Synthesis of 5-O-benzyl-2-C- β -fluoromethyl-1,2,3-tri-O-acetyl-D-ribofuranose

Dirk Elend, M., Jonathan Fray,* and David Pryde

*Department of Discovery Chemistry, Pfizer Global Research and Development,
Sandwich, Kent CT13 9NJ, U.K.*

E-mail: jonathan.fray@pfizer.com

Abstract

The novel, protected fluoromethylribose (**10**) was prepared in 7 steps (26% overall yield) from commercially available D-ribonolactone. First, the three hydroxyl groups were protected as the 2,3-isopropylidene-5-benzyl derivative. Reduction of the resulting fully protected ribonolactone to the lactol was achieved by using Cp_2TiF_2 -catalysed hydrosilylation, followed by hydrolysis. Reaction with formaldehyde installed the 2-C- β -hydroxymethyl group. Treatment with DAST gave the 1-fluoro-2-C- β -fluoromethyl derivative, which, on hydrolysis and acetylation, afforded 5-O-benzyl-2-C- β -fluoromethyl-1,2,3-tri-O-acetyl-D-ribofuranose.

Keywords: Fluorination, fluoromethylribose, DAST, hydrosilylation, D-ribonolactone

Introduction

The introduction of fluorine atoms into molecules may change biological activity, vulnerability towards metabolism, lipophilicity and pKa with minimal change in steric bulk, and is therefore of particular interest to the pharmaceutical industry.¹ For example, fluorinated carbohydrates have been investigated for their biological properties, and as tools to study enzyme-carbohydrate interactions.²

Starting with the pioneering work of Walton,³ who prepared 2'-C-methyladenosine (an inhibitor of adenosine demethylase and of KB cells in culture) and 2'-C-methylcytidine (**1**), (an inhibitor of hepatitis C virus RNA polymerase), much interest has been shown in the synthesis of modified nucleosides as anti-tumour and anti-viral agents.⁴ It is not surprising therefore that the fluorinated modifications of nucleosides have also been investigated.⁵ For example, Piccirilli and co-workers have recently reported the synthesis of 2'-C- β -trifluoromethylribonucleosides (**2**).⁶

1 **2**

Base = uracil, cytosine, thymine

In the particular case of 2'-C-methyl nucleosides bearing a single fluorine substituent, however, the only successful synthetic strategy so far has been to introduce the fluoromethyl group after the nucleoside base (Scheme 1), but these approaches suffer from moderate yields and lack the flexibility to incorporate the nucleoside base at a late stage in the synthesis. In the first example, ring-opening of epoxide (**3**) under harsh conditions gave 2'-C- α -fluoromethyl derivative (**4**), which was converted to 2'-C- β -fluoromethyl-2-deoxycytidine in six steps.⁷ The fluorine was introduced similarly in the second example, and three further steps were required to afford 2'-C- β -fluoromethyluridine (**5**).⁸ Two patents^{4c,9} describe remarkably mild fluoride displacement of tosylate (**6**) and triflate (**7**) to give compounds (**8**) and (**9**), respectively.

Scheme 1. Reagents and conditions: a) KHF_2 , methoxyethanol, reflux, 24 h; b) $n\text{-Bu}_4\text{NF}$, THF, 20°C , 4 h.

We thus became interested in the synthesis of the novel 2-C- β -fluoromethyl ribofuranose (**10**), as a potentially useful late-stage intermediate for the preparation of new nucleosides, because only three further steps would be required, namely introduction of the nucleoside base, followed by hydroxyl deprotection (Scheme 2).

Scheme 2

Results and Discussion

Our synthesis commenced with the protection of the three hydroxyl groups of commercially available (D)-ribonolactone (**11**) (Scheme 3). Thus, treatment of **11** with acetone in the presence of anhydrous cupric sulphate gave acetonide (**12**) in almost quantitative yield.¹⁰ Benzyl ether (**13**) has been previously described.¹¹ In our own hands, benzylation proceeded more cleanly and rapidly with sodium hydride and benzyl bromide in dimethylformamide rather than tetrahydrofuran solvent.

We then sought a convenient method to reduce **13** to lactol (**14**). Although this can be achieved with diisobutylaluminium hydride at low temperature, precedent suggested a significant excess of reagent would be required, which is disadvantageous when working on a large scale.¹² We were therefore drawn to Buchwald's hydrosilylation, which is achieved by using inexpensive polyhydromethylsiloxane and a number of titanium catalysts under ambient conditions.^{13,14} We chose dicyclopentadienyltitanium difluoride as the catalyst since it is easy to prepare from the commercially available dichloride and sodium fluoride in water at 50°C, followed by thorough drying.^{14,15} The catalyst was dissolved in anhydrous tetrahydrofuran and the polyhydromethylsiloxane added. The mixture was heated to 50°C, whereupon there was brief, rapid gas evolution (presumably hydrogen) and the mixture turned blue, indicative of the formation of a titanium (III) species.¹⁶ The lactone (**13**) was then added at room temperature and the mixture stirred until the reduction was complete. We employed 4 mol% catalyst as the reaction did not go to completion with 2 mol%. Work-up consisted of dilution with seven volumes of tetrahydrofuran and slow addition of dilute aqueous sodium hydroxide, which hydrolyses the silylated lactol and destroys excess hydride equivalents, liberating hydrogen. Work-up as a dilute solution is essential to avoid precipitation of a silicone polymer that occludes product and leads to lower yields. We were thus able to prepare >100g of **14**, as a 4:1 mixture of anomers, in 80% yield.

Scheme 3

With lactol (**14**) in hand, we then performed an aldol reaction with aqueous formaldehyde to give **15** as a single stereoisomer at C-2 in 55% yield. This transformation has been described for the related 5-*O*-trityl derivative.¹⁷ The reaction was quite slow, presumably because the formaldehyde and open-chain ribose aldehyde are in low concentration. The product (**15**) was isolated as a pair of anomers (2:1 ratio). The stereochemistry obtained at C-2 can be readily explained by Figure 1, in which the formaldehyde preferentially approaches the enol syn to the adjacent hydrogen, that being the smaller substituent.

Figure 1

The key transformation in the synthesis was introduction of the fluorine atom. Initially, we tried to activate the primary alcohol of **15** *via* tosylate (**16**) (Scheme 4).

Scheme 4

The anomeric hydroxyl of **16** was protected as the pivalate ester from which a single anomer (**17**) was obtained by recrystallisation. Heating **17** with tetrabutylammonium fluoride in tetrahydrofuran failed to yield any **18**, which was perhaps not entirely unexpected given the steric hindrance and electronic deactivation by the oxygen substituents. Other conditions were tried (e.g. caesium fluoride as fluoride source, DMF or DMSO solvent, at different temperatures) but all gave complex mixtures. There was evidence for both loss and migration of the pivalate ester. Although compound (**17**) was synthetically a dead-end, it was nevertheless useful for establishing the relative stereochemistry at C-1 and C-2 relative to C-5. Measurement of a series of nuclear Overhauser effects and long-range proton-carbon correlations were employed to confirm that the aldol reaction (**14** – **15**) had indeed proceeded with the intended selectivity. Spectra were measured using a Varian Inova 500 MHz spectrometer in deuterochloroform. Assignment of the ^1H and ^{13}C nmr spectra was made using a combination of proton-proton correlation experiments (COSY/TOCSY) and one bond proton-carbon correlations (HSQC). Stereochemical information was gathered from long-range proton-carbon (HMBC), 1D n.O.e. and 2D n.O.e. (ROESY/NOESY) experiments. The proton and carbon shift assignments are in the experimental section. The key correlations used to assign the stereochemistry are shown in Figure 2.

from ROESY/NOESY

from HMBC

Figure 2

We therefore turned our attention to DAST (diethylaminosulfur trifluoride), which is a powerful reagent for converting alcohols into fluorides,¹⁸ including those imbedded in a monosaccharide, without cleavage of ketal protecting groups.¹⁹ Thus, treatment of **15** with two equivalents of DAST gave difluoride (**19**) as a 45:55 mixture of anomers in good yield (Scheme 5). The ^{19}F nmr spectrum of **19** showed two pairs of signals at δ -120.8 (d, J 64 Hz), and -129.1 (d, J 63 Hz), corresponding to the anomeric fluorine, and -230.7 (t, J 48 Hz), and -231.2 (t, J 47 Hz), corresponding to the fluoromethyl. Methods for converting **19** into **10** were then sought, although direct glycosyl fluoride to nucleoside conversion is known.²⁰

Scheme 5

Attempts to convert **19** directly into **10** were unsuccessful. A mixture of acetic anhydride and acetic acid at room temperature only returned starting material, and addition of a strong acid such as boron trifluoride or sulphuric acid to this mixture produced **20** without cleaving the ketal. However, hydrolysis under relatively forcing conditions (50% aq. TFA, 20°C or HOAc/H₂O/Dowex ion-exchange resin H⁺ form, 50°C) yielded triol (**21**) quantitatively. Acetylation then gave **10** in 72% overall yield from **15**.¹² The anomers of **10** were readily separated by column chromatography, thereby facilitating their characterisation (see Experimental Section).

Conclusions

We have developed a relatively short, high yielding synthesis of a novel protected ribose, which should be a convenient intermediate for preparing a range of nucleoside analogues.

Experimental Section

General Procedures. Melting points were determined using open glass capillary tubes and a Gallenkamp melting point apparatus and are uncorrected. Spectroscopic data were recorded on a Perkin-Elmer 983 (IR), Finnigan Mat. Navigator (LRMS, either positive (ES⁺) or negative (ES⁻) electrospray mode), and Varian Unity Inova (¹H NMR 300, 400 or 500 MHz) instruments and are consistent with the assigned structures. Combustion analyses were performed by Exeter Analytical (UK) Limited, Uxbridge, Middlesex, U.K. Optical rotations were performed by

Warwick Analytical Service Ltd., Coventry, U.K. using a Perkin-Elmer 341 polarimeter. Accurate mass determinations for molecular ions were obtained using a commercially available Apex II Fourier Transform Mass Spectrometer (Bruker Daltonics, Inc. Billerica, MA, USA) equipped with a 4.7 Tesla, passively shielded, superconducting magnet and an electrospray ionisation source (ESI), used in positive ion mode (Analytica of Branford, Branford, CT, USA) and calibrated using sodium trifluoroacetate. Ether refers to diethyl ether. All reactions were conducted under a positive pressure of dry nitrogen unless stated otherwise. Anhydrous solvents were purchased from Sigma-Aldrich and used directly. Flash chromatography refers to column chromatography on silica gel (Kieselgel 60, 230-400 mesh, from E. Merck, Darmstadt). Kieselgel 60 F₂₅₄ plates from E. Merck were used for TLC, and compounds were visualised using u.v. light or 0.5% aqueous potassium permanganate solution.

2,3-*O*-Isopropylidene-D-ribo-1,4-lactone (12). A mixture of **11** (220 g, 1.49 mol), anhydrous cupric sulphate (500 g, 3.13 mol) in anhydrous acetone (2.5 L) was stirred mechanically at 20°C for 18 h. Celite (ca. 100 g) was added and the mixture was filtered. Removal of the solvent under reduced pressure gave **12** as a cream-coloured solid (274.6 g, 98%). NMR data were identical to the published data.¹⁰ δ_{H} (CDCl₃, 400 MHz) 1.38 and 1.41 (3H, s, CH₃), 3.65-3.75 (2H, m, H-5), 4.47 (1H, s, OH), 4.62 (1H, t, J 2.0 Hz, H-4), 4.78 (1H, d, J 5.5 Hz, H-3), 4.82 (1H, d, J 5.5 Hz, H-2); m/z (ES⁺) 189 (MH⁺).

5-*O*-Benzyl-2,3-*O*-isopropylidene-D-ribo-1,4-lactone (13)¹¹. Sodium hydride (30 g, 60% oil dispersion, 0.75 mol) was added in portions to a stirred solution of **12** (110 g, 0.58 mol) in anhydrous dimethylformamide (1 L) at 0°C. After 1 h, when gas evolution had almost completely ceased, benzyl bromide (75 mL, 0.63 mol) was added, maintaining the temperature below 10°C. The mixture was allowed to warm to room temperature and stirred for another 20 h. Glacial acetic acid (20 mL) was added, followed by saturated aqueous sodium bicarbonate (1 L). The product was extracted into ether:pentane (2:1, 3 × 1.5 L). The extracts were dried (MgSO₄) and concentrated under reduced pressure to give **13** as brown oil (135 g, 83%). δ_{H} (CDCl₃, 400 MHz) 1.34 (3H, s), 1.44 (3H, s), 3.65 (1H, dd, J 2 and 10.5 Hz), 3.68 (1H, dd, 2.5 and 10.5 Hz), 4.43 (1H, d, J 12 Hz), 4.52 (1H, d, J 12 Hz), 4.61 (1H, t, J 2 Hz), 4.67 (1H, m), 4.75 (1H, d, J 5.5 Hz), 7.31 (5H, m). m/z (ES⁺) 579 (2MNa⁺), 301 (MNa⁺), 296 (MNH₄⁺).

5-*O*-Benzyl-2,3-*O*-isopropylidene-D-ribofuranose (14)¹⁴. Polymethylhydrosiloxane (85 ml) was added to a solution of dicyclopentadienyltitanium difluoride (2.8 g, 13 mmol) in anhydrous tetrahydrofuran (300 ml) at room temperature under nitrogen. The yellow solution was warmed to ca. 30°C, whereupon the solution turned dark-blue and evolved a burst of gas (presumably hydrogen). The solution was cooled to 0°C and a solution of 5-*O*-benzyl-2,3-*O*-isopropylidene-D-ribo-1,4-lactone (**13**) (80.0 g, 0.29 mol) in anhydrous tetrahydrofuran (200 ml) was added dropwise to the solution resulting in the slow evolution of more gas. The resulting solution was stirred at room temperature for 20 h. The solution was then poured into tetrahydrofuran (3.5 L) and treated with excess 1N aqueous sodium hydroxide (NB effervescence). After being stirred for 1 h, the layers were separated and the aqueous phase extracted twice with ether. The combined organic phases were dried (Na₂SO₄), concentrated under reduced pressure and

purified by flash chromatography (gradient elution with ether:pentane = 1:1 to 100% ether) to give **14** (65g, 80%), as a colourless oil. δ_{H} (CDCl_3 , 400 MHz) major anomer: 1.20 (3H, s), 1.37 (3H, s), 3.47 (1H, dd, J 3.8 and 10.5 Hz, H-5), 3.55 (1H, dd, J 3 and 10.5 Hz, H-5), 3.82 (1H, br d, J 11 Hz, OH), 4.27 (1H, m, H-4), 4.40 (1H, d, J 6 Hz, H-2), 4.45 (1H, d, J 12 Hz, PhCH_2), 4.52 (1H, d, J 12 Hz, PhCH_2), 4.63 (1H, d, J 6 Hz, H-3), 5.17 (1H, d, J 11 Hz, H-1), 7.26-7.35 (5H, complex); minor anomer: 1.27 (3H, s), 1.44 (3H, s), 3.42 (1H, dd, J 3 and 10 Hz, H-5), 3.51 (1H, dd, J 3 and 10 Hz, H-5), 4.11 (1H, m, H-4), 4.36 (1H, d, J 12 Hz, PhCH_2), 4.44 (1H, d, J 12 Hz, PhCH_2), 4.47 (1H, dd, J 4.5 and 6.5 Hz, H-2), 4.64 (1H, dd, J 6 and 1 Hz, H-3), 5.36 (1H, dd, J 4.5 and 11 Hz, H-1), 7.26-7.35 (5H, complex); m/z (ES^+) 583 (2MNa^+), 303 (MNa^+).

5-O-Benzyl-2-C- β -hydroxymethyl-2,3-O-isopropylidene-D-ribofuranose (15). Formaldehyde (180 mL, 33% aqueous solution, 1.98 mol) was added to a solution of 5-O-benzyl-2,3-O-isopropylidene-D-ribofuranose (**14**) (130 g, 0.46 mol) in methanol (50 mL). Anhydrous potassium carbonate (40 g, 0.29 mol) was added and the mixture was heated at 60°C under nitrogen for 2 days. The mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate (1 L) and saturated aqueous sodium bicarbonate (1 L). The aqueous layer was extracted with ethyl acetate (1 L) and the combined organic solutions were washed with saturated brine (1 L), dried (Na_2SO_4) and concentrated under reduced pressure to give an orange oil (147 g). Purification by repeated column chromatography (first column eluted with dichloromethane:methanol = 95:5, second column eluted with pentane:ether = 2:1) gave **15** (79 g, 55%), as a colourless, highly viscous oil. δ_{H} (CDCl_3 , 400 MHz) (mixture of anomers) 1.39 (3H, s), 1.44 (3H, s), 1.47 (3H, s), 1.55 (3H, s), 3.55 (1H, dd, J 3 and 10 Hz, H-5), 3.58 (1H, dd, J 3 and 10 Hz, H-5), 3.61 (1H, dd, J 3 and 10 Hz, H-5), 3.65 (1H, dd, J 3 and 10 Hz, H-5), 3.66 (1H, d, J 12 Hz, H-2'), 3.69 (1H, d, J 12 Hz, H-2'), 3.74 (1H, d, J 12 Hz, H-2'), 3.77 (1H, d, J 12 Hz, H-2'), 4.21 (1H, m, H-4), 4.33 (1H, m, H-4), 4.46 (1H, d, J 11.5 Hz, PhCH_2), 4.51 (3H, m, H-3 and 2 $\times$ PhCH_2), 4.60 (1H, d, J 11.5 Hz, PhCH_2), 4.62 (1H, m, H-3), 5.20 (1H, s, H-1), 5.26 (1H, s, H-1), 7.25-7.37 (10H, complex); m/z (ES^+) 659 (2MH^+), 349 (MH^+); Found: m/z 333.1307050 (MNa^+), $\text{C}_{16}\text{H}_{22}\text{NaO}_6$ requires 333.1308595.

(5-O-Benzyl-1-hydroxy-2,3-O-isopropylidene-D-ribofuranos-2 β -yl)methyl

4-methylbenzenesulfonate (16). A solution of p-toluenesulphonyl chloride (4.2 g, 21.6 mmol) in dichloromethane (10 mL) was added to a stirred solution of 5-O-benzyl-2-C- β -hydroxymethyl-2,3-O-isopropylidene-D-ribofuranose (**15**) (4.5 g, 14.4 mmol) in anhydrous pyridine (20 mL) at room temperature, and the resulting mixture was stirred at room temperature for 48 h. The solvents were removed under reduced pressure and the residue was dissolved in ether (100 mL) and washed with water (50 mL), 1N hydrochloric acid (50 mL), and saturated aqueous sodium bicarbonate (50 mL). The solution was dried (Na_2SO_4) and concentrated under reduced pressure to give an orange oil (7.0 g), which was used to make **17** without further purification. A sample was purified by flash chromatography (eluting with dichloromethane:methanol = 95:5) to give a colourless glass. δ_{H} (CDCl_3 , 400 MHz) approx. 3:1 mixture of anomers. Major anomer: 1.34 (3H, s), 1.41 (3H, s), 2.41 (3H, s), 3.55 (1H, dd, J 2.5 and 10.5 Hz), 3.62 (1H, dd, 2.5 and 10.5 Hz), 3.97 (1H, d, J 11.5 Hz), 4.19 (1H, d, J 11.5 Hz),

4.32 (1H, m), 4.53 (1H, d, J 11 Hz), 4.54 (1H, d, J 12 Hz, OH), 4.57 (1H, d, J 11 Hz), 4.66 (1H, s), 5.43 (1H, d, J 12 Hz), 7.22 –7.38 (7H, complex), 7.73 (2H, d, J 8.5 Hz); Minor anomer: 1.39 (3H, s), 1.49 (3H, s), 2.39 (3H, s), 3.48 (1H, dd, J 2 and 10 Hz), 3.55 (1H, dd, 2 and 10 Hz), 3.69 (1H, br d, J 10 Hz, OH), 4.00 (1H, d, J 10.5 Hz), 4.15 (1H, m), 4.23 (1H, d, J 10.5 Hz), 4.39 (1H, d, J 12 Hz), 4.44 (1H, d, J 12 Hz), 4.65 (1H, s), 5.09 (1H, br d, J 10 Hz), 7.22 –7.38 (7H, complex), 7.67 (2H, d, J 8.5 Hz); m/z (ES^+) 482 (MH^+).

(5-*O*-Benzyl-2,3-*O*-isopropylidene-1-*O* - β -pivaloyl-D-ribofuranos-2 β -yl)methyl 4-methylbenzenesulfonate (17).

A solution of pivaloyl chloride (2.6 g, 21.6 mmol) in dichloromethane (5 mL) was added to a stirred solution of (5-*O*-benzyl-1-hydroxy-2,3-*O*-isopropylidene-D-ribofuranos-2 β -yl)methyl 4-methylbenzenesulfonate (**16**) (4.5 g, 9.7 mmol) in anhydrous pyridine (10 g) at room temperature, and the resulting mixture was stirred at room temperature for 18 h. The mixture was diluted with ether (100 mL) and washed with saturated aqueous sodium bicarbonate (50 mL), water (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give an oil (6.2 g), which solidified on standing. Recrystallisation from toluene gave compound (**17**) (2.8 g, 53%), as fluffy, colourless needles. δ_H ($CDCl_3$, 500 MHz) 1.13 (9H, s, $C(CH_3)_3$), 1.27 (3H, s, $OC(CH_3)O$), 1.46 (3H, s, $OC(CH_3)O$), 2.44 (3H, s, $ArCH_3$), 3.40 (1H, dd, J 8 and 10 Hz, ribose H-5), 3.48 (1H, dd, J 5 and 10 Hz, ribose H-5), 4.13 (1H, d, J 10 Hz, CH_2OTs), 4.26 (1H, d, J 10 Hz, CH_2OTs), 4.39 (1H, dd, J 5 and 8 Hz, ribose H-4), 4.49 (1H, d, J 12 Hz), 4.54 (1H, d, J 12 Hz), 4.62 (1H, s, ribose H-3), 6.15 (1H, s, ribose H-1), 7.31-7.35 (7H, complex, $Ar-H$), 7.79 (2H, d, J 8 Hz). δ_C ($CDCl_3$, 125 MHz) 21.8 ($C_6H_4CH_3$), 27.0 (3C, $C(CH_3)_3$), 27.3 ($OC(CH_3)O$), 27.8 ($OC(CH_3)O$), 38.9 ($C(CH_3)_3$), 68.4 (CH_2OTs), 70.1 (ribose C-5), 73.7 (CH_2Ph), 84.2 (ribose C-3), 86.2 (ribose C-4), 92.4 (ribose C-2), 102.0 (ribose C-1), 114.9 ($OC(CH_3)O$), 128.1 ($2 \times C-2$, $PhCH_2$), 128.2 (C-4, $PhCH_2$), 128.3 ($2 \times C-3$, $PhCH_2$), 128.7 ($2 \times C-2$, Ts), 130.0 ($2 \times C-3$, Ts), 132.9 (C-1, Ts), 137.6 (C-1, $PhCH_2$), 145.3 (C-4, Ts), 176.4 (C=O).

5-*O*-Benzyl-2-*C*- β -fluoromethyl-2,3-*O*-isopropylidene-D-ribofuranosyl fluoride (19). DAST (13 mL, 99.2 mmol) was added dropwise to a stirred solution of **15** (13.0 g, 41.9 mmol) in dichloromethane (50 mL) at $-78^\circ C$. The mixture was allowed to warm to room temperature overnight with the cooling bath in place. After 20 h, the orange solution was poured slowly into a vigorously stirred mixture of ice and excess saturated aqueous sodium bicarbonate. When effervescence had ceased, the product was extracted into pentane (200 mL). The extract was washed with aqueous sodium hydroxide (2N), brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a brown oil (12.8 g). Purification by flash chromatography (eluting with pentane:ether = 6:1) gave **19** (10.5 g, 80%), as pale yellow oil. δ_H ($CDCl_3$, 400 MHz) approx. 55:45 mixture of anomers. 1.39 (3H, s, CH_3 major anomer), 1.40 (3H, s, CH_3 minor anomer), 1.45 (3H, s, CH_3 minor anomer), 1.55 (3H, s, CH_3 major anomer), 3.45 (1H, ddd, J 10.2, 7 and 1.8 Hz, H-5 minor anomer), 3.58 (1H, J 10.2 and 5.3 Hz, H-5 minor anomer), 3.63 (1H, dd, J 10.8 and 3 Hz, H-5 major anomer), 3.66 (1H, dd, J 10.8 and 3 Hz, major anomer), 4.40-4.65 (12H, complex, CH_2F , H-3, H-4, $PhCH_2$ both anomers), 5.40 (1H, d, J 63 Hz, H-1, major anomer), 5.76 (1H, J 64 Hz, H-1, minor anomer), 7.29 (10H, m, ArH , both anomers). δ_F

(CDCl₃, 376 MHz) –120.8 (d, J 64 Hz), –129.1 (d, J 63 Hz), –230.7 (t, J 48 Hz), –231.2 (t, J 47 Hz). *m/z* (ES⁺) 332 (MNH₄⁺), 339 (M⁺ – OAc). Found: *m/z* 337.1217330 (MNa⁺), C₁₆H₂₀F₂NaO₄ requires 337.1221866.

5-*O*-Benzyl-2-*C*-β-fluoromethyl-D-ribofuranose (21). A solution of **19** (5.00 g, 15.9 mmol) in 50% aqueous trifluoroacetic acid (16 mL) was stirred at 20°C for 3 d. The mixture was neutralised by the addition of solid sodium bicarbonate and the solvent was removed under reduced pressure. The residue was adsorbed on silica gel and applied to the top of a silica gel pad. Elution with ether gave **21** as a gum (4.55 g, 100%), which was carried on to the next step without further purification. δ_H (CDCl₃, 400 MHz) approx. 2.5:1 mixture of anomers. 3.67 (2H, m, H-5 both anomers, and 1H, H-3, minor anomer), 3.90 (1H, d, J 6.7 Hz, H-3 major anomer), 4.08 (1H, dt, J 4 and 8 Hz, H-4 major anomer), 4.11 (1H, dt, J 2.6 and 5 Hz, H-4 minor anomer), 4.34 (1H, dd, J 10 and 45 Hz, CH₂F, major anomer), 4.38 (1H, dd, J 10 and 45 Hz, CH₂F, major anomer), 4.53 (1H, J 13 Hz, PhCH₂ major anomer), 4.54 (1H, dd, J 10 and 45 Hz, CH₂F minor anomer), 4.58 (1H, J 13 Hz, PhCH₂ major anomer and 1H, J 11 Hz, minor anomer), 4.62 (1H, d, J 11 Hz, PhCH₂ minor anomer), 4.70 (1H, dd, J 10 and 45 Hz, CH₂F, minor anomer), 5.14 (1H, s, H-1 minor anomer), 5.31 (1H, s, H-1 major anomer), 7.29 (10H, m, ArH, both anomers).

5-*O*-Benzyl-2-*C*-β-fluoromethyl-1,2,3-tri-*O*-acetyl-D-ribofuranose (10). To a solution of **21** (4.50 g, 16.5 mmol), triethylamine (5.05 g, 50 mmol), 4-(*N,N*-dimethylamino)pyridine (2.01 g, 16.5 mmol) in dichloromethane (30 mL) was added acetic anhydride (5.05 g, 49.5 mmol) and the resulting solution was stirred at 20°C for 24 h. The solvent was removed under reduced pressure and the residue was partitioned between water and ether. The ether extracts were washed with dilute aqueous sodium bicarbonate, dried (Na₂SO₄) and evaporated to give **10** (6.0 g, 91%) as brown oil. A portion was purified by flash chromatography, eluting with diethyl ether/pentane (1:1) to give first the β-anomer as a colourless solid, m.p. 59–60°C; δ_H (CDCl₃, 400 MHz) 1.89, 2.01 and 2.09 (each 3H, s, CH₃O), 3.52 (1H, dd, J 11 and 3.7 Hz, H-5), 3.64 (1H, dd, J 11 and 3.7 Hz, H-5), 4.30 (1H, dt, J 3.7 and 7.6 Hz, H-4), 4.50 (2H, AB quartet, J 13 Hz, PhCH₂), 4.84 (1H, dd, J 10 and 47 Hz, CH₂F), 5.23 (1H, dd, J 10 and 47 Hz, CH₂F), 5.50 (1H, d, J 7.6 Hz, H-3), 6.30 (1H, s, H-1), 7.29 (5H, m, ArH); δ_C (CDCl₃, 75 MHz) 20.6, 20.9, 21.5 (CH₃), 69.0 (C-5), 71.7 (d, J 5 Hz, C-3), 73.4 (PhCH₂), 80.1 (d, J 170 Hz, C-2'), 80.2 (C-4), 86.8 (d, J 18 Hz, C-2), 97.4 (d, J 3.5 Hz, C-1), 127.6 (2C, Ar), 127.7 (Ar), 128.4 (2C, Ar), 137.8 (Ar), 168.6, 169.6, 170.2 (C=O); δ_F (CDCl₃, 376 MHz) –233.5 (t, J 47 Hz); *m/z* (ES⁺) 416 (MNH₄⁺), 339 (M⁺ – OAc); Found: C, 57.29; H, 5.81; C₁₉H₂₃FO₈ requires C, 57.28; H, 5.82%; [α]_D²⁵ = –0.27° (c = 0.375, MeOH).

Second eluted was the α-anomer, colourless solid, m.p. 58–60°C; δ_H (CDCl₃, 400 MHz) 2.06, 2.07 and 2.08 (each 3H, s, CH₃O), 3.70 (1H, dd, J 11 and 3 Hz, H-5), 3.77 (1H, dd, J 11 and 3 Hz, H-5), 4.19 (1H, q, J 3 Hz, H-4), 4.54 (2H, s, PhCH₂), 4.75 (1H, dd, J 10 and 47 Hz, CH₂F), 4.82 (1H, dd, J 10 and 47 Hz, CH₂F), 5.32 (1H, d, J 3.7 Hz, H-3), 6.49 (1H, s, H-1), 7.29 (5H, m, ArH); δ_C (CDCl₃, 75 MHz) 20.6 (CH₃), 20.9 (2C, CH₃), 68.5 (C-5), 69.6 (d, J 5 Hz, C-3), 73.8 (PhCH₂), 80.0 (d, J 177 Hz, C-2'), 82.8 (d, J 17.5 Hz, C-2), 84.1 (C-4), 94.9 (d, J 6 Hz, C-1), 127.6 (2C, Ar), 127.8 (Ar), 128.4 (2C, Ar), 137.5 (Ar), 169.1 (2C, C=O), 169.7 (C=O); δ_F

(CDCl₃, 376 MHz) -233.6 (t, J 47 Hz); m/z (ES⁺) 416 (MNH₄⁺), 339 (M⁺ – OAc); Found: m/z 421.1269700 [MNa⁺], C₁₉H₂₃FO₈ requires 421.1269170; Found: C, 57.29; H, 5.80; C₁₉H₂₃FO₈ requires C, 57.28; H, 5.82%; $[\alpha]^{25}_D = +66.1^\circ$ (c = 0.295, MeOH).

Assignment of the H-1 configuration was made on the basis of the H-3 coupling constants; as suggested in the literature,¹⁷ values of <3 Hz and > 5Hz are typical for α - and β -anomers, respectively. The coupling constants J_{3,4} were found to be 3.7 and 7.6 Hz, consistent with α - and β -stereochemistry, respectively.

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