic esters of 1,2:4,5-di-*O*-isopropylidene-β-D-psicopyranose with fluoride were not successful,[7] because of elimination. Thus a different approach was needed. We have recently prepared 2-deoxy-2-fluoro-D-arabinono-1,4-lactone **2** from D-ribono-1,4-lactone **3**.[8] Since organometallic reagents have been reported to add to aldonolactones to form hemiketals in high yield,[9] addition of an α-alkoxymethyl organometallic reagent to **2** would be

expected to lead to the target **1**. Treatment of **2** with $CH_2(OMe)_2$ and P_2O_5[10] gave the protected lactone **2a**† in 78% yield. (Benzyloxymethyl)lithium is thermally unstable, but can be prepared effectively at −78 °C[11] from the corresponding stannane, (benzyloxymethyl)tri-n-butylstannane,[12] and LiBu. Fluorolactone **2a** reacted with (benzyloxymethyl)-lithium to give hemiketal **4**† as the only observable product in 60% yield.‡ We believe that the selective monoaddition of (benzyloxymethyl)lithium is attributable to the stability of the lithium salt of the hemiketal preventing further attack. Hydrolysis of **4** with 0.5 mol dm^{-3} HCl in 50% aqueous tetrahydrofuran (THF) (reflux, 2.5 h) gave **5**† in 66% yield. Finally hydrogenolysis with Pd/C catalyst in EtOH gave 3-deoxy-3-fluoro-D-fructose **1** in 86% yield.

In conclusion, the synthesis described in this communication is the first route to the hitherto inaccessible **1**. Moreover, we believe that this method for hydroxyalkylation of aldonolactones will be of value in the synthesis of ketoses.

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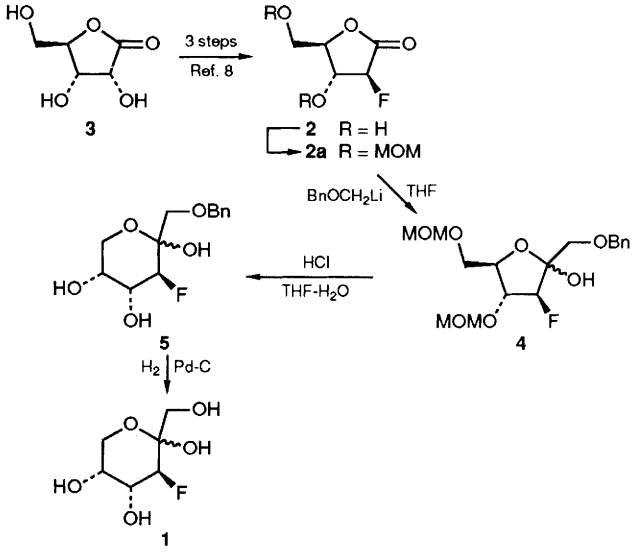

Scheme 1 Bn = $PhCH_2$; MOM = $MeOCH_2$

† Relevant data for new compounds: **2a**: $[\alpha]_D^{20}$ + 51.2 (*c* 1.4, $CHCl_3$), ^{13}C NMR ($CDCl_3$): δ 90.8 (d, $J_{2,F}$ 199.2 Hz, C-2), 78.0 (d, $J_{4,F}$ 10.0 Hz, C-4), 76.2 (d, $J_{3,F}$ 20.8 Hz, C-3), 64.5 (C-5); **4**: $[\alpha]_D^{20}$ + 46.3 (*c* 0.1, $CHCl_3$), ^{13}C NMR ($CDCl_3$), α : β ratio *ca.* 1 : 1, α-anomer: δ 103.7 (d, $J_{2,F}$ 27.0 Hz, C-2), 99.0 (d, $J_{3,F}$ 188.8 Hz, C-3), 81.4 (d, $J_{5,F}$ 3.1 Hz, C-5) 78.7 (d, $J_{4,F}$ 21.8 Hz, C-4), 69.9 (d, $J_{1,F}$ 6.9 Hz, C-1); β-anomer: δ 100.6 (d, $J_{2,F}$ 15.6 Hz, C-2), δ 94.8 (d, $J_{3,F}$ 192.5 Hz, C-3), 81.2 (d, $J_{4,F}$ 27.2 Hz, C-4), 79.3 (d, $J_{5,F}$ 9.7 Hz, C-5); **5**: $[\alpha]_D^{20}$ −19.5 (*c* 0.2, EtOH), ^{13}C NMR ($CDCl_3$): δ 89.4 (d, $J_{3,F}$ 187.0 Hz, C-3), 74.1 and 71.1 (C-1 and CH_2Ph), 69.9 (d, $J_{5,F}$ 7.8 Hz, C-5), 68.5 (d, $J_{4,F}$ 18.4 Hz, C-4), 62.9 (C-6); **1**: $[\alpha]_D^{20}$ −55.4 (*c* 0.26, MeOH), ^{13}C NMR (D_2O): δ 97.1 (d, $J_{2,F}$ 19.1 Hz, C-2), 89.2 (d, $J_{3,F}$ 183.1 Hz, C-3), 70.5 (d, $J_{5,F}$ 8.4 Hz, C-5), 68.9 (d, $J_{4,F}$ 17.5 Hz, C-4), 64.4 and 64.3 (C-1 and C-6); ^1H NMR (D_2O): δ 4.51 (dd, $J_{3,F}$ 50.3 Hz, $J_{3,4}$ 9.8 Hz, H-3), 3.98 (ddd, $J_{4,F}$ 13.3 Hz, $J_{4,5}$ 3.6 Hz, H-4), 3.89 (m, H-5), 3.88 (dd, $J_{1,1'}$ 12.9 Hz, $J_{1,F}$ 1.2 Hz, H-1), 3.55 (dd, $J_{1',F}$ 2.0 Hz, H-1′), 3.53 (dd, $J_{6,6'}$ 12.1 Hz, $J_{5,6}$ 1.6 Hz, H-6), 3.41 (dd, $J_{5,6'}$ 1.5 Hz, H-6′).

‡ A typical preparative procedure: to (benzyloxymethyl)tri-*n*-butylstannane (1.1 g, 2.7 mmol) in THF (11 ml) at −78 °C was added LiBu in hexanes (1.6 mol dm^{-3}; 1.65 ml, 2.64 mmol). After 5 min at −78 °C a solution of the lactone (1.3 mmol) in THF (4 ml) was added, and the mixture was stirred for an additional 30 min at −78 °C. Addition of H_2O (20 ml), extraction with CH_2Cl_2 (3 × 20 ml), drying, concentration, and flash-chromatography (EtOAc–pentane, 1 : 2 v/v) to remove $SnBu_4$ gave the desired ketose.

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