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Hydroxymethylation of aldonolactones and a chemical synthesis of 3-deoxy-3-fluoro-D-fructose *

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ABSTRACT

(Benzyloxymethyl)lithium, generated in situ from butyllithium and (benzyloxymethyl)tri-*n*-butylstannane, was found to be an efficient reagent for the monohydroxymethylation of aldono-1,4-lactones to form ketoses. Thus, 4-hydroxy butanoic-1,4-lactone, 2-deoxy-2-fluoro-3,5-di-*O*-(methoxymethyl)-D-arabinono-1,4-lactone, 2,3,5-tri-*O*-(methoxymethyl)-D-arabinono-1,4-lactone, 5-*O*-(methoxymethyl)-2,3-*O*-methylidene-D-ribono-1,4-lactone, 2,3,5,6-tetra-*O*-(methoxymethyl)-D-altrono-1,4-lactone, 2,3:5,6-di-*O*-isopropylidene-D-gulono-1,4-lactone and 2,3-*O*-isopropylidene-L-erythrono-1,4-lactone were respectively converted to 1-benzyloxy-5-hydroxy-2-pentanone, 1-*O*-benzyl-3-deoxy-3-fluoro-4,6-di-*O*-(methoxymethyl)-D-fructofuranose, 1-*O*-benzyl-3,4,6-tri-*O*-(methoxymethyl)-D-fructofuranose, 1-*O*-benzyl-6-*O*-(methoxymethyl)-2,3-*O*-methylidene-D-psicofuranose, 1-*O*-benzyl-3,4,6,7-tetra-*O*-(methoxymethyl)-D-*altro*-heptulofuranose, 1-*O*-benzyl-3,4:6,7-di-*O*-isopropylidene-D-*gulo*-heptulofuranose, and 1-*O*-benzyl-3,4-*O*-isopropylidene-L-*erythro*-pentulofuranose in 63–81% yields. By deprotection of 1-*O*-benzyl-3-deoxy-3-fluoro-4,6-di-*O*-(methoxymethyl)-D-fructose, 3-deoxy-3-fluoro-D-fructose was prepared for the first time.

INTRODUCTION

Fluorinated carbohydrates are important probes in the study of transport, metabolism and enzymology of sugars[2]. The reason for this is the close similarity in size between the hydroxyl group and the fluorine atom, allowing a deoxyfluoro analogue of a sugar to mimic most of its parent's biological functions, while being restricted from involvement in certain pathways. In addition, fluorinated metabolites can be traced by ^{19}F NMR spectroscopy[3]. A large number of deoxyfluoro analogues of sugars have been synthesized including all the monofluoro analogues of the common monosaccharides involved in metabolism[4]. A notable exception has been 3-deoxy-3-fluoro-D-fructose (**1**), although several attempts have been made to synthesize the compound[5,6].

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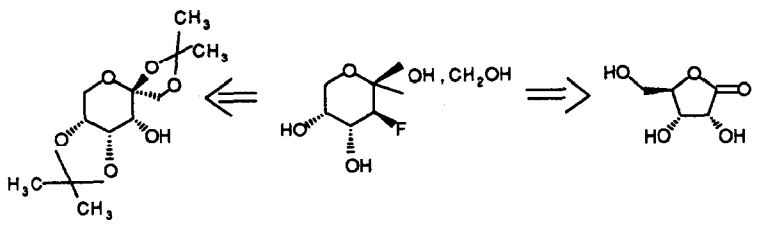
3-Deoxy-3-fluoro-D-fructose (**1**) is a confirmed metabolite of 3-deoxy-3-fluoro-D-glucose, an important compound in studies of carbohydrate metabolic pathways in insects, microorganisms[7], and mammals[8], however its further metabolism is unknown.

RESULTS AND DISCUSSION

As an attractive and straightforward route to **1**, we and other[9] investigated the nucleophilic substitution at C-3 of 1,2:4,5-di-*O*-isopropylidene-β-D-psicopyranose (**2**), readily available from 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose by configurational inversion at C-3 (Scheme 1). However all attempts using diethylaminosulphur trifluoride (DAST) or reacting the 3-triflate of **2** with tris(dimethylamino)sulphonium difluorotrimethylsilicate (TASF) failed, resulting in elimination product. Consequently, we decided to investigate other possibilities.

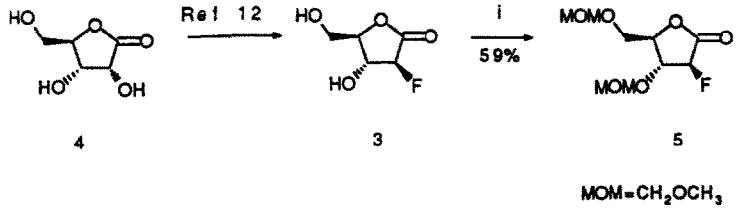
It has been reported that organometallic reagents add to aldonolactones at −78°C to form hemiketals in good yield[10,11]. Thus, from the known 2-deoxy-2-fluoro-D-arabinono-1,4-lactone (**3**), available[12] in three steps from D-ribono-1,4-lactone (**4**), addition of an organometallic reagent with α-alkoxy or oxygen function would be expected to lead to **1**. A general method to hydroxymethylate aldonolactones would be a useful route to ketoses, since a wealth of readily available functionalised aldonolactones exists[12–16].

To study the reaction between aldonolactones and organometallic reagents, we needed a base stable protecting group. However, such protecting groups are normaly introduced under basic conditions, where sugar lactones are prone to β-elimination. Therefore *O*-alkyl-protected lactones have mostly been prepared by oxidation of the corresponding aldose[17]. As a base stable group to be introduced under acidic conditions, we found the methoxymethyl group suitable. Thus, the α-fluorolactone **3** was converted, with dimethoxymethane in the presence of phosphorus pentaoxide[18,19], into the 3,5-di-*O*-methoxymethyl derivative **5** in 59% yield (Scheme 2). The protected lactones **6**, **7** and **8** were similarly prepared. First, the action of simple Grignard reagents on the fluorolactone **5** was investigated. However, reaction of **5** with ethylmagnesium bromide at −78°C did not proceed



2 1 4

Scheme 1.



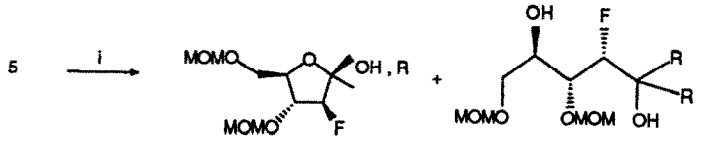
i : $(CH_3O)_2CH_2$, P_2O_5

Scheme 2.

with the expected selectivity since a 3:2 ratio of the desired hemiketal **9a** and the tertiary alcohol **10a** was obtained (Scheme 3). Similarly vinylmagnesium bromide, which adds selectively to 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone[10], reacted with **4** to give a 3:2 ratio of the hemiketal **9b** and the tertiary alcohol **10b**.

A number of organometallic hydroxymethylating agents have been applied in synthesis. We found the thermally unstable (benzyloxymethyl)magnesium chloride[20] difficult to prepare and to handle in a quantitative manner. Attention was then shifted to (dimethylisopropyloxysilyl)methylmagnesium chloride[21] and (dimethylphenylsilyl)methylmagnesium chloride[22]. However, we found that none of these Grignard reagents reacted by addition to **5**, but rather an epimerisation at C-2 of the lactone was observed, probably due to enolisation. It is well known that bulky Grignard reagents have a tendency to cause enolisation.

(Benzyloxymethyl)lithium is thermally unstable, but can be prepared very effectively at −78°C from (benzyloxymethyl)tri-*n*-butylstannane[23,24] and butyllithium; a report on its addition to aldono-1,5-lactones appeared recently[25]. When γ-butyrolactone (**11**) was allowed to react with 2 equiv of this reagent, the hemiketal **12** was isolated as the only product in 74% yield. Similarly, the fluorolactone **5** reacted with (benzyloxymethyl)lithium to give the hemiketal **13** as the only observable



9a R=Et
9b R=CH=CH$_2$

10a R=Et
10b R=CH=CH$_2$

MOM=CH_2OCH_3

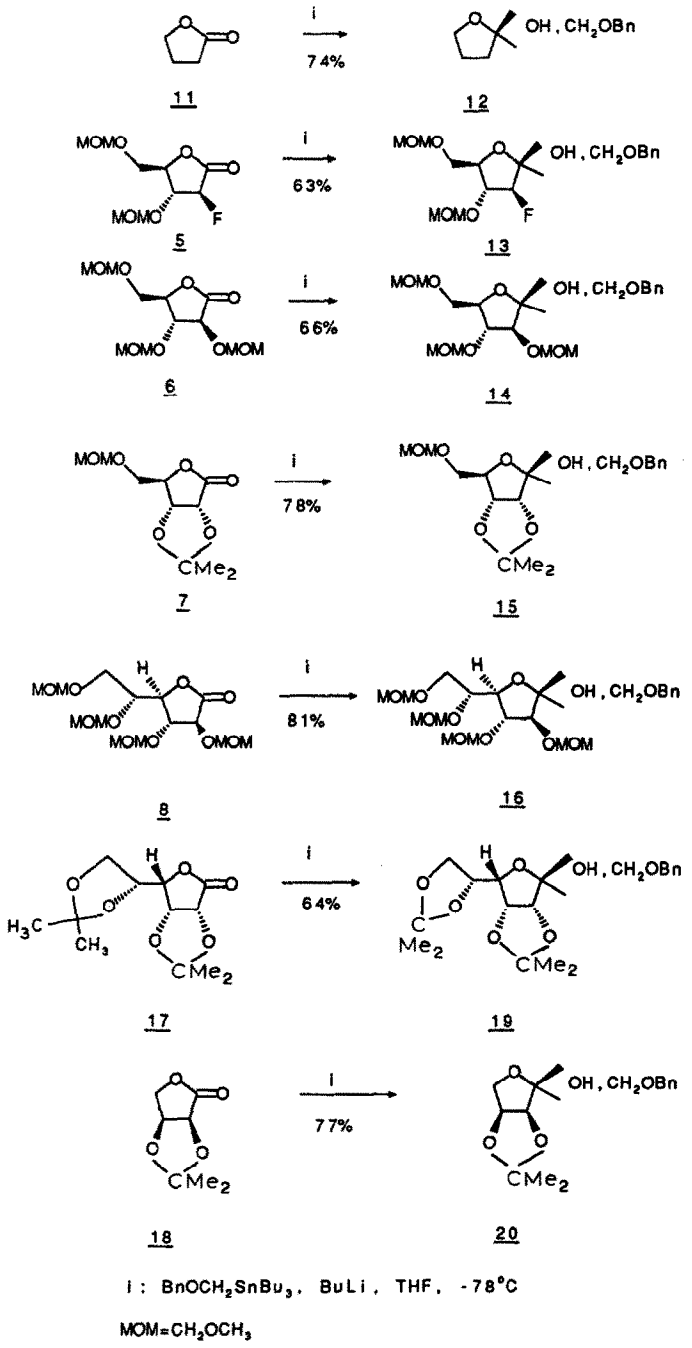
: RMgBr

Scheme 3.

product in 63% yield. Compound **13** was a 1:1 mixture of α and β anomers, and both of them had a large difference in the $J_{3,4}$ coupling constant (6.3 and 1.3 Hz, respectively) which might indicate that epimerization at C-3 had occurred. However, since **13** was converted to a single compound by hydrolysis, this difference must be caused by a large conformational change in the furanose ring. The selectivity of the lithium reagent in the addition to **5**, in contrast to the Grignard reagents, may be due to the greater stability of the lithium alkoxide of the hemiketal, preventing further attack. A number of other protected lactones were also reacted with 2 equiv of (benzyloxymethyl)lithium (Scheme 4). The arabinonolactone **6** gave the fructofuranose derivative **14** in 66% yield; the ribonolactone **7** gave the psicofuranose derivative **15** in 78% yield and the altronolactone **8** gave the *altro*-heptuloside **16** in 81% yield. 2,3:5,6-Di-*O*-isopropylidene-D-gulono-1,4-lactone (**17**) and 2,3-*O*-isopropylidene-L-erythrono-1,4-lactone (**18**) gave the *gulo*-benzylheptuloside **19** and L-ribuloside **20** in 64 and 77% yields, respectively. In all cases, the best yields were obtained by using 2 equiv of the organometallic reagent and a reaction time of 0.5–1 h at −78°C. For instance, reaction of 4-hydroxybutanoic-1,4-lactone (**11**) with 1 equiv of the reagent for 1 h at −78°C gave 55% of **12**, while reaction of **5** with 1.5 equiv of the same reagent for 1 h at −78°C gave 40% of **13**. Longer reaction times resulted in slight decreases in yield. The hemiketals **13–16**, **19–20** were mixtures of anomers with a relatively large variation in anomeric ratio. In the case of **13–15**, the anomers could be assigned by comparing the ^{13}C NMR chemical shift of C-2 with published values for ketohexofuranoses with similar configuration[26].

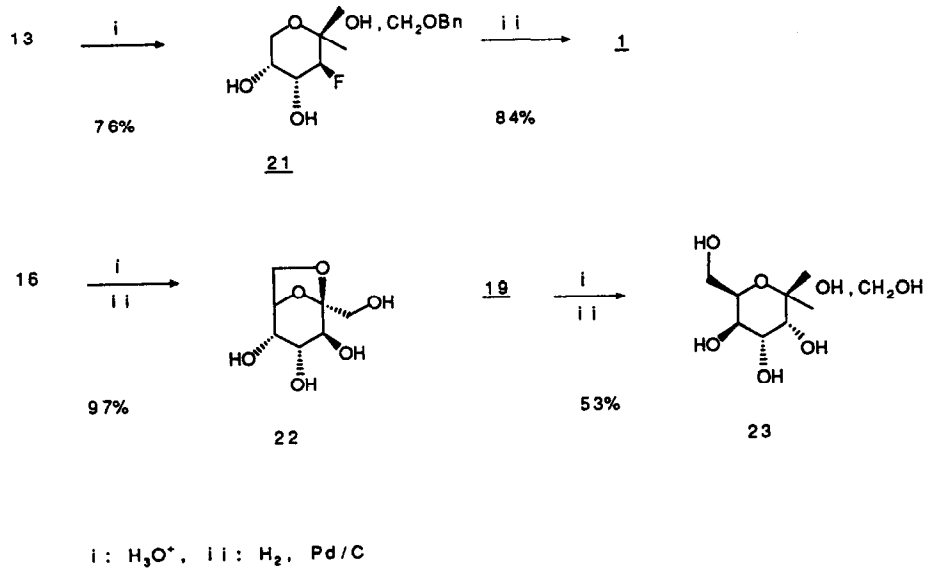
Hydrolysis of **13** with 0.5 M HCl in boiling 50% aq THF gave 1-*O*-benzyl-3-deoxy-3-fluoro-D-fructose (**21**) in 76% yield (Scheme 5). NMR revealed that **21** in aqueous solution was largely in the β-D-pyranose form. Hydrogenolysis of **21** with palladium on carbon gave 3-deoxy-3-fluoro-D-fructose (**1**) in 84% yield as a colourless syrup, which crystallized on prolonged standing. Confirmation of the structure of **1** came from the elemental analysis and from the NMR spectra. Downfield in the ^{13}C NMR spectrum, the characteristic large doublet of a fluorinated carbon was observed (89.2 ppm, 183.1 Hz), and all carbons, except the two primary carbons, coupled with fluorine. This was consistant with the presence of a fluorine atom at C-3 or C-4. The large coupling constant (19.1 Hz) for C-2 and its upfield shift of ~ 1 ppm as compared to C-2 of D-fructose, showed that fluorine was located at C-3. It was observed that **1**, in aqueous solution, was mostly in the β-D-pyranose form and the $^2C_5$ conformation. ^{19}F NMR revealed however that two other anomers were also present in respective amounts of 9 and 5%. The two sets of signals were assigned to be the two furanoses by analogy to the composition of anomers of fructose in solution, and because $J_{4,F}$ in the two anomers had very similar values (19.1 and 23.8 Hz) which differed from $J_{4,F}$ of the β-pyranose form (13.3 Hz).

The *altro*-heptulose derivative **16** and the *gulo*-heptulose derivatives **19** were also deprotected by acidic hydrolysis and hydrogenolysis to 2,7-anhydro-D-*altro*-



Scheme 4.

heptulose (**22**) and D-*gulo*-heptulose (**23**), respectively. The formation of the 2,7-anhydride in the altroheptulose case was to be expected from similar behaviour of *altro*-heptulose.[27]



Scheme 5.

In this paper, we have introduced a one step route from aldonolactones to ketoses, especially useful for preparing functionalised ketoses. This allowed the first synthesis of 3-deoxy-3-fluoro-D-fructose, a compound which may be of importance in future studies of the metabolism of carbohydrates.

EXPERIMENTAL

General.—NMR spectra were obtained on either a Bruker AC-250 or a Bruker AM-500 instrument. Spectra recorded in $CDCl_3$ were referenced to Me_4Si for ^1H, and $CDCl_3$ (δ 76.93) for ^{13}C. Spectra recorded in D_2O were referenced to acetone (δ 2.22 or 29.8, respectively). ^{19}F NMR spectra were referenced to trifluoroacetic acid. Optical rotations were measured on a Perkin–Elmer 141 polarimeter. Microanalysis were carried out by Leo Microanalytical Laboratory. Concentrations were performed on a rotary evaporator at a temperature below 40°C.

2-Deoxy-3,5-di-O-(methoxymethyl)-2-fluoro-D-arabinono-1,4-lactone (**5**).—To a stirred suspension of P_2O_5 (8.5 g) in dimethoxymethane (35 mL) was added a solution of 2-deoxy-2-fluoro-D-arabinono-1,4-lactone[12] (**3**, 828 mg, 5.52 mmol) in dimethoxymethane (15 mL). The mixture was stirred for 2 h at 25°C. Ice (200 mL) and satd aq $NaHCO_3$ (300 mL) were added, and the mixture was extracted with EtOAc (3 × 100 mL), dried ($MgSO_4$), and concentrated to give an oil (1.12 g). Flash chromatography using 1:2 EtOAc–pentane gave syrupy **5** (0.77 g, 59%); $[\alpha]_D^{20}$ +51.2° (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.24 (dd, $J_{2,F}$ 51.0, $J_{2,3}$ 7.5 Hz, H-2), 4.80 (dd, *J* 6.8, $J_{H,F}$ 0.6 Hz, H-CH), 4.71 (d, H-CH), 4.66 (s, CH_2-5), 4.61 (dd, $J_{3,F}$ 18.4 Hz, H-3), 4.36 (ddd, $J_{4,F}$ 7.7, $J_{4,5'}$ 3.6, $J_{4,5}$ 2.5 Hz, H-4), 3.89 (ddd,

$J_{5,5'}$ 11.9, $J_{5,F}$ 1.6 Hz, H-5), 3.77 (dd, H-5'), 3.41 (s, OCH_3), 3.37 (s, OCH_3); ^{13}C NMR ($CDCl_3$): δ 168.2 (d, $J_{1,F}$ 22.7 Hz, C-1), 95.8 (s, 2 C, CH_2O's), 90.4 (d, $J_{2,F}$ 197.6 Hz, C-2), 77.4 (d, $J_{4,F}$ 10.2 Hz, C-4), 75.7 (d $J_{3,F}$ 20.6 Hz, C-3), 64.1 (s, C-5), 55.0 (s, OCH_3), 54.6 (s, OCH_3). Anal. Calcd for $C_9H_{15}FO_6$: C, 45.38; H, 6.35. Found: C, 45.48; H, 6.49.

2,3,5-Tri-O-(methoxymethyl)-D-arabinono-1,4-lactone (**6**).—The reaction was carried out as above for the preparation of **5**, with P_2O_5 (12 g) in dimethoxymethane (100 mL) and adding D-arabinono-1,4-lactone[28] (2.52 g) in dimethoxymethane (200 mL). After stirring for 30 min and workup, the protected lactone **6** was obtained as a syrup (2.77 g, 58%); $[\alpha]_D^{20}$ +21.1° (*c* 1.4, $CHCl_3$), ^{13}C NMR ($CDCl_3$): δ 171.6, (C-1), 96.4, 96.3, 95.8 (OCH_2O's), 79.1 (C-4), 77.5, 75.8 (C-2, C-3), 65.1 (C-5), 55.8, 55.6, 55.2 (CH_3O's). Anal. Calcd for $C_{11}H_{20}O_8$: C, 47.14; H, 7.19. Found: C, 46.98; H, 7.22.

5-O-(Methoxymethyl)-2,3-O-methylidene-D-ribono-1,4-lactone (**7**).—The reaction was carried out as described above for the preparation of **5**, with P_2O_5 (92 g) in dimethoxymethane (375 mL) and D-ribono-1,4-lactone (6.46 g) in dimethoxymethane (200 mL). After stirring for 20 h, workup and flash chromatography in 1:1 EtOAc–pentane, the protected lactone **7** was obtained as a syrup (8.26 g, 84%); $[\alpha]_D^{20}$ −39.2° (*c* 1.3, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 172.8 (C-1), 96.3, 96.1 (OCH_2O's), 81.5 (C-4), 77.7, 75.0 (C-2, C-3), 66.3 (C-5), 55.4 (CH_3O). Anal. Calcd for $C_8H_{12}O_6$: C, 47.06; H, 5.92. Found: C, 46.85; H, 6.16.

2,3,5,6-Tetra-O-(methoxymethyl)-D-altrono-1,4-lactone (**8**).—The reaction was carried out as above for the preparation of **5**, with P_2O_5 (60 g) in dimethoxymethane (500 mL) and D-altrono-1,4-lactone[28,29] (5.00 g) in THF (500 mL). After stirring for 6 h, workup (8.7 g, 87%) and flash chromatography in 1:1 EtOAc–pentane, the protected lactone **8** was obtained as a colourless oil (6.75 g, 68%); $[\alpha]_D^{20}$ −33.4° (*c* 1.7, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 172.3 (C-1), 96.5, 96.4, 96.0, 95.9 (OCH_2O), 80.6 (C-4), 76.7, 76.4, 74.4 (C-2, C-3, C-5), 65.7 (C-6), 56.1, 56.0, 55.7, 55.3 (CH_3O). Anal. Calcd for $C_{14}H_{26}O_{10}$: C, 47.45; H, 7.40. Found: C, 47.46; H, 7.52.

Reaction of 2-deoxy-2-fluoro-3,5-di-O-(methoxymethyl)-D-arabinono-1,4-lactone (**5**) *with ethylmagnesium bromide*.—A solution of the fluorolactone **5** (106 mg, 0.45 mmol) in THF (4.5 mL) was stirred at −78°C, and a solution of EtMgBr (0.8 mL, 0.82 M, 1.5 equiv) in ether was added. The solution was stirred for 45 min at −78°C, then allowed to reach 0°C. A solution of NH_4Cl (10 mL, 5%) was added and the mixture extracted with EtOAc (3 × 10 mL). Drying ($MgSO_4$) and concentration of the combined organic layers left a clear syrup (99 mg) containing the hemiketal **9a** and the tertiary alcohol **10a** in the ratio 3:2. Flash chromatography with 1:2 EtOAc–pentane gave the faster moving product **9a** (36 mg, 30%); $[\alpha]_D^{20}$ +38.3° (*c* 1.8, $CHCl_3$); ^{13}C NMR ($CDCl_3$): 1st anomer (60%): δ 97.3 (d, $J_{4,F}$ 185.8 Hz, C-4), 96.5–96.0 (OCH_2O's), 81.4 (d, $J_{5,F}$ 19.7 Hz, C-5), 78.1 (d, $J_{6,F}$ 9.8 Hz, C-6), 67.2 (d, $J_{7,F}$ 6.2 Hz, C-7), 55.9–55.2 (CH_2O's), 29.9 (C-2), and 7.7 (C-1); 2nd anomer (40%): δ 96.5–96.0 (OCH_2O's), 90.8 (d, $J_{4,F}$ 199.3 Hz, C-4), 79.2 (d, $J_{5,F}$ 21.9 Hz, C-5), 78.8 (d, $J_{6,F}$ 9.5 Hz, C-6), 64.6 (C-7), 55.9–55.2 (CH_2O's), 27.6 (C-2)

and 7.2 (C-1), C-3's too weak to be measured. The slower moving product was **10a** (26 mg, 20%); $[\alpha]_D^{20}$ +4.4° (*c* 1.2, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 98.4, 97.2 (OCH_2O's), 93.2 (d, $J_{4,F}$ 181.6 Hz, C-4), 78.3 (d, $J_{5,F}$ 18.1 Hz, C-5), 75.3 (d, $J_{3,F}$ 19.6 Hz, C-3), 70.2 (d, $J_{6,F}$ 3.3 Hz, C6), 69.6 (C-7), 56.5, 55.5 (CH_3O's), 27.4 (d,*J* 3.8 Hz, C-2), 26.9 (d, *J* 3.9 Hz, C-2′), 7.5 and 7.1 (C-1, C-1′).

*Reaction of 2-deoxy-2-fluoro-3,5-di-*O*-(methoxymethyl)-*D*-arabinono-1,4-lactone* (**5**) *with vinylmagnesium bromide.*—The reaction was performed as above with **5** (109 mg, 0.46 mmol) in THF (5 mL) by adding a solution of vinylmagnesium bromide (0.4 mL, 1.73 M, 1.5 eq) in THF. The crude product (99 mg) contained the hemiketal **9b** and the tertiary alcohol **10b** in a 3:2 ratio. Chromatography in 1:2 EtOAc–pentane gave successively: **9b** (31 mg, 25%); $[\alpha]_D^{20}$ +24.8° (*c* 1.3, $CHCl_3$); ^{13}C NMR ($CDCl_3$), 1st anomer (50%): δ 134.3 and 118.7 (C-1, C-2) 96.8–96.3 (OCH_2O's), 93.9 (d, $J_{4,F}$ 181.2 Hz, C-4), 81.8 (C-6), 81.4 (d, $J_{5,F}$ 7.0 Hz, C-5), 67.1 (C-7), 55.7–55.2 (CH_3O's), C-3 too weak to be measured; 2nd anomer (50%): δ 135.6 and 118.1 (C-1, C-2) 96.8–96.3 (OCH_2O's), 90.7 (d, $J_{4,F}$ 189.2 Hz, C-4), 79.0 (d, $J_{5,F}$ 32.4 Hz, C-5), 77.9 (d, $J_{6,F}$ 9.6 Hz, C-6), 67.3 (C-7), 55.7–55.2 (CH_3O's), C-3 too weak to be measured, and: **10b** (23 mg, 17%); $[\alpha]_D^{20}$ +18.3° (*c* 1.0, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 138.9, 138.3, 115.0 and 114.7 (C-1, C-1′, C-2, C-2′), 98.7, 97.2 (OCH_2O's), 93.5 (d, $J_{4,F}$ 186.4 Hz, C-4), 78.5 (d, $J_{5,F}$ 18.0 Hz, C-5), 70.0 (d, J_{6F} ~ 0.1 Hz, C-6), 69.6 (C-7), 56.5, 55.5 (CH_2O's).

1-Benzyloxy-5-hydroxy-2-pentanone (**12**).—To a solution of (benzoxymethyl)tri-*n*-butylstannane[24] (1.1 g, 2.7 mmol) in dry THF (11 mL) at −78°C was added butyllithium (1.6 M, 1.65 mL, 2.64 mmol) in hexane. The mixture was stirred under N_2 for 5 min at −78°C and 4-hydroxybutanoic-1,4-lactone (**11**, 100 μL, 112 mg, 1.3 mmol) was added. After stirring for 30 min at −78°C, the mixture was allowed to warm to 0°C, and then quenched with water (20 mL). Extraction with CH_2Cl_2 (3 × 20 mL), drying, and concentration of the combined organic layers left an oily residue (1.21 g). Flash chromatography in 1:2 EtOAc–pentane gave the title compound **12** as a colourless syrup (200 mg, 74%); ^{13}C NMR ($CDCl_3$): hemiacetal (80%): δ 137.8 and 128.5–127.7 (Ph), 104.8 (C-2), 74.1, 73.6 (C-1 and Bn), 68.1 (C-5), 34.3, 24.2 (C-3, C-4); hydrate (20%): δ 137 and 128.5–127.7 (Ph), 95.1 (C-2), 74.9 and 73.3 (C-1 and Bn), 61.9 (C-5), 35.6 and 26.1 (C-2 and C-3). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H. 7.74. Found: C, 69.73; H, 7.36.

*1-*O*-Benzyl-3-deoxy-3-fluoro-4,6-di-*O*-(methoxymethyl)-*D*-fructofuranose* (**13**).—To a solution of (benzyloxymethyl)tri-*n*-butylstannane[24] (2.27 g, 5.53 mmol) in THF (20 mL) stirred at −78°C under N_2, a solution of *n*-butyllithium (3.4 mL, 1.6 M, 5.44 mmol) in hexane was added, and the yellow mixture was stirred for 10 min at −78°C. The fluorolactone **5** (658 mg, 2.76 mmol) in THF (3 mL) was then added, and the resulting colourless solution was stirred at −78°C for 1 h. After following the temperature to rise to 0°C, water (100 mL) was added and the aq layer was extracted with CH_2Cl_2 (4 × 50 mL). Drying and concentration left a residue (2.85 g) containing the desired fluoroketose, tetrabutylstannane and benzyl methyl ether. Flash chromatography in 1:2 EtOAc–pentane gave 1-*O*-benzyl-3-deoxy-3-fluoro-

4,6-di-*O*-(methoxymethyl)-D-fructofuranose (**13**, 626 mg, 63%) as a colourless syrup; $[\alpha]_D^{20}$ +46.3° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$): 1st anomer (50%): δ 7.35–7.30 (m, Ph), 5.03 (dd, $J_{3,F}$ 53.5, $J_{3,4}$ 6.3 Hz, H-3), 4.8–4.6 (m, CH_2Ph, OCH_2O), 4.50 (dt, $J_{4,F}$ 18.2 $J_{4,5}$ 6.1 Hz, H-4), 4.11 (dt, $J_{5,6}$, $J_{5,F}$ both 3.6 Hz, H-5), 3.7–3.74 (m, H-6, H-6′, H-1′), 3.64 (dd, $J_{1,1'}$ 10.3, $J_{1,F}$ 2.9 Hz, H-1), 3.40 and 3.38 (s, CH_3O's); 2nd anomer (50%): δ 7.30–7.35 (m, Ph), 4.93 (dd, $J_{3,F}$ 50.9, $J_{3,4}$ 1.3 Hz, H-3), 4.31 (q, $J_{4,5} = J_{5,6} = J_{5,F} = 5.1$ Hz, H-5), 4.15 (ddd, $J_{4,F}$ 24.2 Hz, H-4), 3.7–3.74 (m, H-6, H-6′), 3.61 (dd, $J_{1,1'}$ 10.8, $J_{1,F}$ 1.1 Hz, H-1), 3.56 (d, H-1′), 3.40 and 3.37 (s, OMe's); ^{13}C NMR ($CDCl_3$); α anomer: δ 137.3 and 127.7–128.4 (Ph), 103.7 (d, $J_{2,F}$ 27.0 Hz, C-2), 99.0 (d, $J_{3,F}$ 188.8 Hz, C-3), 96.5–96.3 (OCH_2O's), 81.4 (d, $J_{5,F}$ 3.1 Hz, C-5), 78.7 (d, $J_{4,F}$ 21.8 Hz, C-4), 73.8 (CH_2Ph), 69.9 (d, $J_{1,F}$ 6.9 Hz, C-1), 66.8 (C-6), 55.2–55.7 (OMe's); β-anomer: δ 137.5 and 127.7–128.4 (Ph), 100.6 (d, $J_{2,F}$ 15.6 Hz, C-2), 96.3–96.5 (OCH_2O's), 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), 73.6 (CH_2Ph), 70.3 (C-1), 67.1 (C-6), 55.2–55.7 (CH_3O's). Anal. Calcd for $C_{17}H_{25}FO_7$: C, 56.66; H. 6.99. Found: C, 56.80; H, 7.14.

1-O-Benzyl-3,4,6-tri-O-(methoxymethyl)-D-fructofuranose (**14**).—The reaction was carried out as above for the preparation of **13** with (benzyloxymethyl)tri-*n*-butylstannane (1.1 g, 2.7 mmol) in THF (11 mL), butyllithium (1.65 mL, 2.64 mmol), and the lactone **6** (0.38 g, 1.36 mmol) in THF (4 mL). After stirring for 30 min at −78°C, workup and flash chromatography in 1:2, then 1:1 EtOAc–pentane gave the ketofuranose **14** as a syrup (0.36 g, 66%); $[\alpha]_D^{20}$ +42.5° (*c* 1.1, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): β anomer (71%): δ 101.7 (C-2), 96.5 (2C), 96.4 (OCH_2O's), 81.5, 81.4 (C-5, CH_2Ph), 79.7, 73.5, 71.1 (C-1, C-3, C-4), 67.6 (C-6), 55.5, 55.3, 55.2 (CH_3O's); α anomer (29%): δ 104.8 (C-2), 96.3, 95.7, 95.6 (OCH_2O's), 84.7 (C-5), 81.7 (CH_2Ph), 81.3, 73.5, 70.7 (C-1, C-3, C-4), 67.3 (C-6), 55.2, 54.9 (CH_3O's). Anal. Calcd for $C_{19}H_{30}O_9$: C, 56.71; H, 7.51. Found: C, 56.45; H, 7.47.

1-O-Benzyl-6-O-(methoxymethyl)-2,3-O-methylidene-D-psicofuranose (**15**).—The reaction was carried out as above for preparation of **13** with (benzyloxymethyl)tri-*n*-butylstannane (5.5 g, 13.4 mmol) in THF (55 mL), *n*-butyllithium (8.25 mL, 13.2 mmol), and the lactone **7** (1.82 g, 6.1 mmol) in THF (20 mL). After stirring for 1 h at −78°C, workup and flash chromatography in 1:2 EtOAc–pentane gave **15** as a syrup (1.54 g, 78%); $[\alpha]_D^{20}$ −4.4° (*c* 0.9, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): β anomer (75%): δ 105.3 (C-2), 96.5, 95.6 (OCH_2O's), 85.0 (C-5), 83.9 (CH_2Ph), 82.0, 73.8, 71.0 (C-1, C-3, C-4), 68.9 (C-6), 55.5 (CH_3O); α anomer (25%): δ 102.9 (C-2), 97.6, 96.5 (OCH_2O's), 81.2 (C-5), 80.2 (CH_2Ph), 79.2, 73.6, 72.7 (C-1, C-3, C-4), 67.3 (C-6), 55.5 (CH_3O). Anal. Calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.79. Found: C, 58.91; H, 6.88.

1-O-Benzyl-3,4,6,7-tetra-O-(methoxymethyl)-D-altro-heptulofuranose (**16**).—The reaction was carried out as above for the preparation of **13** with (benzyloxymethyl)tri-*n*-butylstannane (2.2 g, 5.4 mmol) in THF (22 mL), butyllithium (3.3 mL, 5.3 mmol), and the lactone **8** (0.92 g, 2.6 mmol) in THF (6 mL). After stirring for 30 min at −78°C, workup and flash chromatography in 1:2

EtOAc–pentane gave **16** as a syrup (1.00 g, 81%); $[\alpha]_D^{20}$ +19.6° (*c* 0.7, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): 1st anomer 57%): δ 102.9 (C-2), 96.4, 95.2 (OCH_2O's), 83.2, 80.8, 80.6, 76.4, 73.3, 71.6 (C-1, C-3, C-4, C-5, C-6, CH_2Ph), 66.4 (C-7), 55.7–55.0 (CH_3O's); 2nd anomer (43%): δ 105.3 (C-2), 96.4–95.2 (OCH_2O's), 83.7 (C-5), 81.5 (CH_2Ph), 80.2, 75.4, 73.5, 70.4 (C-1, C-3, C-4, C-6), 66.6 (C-7), 55.7, 55.0 (CH_3O's). Anal. Calcd for $C_{22}H_{36}O_{11}$: C, 55.45; H, 7.61. Found: C, 55.20; H, 7.28.

1-O-Benzyl-3,4:6,7-di-O-isopropylidene-D-gulo-*heptulofuranose* (**19**).—The reaction was carried out as above for the preparation of **13** with (benzyloxymethyl)tri-*n*-butylstannane (1.1 g, 2.7 mmol) in THF (11 mL), *n*-butyllithium (1.65 mL, 2.64 mmol), and 2,3:5,6-di-*O*-isopropylidene-D-gulono-1,4-lactone[30] (**17**, 336 mg, 1.3 mmol) in THF (6 mL). Stirring for 30 min at −78°C, workup and flash chromatography in 1:4 EtOAc–pentane than 1:2 gave **19** as a syrup (316 mg, 64%); $[\alpha]_D^{20}$ −17.3° (*c* 1.3, $CHCl_3$); ^{13}C NMR ($CDCl_3$): 1st anomer (80%): δ 112.9, 109.7 (OCO's), 104.3 (C-2), 85.1, 81.7, 80.1, 75.5, 73.7, 70.4 (C-1, C-3, C-4, C-5, C-6, CH_2Ph), 65.9 (C-7), 26.6–24.3 (CH_3's); 2nd anomer (20%): δ 113.2, 103.6, 103.1 (OCO's, C-2), 85.7 (C-5), 80.4 (CH_2Ph), 79.0, 73.6, 70.8, 70.6 (C-1, C-3, C-4, C-6), 65,7 (C-7), 26.6–24.3 (CH_3's). Anal. Calcd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42. Found: C 62.73; H, 7.43.

1-O-Benzyl-3,4-O-isopropylidene-L-*ribulofuranose* (**20**).—The reaction was carried out as above for the preparation of **13** with (benzyloxymethyl)tri-*n*-butylstannane (1.1 g, 2.7 mmol) in THF (11 mL), *n*-butyllithium (1.65 mL, 2.7 mmol), and 2,3-*O*-isopropylidene-L-erythrono-1,4-lactone (**18**, 205 mg, 1.3 mmol, obtained from L-erythrono-1,4-lactone[31] by the method in ref 32). After stirring 0.5 h at −78°C, workup and flash chromatography in 1:2 EtOAc–pentane gave **20** as a syrup (280 mg, 77%); $[\alpha]_D^{20}$ +44.2° (*c* 1.0, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): δ 112.4 (OCO), 104.6 (C-2), 84.9 (C-1), 80.3 (C-5), 73.7, 73.2, 71.2 (OCH_2, C-3, C-4), 26.0, 25.9 (CH_3's), (anomeric ratio: 1:0). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 63.77; H, 7.26.

1-O-Benzyl-3-deoxy-3-fluoro-D-*fructose* (**21**).—The fluoroketose **13** (623 mg, 1.73 mmol) was refluxed for 3.5 h in a mixture of M HCl (30 mL) and THF (30 mL). The mixture was neutralized with a weakly basic ion-exchange resin (Amberlite IR-45, 15 mL, OH^-) for 1 h. Filtration and concentration of the filtrate left **21** as a clear syrup (359 mg, 76%); $[\alpha]_D^{20}$ −19.5° (*c* 0.2, EtOH); ^1H NMR (D_2O): δ 7.45–7.38 (m, Ph), 4.66 (dd, $J_{3,F}$ 50.2, $J_{3,4}$ 9.7 Hz, H-3), 4.66 (d, *J* 11.8 Hz, CH_2Ph), 4.60 (d, CH_2Ph), 4.12 (ddd, $J_{4,F}$ 13.4, $J_{4,5}$ 3.6 Hz, H-4), 4.04 (dd, $J_{6,6'}$ 13.0, $J_{5,6}$ 1.3 Hz, H-6), 4.03 (m, H-5), 3.70 (dt, $J_{5,6'} = J_{6',F} = 1.8$ Hz, H-6'), 3.68 (dd, $J_{1,1'}$ 10.7, $J_{1,F}$ 1.7 Hz, H-1), 3.57 (dd, $J_{1',F}$ 1.6 Hz, H-1'); ^{13}C NMR (D_2O): δ 139.4, 131.0, 130.6 (Ph), 98.4 (d, J_{2F} 19.1 Hz, C-2), 91.0 (d, J_{3F} 184.2 Hz, C-3), 75.8, 75.3 (C-1 and CH_2Ph), 72.1 (d, J_{5F} 8.4 Hz, C-5), 70.3 (d, J_{4F} 17.5 Hz, C-4), 65.8 (C-6). Anal. Calcd for $C_{13}H_{17}FO_5$: C, 57.35; H, 6.29. Found: C, 57.32; H, 6.70.

3-Deoxy-3-fluoro-D-*fructose* (**1**).—To 1-*O*-benzyl-3-deoxy-3-fluoro-D-fructose (**21**, 296 mg, 1.1 mmol) in EtOH (30 mL) was added palladium on carbon (5%, 100 mg), and the mixture was hydrogenolyzed (101 kPa) for 18 h at 25°C. Filtration and

concentration left a colourless syrup (206 mg). Flash chromatography in 10:1 EtOAc–MeOH gave **1** (167 mg, 84%). After standing for several months crystals were obtained. Recrystallisation from MeOH–EtOAc–pentane gave a product with mp 101–103°C; $[\alpha]_D^{20}$ −55.4° (*c* 0.26, MeOH, equilibrium); ^{1}H NMR (D_2O): δ 4.51 (dd, $J_{3,F}$ 50.3, $J_{3,4}$ 9.8 Hz, H-3), 3.98 (ddd, $J_{4,F}$ 13.3 $J_{4,5}$ 3.6 Hz, H-4), 3.89 (m, H-5), 3.88 (dd, $J_{1,1'}$ 12.9, $J_{1,F}$ 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'); ^{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); ^{19}F NMR (D_2O): δ 130.9 (dd, $J_{4,F}$ 13.3, $J_{3,F}$ 50.2 Hz, β anomer ~86%), δ 127.7 (dd, *J* 19.1, *J* 53.5 Hz, ~9%), δ 117.0 (dd, *J* 23.8, *J* 51.3 Hz, ~5%). Anal. Calcd for $C_6H_{11}FO_5$: C, 39.56; H, 6.09. Found: C, 39.43; H, 6.12.

2,7-Anhydro-D-altro-*heptulose* (**22**).—The ketofuranoside **16** (319 mg) was dissolved in THF (25 mL) and 0.5 M HCl (25 mL) and refluxed 1.5 h. The cooled solution was neutralized by stirring 1 h with ion-exchange resin (Amberlite IR-45, 15 mL, OH^-), filtered and concentrated to syrupy 2,7-anhydro-1-*O*-benzyl-D-*altro*-heptulose (183 mg, 97%). The syrup was dissolved in EtOH (35 mL), palladium on carbon, (5%, 90 mg) was added, and the mixture was hydrogenolyzed (101 kPa) for 18 h at 25°C. After filtration and concentration, **22** was obtained (126 mg, 97%); $[\alpha]_D^{20}$ −124° (*c* 0.5, H_2O); lit.[33] $[\alpha]_D^{20}$ −121° (*c* 2, H_2O).

D-gulo-*Heptulose* (**23**).—The ketofuranose **19** (227 mg) was dissolved in THF (10 mL) and 0.5 M HCl (10 mL) and refluxed for 2.5 h. The cooled solution was neutralized by stirring for 1 h with ion-exchange resin (Amberlite IR-45, 5 mL, OH^-), filtered, and concentrated to give 1-*O*-benzyl-D-*gulo*-heptulose (116 mg) as a syrup. The syrup was dissolved in EtOH (20 mL), acetic acid (0.32 mL), and palladium on carbon (5%, 90 mg) was added, and the mixture was hydrogenolyzed (101 kPa) for 48 h at 25°C. After filtration and concentration **23** was obtained (66 mg, 53%); $[\alpha]_D^{20}$ +23.7° (*c* 0.5, H_2O); lit.[34] for the L-isomer $[\alpha]_D^{20}$ −28° (*c* 0.8, H_2O).

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