# Some intramolecular rearrangements when pentofuranoses are treated with diethylaminosulphur trifluoride (DAST)

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## Abstract

Treatment of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside with DAST gave a good yield of 2,3-*O*-isopropylidene-5-*O*-methyl-β-D-ribofuranosyl fluoride in which the methoxy group had migrated from C-1 → C-5 and been replaced with retention of configuration by fluorine. The corresponding aldehyde when treated under similar conditions underwent a similar migration to give 5-deoxy-5-fluoro-2,3-*O*-isopropylidene-5-*O*-methyl-β-D-ribofuranosyl fluoride. A similar migration occurred with methyl 2′,3′-di-*O*-acetyl-β-D-ribofuranoside and with acetyl 2,3-*O*-isopropylidene-D-ribofuranose but not with 1,2,3-tri-*O*-acetyl-D-ribofuranose. Thus the migration depends upon the migratory aptitude of the substituent at C-1 and the conformation of the furanose ring. Two ribofuranosyl fluorides were used as starting materials from which to make nucleosides by the method of Noyori and Hayoshi.

## Introduction

Fluorinated nucleosides, particularly those containing F in the sugar moiety, have recently been the subject of intense interest as evidenced by the publication of a recent review paper evaluating the anti-HIV activity of over 100 such nucleoside analogues [1].

There are two fundamentally different approaches to the synthesis of such analogues and both have been used. The first requires the synthesis of a suitable carbohydrate derivative with which to condense the heterocyclic base moiety and the second involves the fluorination of a preformed nucleoside. Both approaches have their advantages and disadvantages; for example modern mild fluorinating agents have enabled considerable progress to be made by fluorination at the nucleoside level but solvent compatibility, lability and the problems of undertaking a structure–activity relationship study with various fluorinated sugar moieties mean that, despite having to separate α- and β-nucleosides, it is often easier to obtain a range of compounds by the condensation of different bases with fluorinated carbohydrates.

The discovery of diethylaminosulphur trifluoride (DAST) [2] has resulted in a revolution in the case of the preparation of hitherto difficult-to-prepare

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analogues associated with the transformations ROH → RF and RCHO → $RCHF_2$. A series of excellent review articles has covered recent advances in this field [3].

We were interested in the synthesis of nucleosides where the normal 5′-$CH_2OH$ group would be replaced by the isosteric and isopolar $CF_2H$ group, which is likely to be involved in hydrogen bonding both as a hydrogen acceptor and, to a lesser extent, as a hydrogen donor. The required analogue has been synthesized in the purine field by McCarthy and coworkers [4, 5], where it was used as an intermediate in the preparation of an SAH-hydrolase inhibitor, but attempts to repeat similar experiments in the pyrimidine field by treatment of a nucleoside-5′-aldehyde with DAST resulted in $O^2$,5′-anhydronucleoside formation (AEL, OWH, PLC and RTW to be submitted elsewhere). We have thus investigated methods for the synthesis of suitable sugar derivatives with which to condense pyrimidine bases to give the corresponding nucleoside analogues. During the course of this work, we discovered some unusual if not totally unprecedented migration reactions which we present here.

## Results and discussion

Starting from D-ribose (**1**), methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**2**) was prepared in high yield. Although this is a known compound, it is important here to describe precisely the method used and particularly the characterization which established the purity of the configuration isolated. Thus compound **2a** could be shown to be exclusively the β-anomer.

Oxidation of this compound to the corresponding aldehyde (**3**) was successfully achieved using chromium trioxide/pyridine [6]. This gave a high yield of a stable aldehyde, the NMR spectrum of which exhibited an aldehyde proton at δ 9.5 ppm which integrated for one proton and thus, unlike many similar aldehydes, does not readily form a hydrate. Other methods of oxidation, notably the Pfitzner–Moffatt, pyridinium chlorochromate, sulphur trioxide–pyridine–DMSO complex and the Swern oxidation, all failed to give satisfactory products. A recent paper describing the oxidation of compound **2a** to **3** using pyridium dichromate commented on the production of a lactone and a dimer [7], but we have seen no sign of either compound in the present investigation.

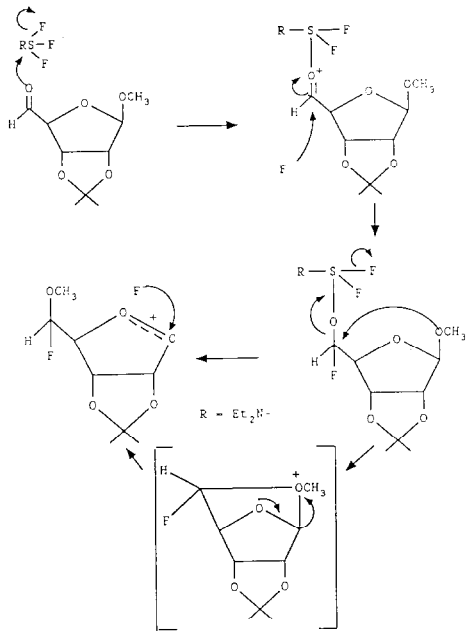
The aldehyde **3** could also be characterized as its crystalline *N*,*N*-diphenylethylenediamino derivative **4** and indeed, with many such aldehydes, this derivative has to be made in order to isolate the aldehyde, the latter being regenerated by the addition of toluene sulphonic acid. However in the present case, the aldehyde was itself isolable and stable.

The aldehyde **3** was then treated at room temperature with 1.2 equiv. diethylaminosulphur trifluoride (DAST). The starting material disappeared within 15 min and a more polar compound was produced. By varying the temperature of the reaction (−78 °C to 20 °C), the reaction time and the

amount of DAST used (up to 2 equiv.), no significant difference in the amount of reaction product isolated was achieved and this could be obtained as a clear gum.

The NMR spectrum, although complex, was clearly not that of the expected 5-difluoromethyl derivative **6**. The $^{1}H$ NMR spectrum at 400 MHz with decoupling showed the compound to be the ribofuranosyl fluoride **5**, where one fluorine atom is present at C-5 and the methoxy group has migrated from position C-1 to C-5. The compound is thus a mixture of diastereoisomers (C-5) and a mechanism for its formation is given in Scheme 1. Only the $\beta$-fluorides are produced, presumably because the isopropylidene group is preventing attack from the lower face. The $^{19}F$ NMR spectrum shows two signals for each diastereoisomer at $\delta$ −117 (F-1) and $\delta$ −138 (F-5) ppm for one isomer and $\delta$ −125 (F-1) and $\delta$ −137 (F-5) ppm for the other.

A paper by Bobek and coworkers in 1977 [8] claimed to have synthesized the required 5-difluoromethyl compound **6** from compound **3** using DAST. Unfortunately the short note gives no experimental details for this particular compound which was the only furanose studied; all the remaining compounds were pyranoses. The compound identified here does not have the same MS or $^{19}F$ NMR data as quoted in the paper and we have no explanation for the discrepancy observed. We note that the authors claimed to have been about to use the compound for the synthesis of *gem*-difluoronucleosides but, to our knowledge, nothing further on this subject has been published during the past 14 years.



Scheme 1.

However, there are many examples of migrations occurring when carbohydrates are treated with DAST, although most of the examples involve pyranose rings or 1,2-migration. Thus Kovac *et al.* [9] reported that when methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**7**) is treated with DAST, a rapid reaction ensues which involves participation of the axial methoxyl group of C-1 to give the 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-methyl-α,β-D-glycopyranosyl fluorides (**8**).

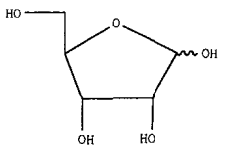
In ribofuranosides, alkoxy migration resulting in the displacement of a 5-trifluoromethanesulphonyloxy group from ribofuranosides has been reported by Iyer and Horowitz [10]. Further examples of 1,2-migration in a furanose ring have been documented by Hasegawa *et al.* [11], aryl migration in the presence of DAST has been reported [12] and other examples of 1,2-migration have also been given [13].

Following this unexpected result, we decided to investigate whether this was a general phenomenon and, incidentally, a convenient method for the production of β-ribofuranosyl fluorides. Thus compound **2a** itself was treated with DAST and indeed the only isolated product was the corresponding ribosyl fluoride **9a**. That migration of the $-OCH_3$ group from C-1 to C-5 had indeed occurred was proved by using the starting material **2b** when the only product isolated was **9b**.

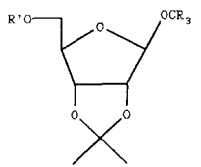
The structures of these compounds were established unequivocally from decoupling and NOE difference spectroscopy experiments at 400 MHz.

The further generality of the phenomenon was investigated by treating acetyl 2,3-*O*-isopropylidene-β-D-ribofuranose (**10b**) with DAST. The starting material was synthesized following standard procedures and, although only the β-anomer was present until the last stage, removal of the t-butyldiphenylsilyl group from C-5 resulted in the production of an inseparable mixture of α- and β-anomers in the ratio 1:3.5. Treatment of this mixture with DAST gave the 5-*O*-acetyl-2,3-*O*-isopropylidene-α,β-D-ribofuranosyl fluorides (**11**) in high yield showing that, once again, migration had occurred. As it is unlikely that the α-acetyl anomer could undergo migration, it is assumed that under acidic conditions the α- and β-anomers are in equilibrium and migration occurs via the β-anomer. The presence of α-fluoro sugar can be explained by the presence of a bridged intermediate (see Scheme 1).

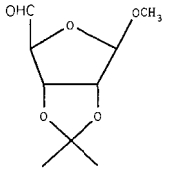
It is well known [14] that the presence of the 2,3-isopropylidene substituent on a D-sugar with a ribofuranose configuration reduces the distance between the β-C-1 and C-5 substituents, and hence could be expected to assist the migration described above. Thus we next investigated the reaction of acetyl 2,3-di-*O*-acetyl-α,β-D-ribofuranose (**12**) with DAST. With the previously described conditions, no reaction had occurred with 3 equiv. DAST after 24 h. When warmed to 30 °C for 1 h, it was possible to isolate a low yield (38%) of a product which was characterized as the 5-deoxy-5-fluoro compound **13**. The $^{19}F$ NMR spectrum was quite characteristic as it lacked the doublet at $\delta$ −116 ppm indicative of a fluoride atom at C-1 and instead has a doublet of triplets at $\delta$ −232 ppm. The product was a mixture of diastereoisomers which could be separated into the individual α- and β-anomers. These



(1)



(2) a, R=R'=H
b, R=D, R'=H
c, R=H, R'=tBDPS



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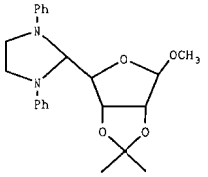

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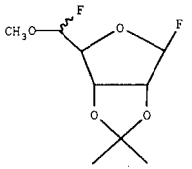

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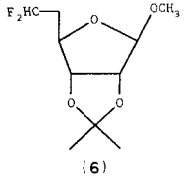

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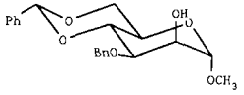

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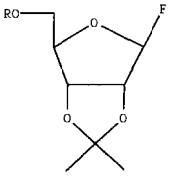
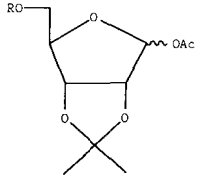
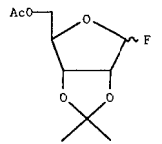


(9) a: R=$CH_3$
b: R=$CD_3$



(10) a: R=tBDPS
b: R=H



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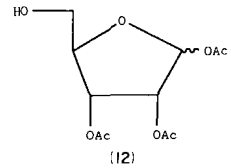

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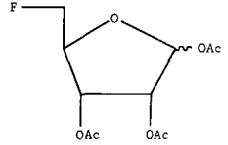
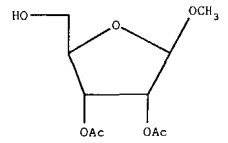
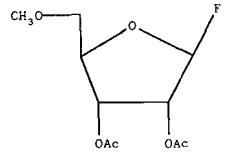


(13)



(14)



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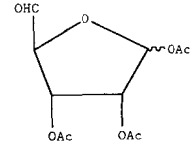

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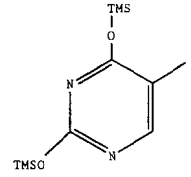
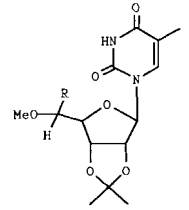


(17)



(18) a: R=H
b: R=F

compounds have been reported previously [15], but they had been prepared by acetylation of the corresponding 5-deoxy-5-fluoro derivative.

To determine whether the presence of 2- and 3-O-acetyl groups were sufficient to prevent migration, a preliminary experiment (data not shown) was performed by treating methyl 2,3-di-O-acetyl-β-D-ribofuranose (**14**) with DAST (1.2 equiv. at room temperature for 24 h). The compound isolated in 50% yield had a $^{19}F$ NMR spectrum containing a doublet at $\delta$ −116 ppm with a coupling constant $J_{F1-H1} = 61$ Hz, confirming that migration of the methoxy group had once again occurred to give compound **15**; only the β-anomer was isolated. Thus it appears that methoxy migrates sufficiently well not to require the advantageous conformation imposed by the presence of the isopropylidene group.

The conclusion to be drawn from this series of experiments was that a feasible way of producing the required sugar containing the 5-$CF_2H$ group would be to oxidize compound **12** to the corresponding aldehyde **16** and to treat this with DAST. By now we had had considerable experience in oxidizing a wide range of ribofuranoses with a wide variety of reagents. Despite this, all our attempts to achieve this oxidation failed to give a reasonable (> 40%) yield. The Pfitzner–Moffatt oxidation alone enabled the *N,N'*-diphenylethylenediamino derivative to be isolated as an α:β mixture (2:1) in 40% yield, but the aldehyde decomposed when regenerated.

Thus, at present, it has proved impossible to synthesise a suitable 5-$CF_2H$-containing ribofuranose from which nucleosides can be made by condensing this with a range of suitably protected bases.

Our successful attempts to synthesize such nucleosides will be described elsewhere. Using compounds **5** and **9a** and the method described by Noyori and Hayashi [16] for the synthesis of nucleosides from glycosyl fluorides using tetrafluorosilane, it was possible to isolate the corresponding nucleosides (**18b** and **18a** respectively) in reasonable yield when they were reacted with 2,4-bis-trimethylsilylthymine (**17**).

## Experimental

*General procedures*

Melting points were obtained on a Gallenkamp apparatus and are reported uncorrected. $^1H$ NMR spectra were recorded with JEOL FX90Q (90 MHz), JEOL GX270 (270 MHz) and Bruker AC200 (200 MHz), 300 (300 MHz) and 400 (400 MHz) spectrometers in $CDCl_3$ (unless otherwise stated), relative to an internal tetramethylsilane as a reference. $^{19}F$ NMR spectra were obtained with a JEOL FX90Q instrument using trichlorofluoromethane as an internal reference. EI or FAB mass spectra (samples dissolved in DMSO and 3-nitrobenzyl alcohol used as a matrix with sodium ion doping to give enhanced peaks where necessary) were obtained on a Kratos MS80 and a Kratos MS902 spectrometer. Samples for UV spectrophotometry were dissolved in spectroscopic grade ethanol and spectra were recorded on a Perkin-Elmer 552

spectrophotometer. Precoated, aluminium-backed, silica gel TLC plates (silica gel $F_{254}$, 0.2 mm thickness) were supplied by E. Merck, AG. Detection was achieved under UV light (254 nm) or by spraying with 30% $H_2SO_4$ in ethanol and heating. Column chromatography was performed on silica gel 60, 70–250 mesh, type 7734 or 230–400 mesh, type 9385 (Merck). Optical rotations were measured in ethanol at a constant temperature of 22 °C on a Perkin-Elmer 241 polarimeter.

*Methyl 2,3-O-isopropylidene-β-D-ribofuranoside (**2a**)*

To D-ribose (**1**) (9 g, 59.95 mmol) was added methanol (33 ml) and acetone (33 ml) followed by conc. HCl (0.9 ml), and the reaction mixture was heated under reflux for 5 h and then allowed to cool to room temperature. Water (90 ml) was added, the solution evaporated to half-volume under reduced pressure, poured into dichloromethane and the organic layer separated and worked-up in the usual way. The product (**2a**) was obtained as a clear oil (9.2 g, 75%): $[\alpha]_D^{22}$, −76.6° (*c*, 2.0, ethanol). $^1$H NMR (90 MHz) $\delta$: 1.3 (3H, s, C−$CH_3$); 1.45 (3H, s, C−$CH_3$); 3.1 (1H, bs, OH); 3.4 (3H, s, $OCH_3$); 3.65 (2H, d, H-5); 4.6 (1H, d, H-3); 4.8 (1H, d, H-2); 5.1 (1H, s, H-1) ppm. MS *m/z*: 205 $(M+H)^+$; 189 $(M^+-15)$. Anal.: Calc. for $C_9H_{16}O_5$: C, 52.8; H, 8.0%. Found: C, 52.5; H, 8.0%.

*Methyl 2,3-O-isopropylidene-β-D-ribo-1,4-pentodialdofuranoside (**3**)*

Chromium trioxide (3 g, 29.4 mmol) was added to a solution of dry dichloromethane (75 ml) and pyridine (5 ml), and the solution stirred until a brick-red solution formed (15 min). Compound **2a** (0.5 g, 2.4 mmol) dissolved in dry dichloromethane (2 ml) was then added to the chromium complex, the reaction stirred for 10 min and then poured into vigorously stirred ethyl acetate. The resulting mixture was then filtered through a silica column using ethyl acetate as eluent, and the filtrate evaporated under reduced pressure to give a white gummy solid which could be reprecipitated from ether petroleum ether (0.45 g, 90%). $^1$H NMR $\delta$: 1.35 (3H, s, C−$CH_3$); 1.5 (3H, s, C−$CH_3$); 3.4 (3H, s, O−$CH_3$); 4.4 (1H, s, H-4); 4.5 (1H, s, H-3); 5.0 (1H, s, H-2); 5.1 (1H, s, H-1); 9.5 (1H, s, CHO) ppm. MS *m/z*: 203 $(M+H)^+$. Anal.: Calc. for $C_9H_{14}O_5$: C, 53.5; H, 7.1%. Found: C, 53.2; H, 7.1%.

*Methyl-$d_3$-2,3-O-isopropylidene-β-D-ribofuranoside (**2b**)*

This was prepared as described above for compound **2a** except that deuteromethanol was used. The $^1$H NMR spectrum was identical except that the resonance at $\delta$ 3.4 ppm (O−$CH_3$) was missing. MS *m/z*: 231 $(M+Na^+)$. Anal.: Found: C, 51.0, H, 7.5%. $C_9H_{13}D_3O_5 \cdot 0.25H_2O$ required: C, 51.1; H, 7.8%.

*Methyl 5,5-(N,N′-diphenylethylenediamino)-2,3-O-isopropylidene-β-D-ribofuranoside (**4**)*

To compound **3** (0.5 g, 2.45 mmol) dissolved in dry acetonitrile (3 ml) was added *N,N*-diphenylethylenediamine (1.1 equiv., 2.70 mmol, 0.57 g) and

glacial acetic acid (0.3 ml), and the reaction stirred for 10 min before pouring into saturated sodium hydrogen carbonate (25 ml) followed by extraction with dichloromethane and work-up in the usual way. The resulting product was recrystallized from ethanol to give white needles (0.45 g, 46%): $[\alpha]_D^{22}$, −92.9° (*c*, 2.0, ethanol). $^1$H NMR (200 MHz) $\delta$: 1.3 (3H, s, C−$CH_3$); 1.4 (3H, s, C−$CH_3$); 3.4 (3H, s, O−$CH_3$); 3.6–3.9 (4H, s, 2×$CH_2$); 4.4 (1H, dd, H-3); 4.6 (1H, d, H-2); 4.8 (1H, dd, H-4); 5.0 (1H, s, H-1); 5.5 (1H, d, H-5); 6.6–7.3 (10H, m, 2×Ph) ppm. MS *m/z*: 397 $(M+H)^+$. Anal.: Calc. for $C_{23}H_{28}N_2O_4$: C, 69.8; H, 7.1; N, 7.1%. Found: C, 69.8; H, 6.9; N, 6.8%.

*5-Deoxy-5-fluoro-2,3-isopropylidene-5-*O*-methyl-β-*D*-ribofuranosyl fluoride (**5**)*

Diethylaminosulphur trifluoride (DAST, 2.98 mmol, 0.36 ml) was added dropwise to compound **3** (0.5 g, 2.48 mmol) dissolved in dry dichloromethane (10 ml) under dry nitrogen and the reaction followed by TLC. After 15 min, no starting material remained and the reaction was quenched with water (5 ml) and stirred for 5 min before pouring into saturated sodium hydrogen carbonate followed by work-up in the usual way. Following chromatography on silica gel with hexane/ethyl acetate (6:4), the title compound was isolated as a clear oil as a diastereoisomeric mixture, 0.31 g, 56%). $^1$H NMR (400 MHz) $\delta$: 1.36 (3H, s, C−$CH_3$); 1.46 (3H, s, C−$CH_3$); 3.58 (3H, d, O−$CH_3$); 4.32 and 4.28 (1H, d ($J_{H4-F5}$ = 16 Hz) of d ($J_{H4-H5}$ = 8 Hz) of d ($J_{H4-H3}$ = 4 Hz) of d ($J_{H4-F1}$ = 2 Hz), H-4); 4.75 (1H, t, H-2); 4.9 (1H, d ($J$ = 6 Hz), H-3); 5.18, 5.17, 5.01 and 4.99 (1H, d ($J_{H5-F1}$ = 2 Hz) of d ($J_{H5-H4}$ = 10 Hz) of d ($J_{H5-F5}$ = 66 Hz), H-5); 5.84 and 5.64 (1H, d ($J_{H1-F1}$ = 60 Hz) of d ($J_{H1-F5}$ = 4 Hz), β-H-1) ppm. $^{19}$F NMR (84.67 MHz) $\delta$: −117.55 and −118.25 d ($J$ = 9.2 Hz) of d ($J_{F1-H1}$ = 59.5 Hz, F-1); −138.64 and −139.44 (t–t ($J_{F5-H5}$ = 67 Hz), F-5) ppm from one diastereoisomer and −125.9 and −126.6 (d ($J$ = 12.5 Hz) of d ($J_{F1-H1}$ = 56.5) F-1) ppm which belong to the second diastereoisomer. The second part of this signal is under the triplet–triplet at $\delta$ −139 ppm and there is a third doublet at $\delta$ −135.7 ($J$ = 70 Hz) ppm. MS *m/z*: 205 (M−F); 225 $(M+H)^+$. Anal.: Found: C, 48.4; H, 6.4%. $C_9H_{14}O_4F_2$ requires: C, 48.2; H, 6.3%.

*2,3-*O*-Isopropylidene-5-*O*-methyl-β-*D*-ribofuranosyl fluoride (**9a**)*

To compound **2a** (0.5 g, 2.45 mmol) dissolved in dry dichloromethane (10 ml) and cooled to −15 °C under dry nitrogen was added dropwise DAST (2.04 mmol, 0.36 ml) and the reaction stirred whilst allowing it to warm to room temperature; stirring was then continued for a further 24 h. Water (5 ml) was then added, the reaction stirred for 5 min, poured into saturated sodium hydrogen carbonate (30 ml) and worked-up in the usual way. The product was recovered as a yellow oil which could be purified on a silica column by elution with hexane/ethyl acetate (8:2) to give the product as a clear oil (0.27 g, 55%). $^1$H NMR (400 MHz) $\delta$: 1.3 (3H, s, C−$CH_3$); 1.46 (3H, s, C−$CH_3$); 3.37 (1H, m, H-5b); 3.3 (3H, s, O−$CH_3$); 3.5 (1H, m, H-5a); 4.5 (1H, m, H-4), 4.7–4.8 (2H, m, H-2, H-3); 5.81 and 5.62 (1H, d

($J_{H1-F1}$ = 62.2 Hz), H-1) ppm. MS *m/z*: 187 (M − F). Anal.: Found: C, 52.0; H, 7.5%. Calc. for $C_9H_{15}O_4F$: C, 52.1; H, 7.4%.

*2,3-O-Isopropylidene-5-O-methyl-*$d_3$*-β-D-ribofuranosyl fluoride (**9b**)*

This was prepared as described for compound **9a** except that compound **2b** (0.4 g, 1.9 mmol) was used as the starting material. The product was isolated as a clear oil (0.12 g, 30%). $^1$H NMR (90 MHz) δ: 1.3 (3H, s, C−$CH_3$); 1.5 (3H, s, C−$CH_3$); 3.3–3.5 (2H, m, H-5); 4.3–4.8 (3H, m, H-2, H-3, H-4); 6.1 and 5.6 (1H, d ($J_{H1-F1}$ = 62 Hz), H-1) ppm. $^{19}$F NMR (84.67 MHz) δ: −116 (1F, d ($J_{F1-H1}$ = 61 Hz), F-1) ppm. MS *m/z*: 190 (M − F). Anal.: Found: C, 49.5; H, 6.95%. $C_9H_{12}D_3O_4F \cdot 0.4H_2O$ requires: C, 49.9; H 6.9%.

*1,2,3-Tri-O-acetyl-5-deoxy-5-fluoro-α(**13a**)- and -β(**13b**)-D-ribofuranose*

1,2,3-Tri-*O*-acetyl-α,β-D-ribofuranose (**12**) [17] (0.4 g, 1.45 mmol) was dissolved in dry dichloromethane (4 ml) under dry nitrogen at −15 °C, DAST (4.35 mmol, 0.58 ml) added dropwise and the reaction allowed to reach room temperature whilst being stirred for 24 h. More DAST (1.45 mmol, 0.19 ml) was then added and the solution warmed to 30 °C for 1 h before being quenched with water (10 ml) and stirring continued for 10 min. The reaction was then poured into sodium hydrogen carbonate solution and worked-up in the usual way. The organic residue was purified on a silica gel column by elution with hexane/ethyl acetate (6:4) and evaporation of the appropriate fraction yielded the title compounds as clear oils (**13a**, α-isomer, 70 mg, 17.5%; **13b**, β-isomer, 90 mg, 22%). For compound **13a**, α-anomer, the more polar isomer): $^1$H NMR (90 MHz) δ: 2.1 (9H, s, 3×acetyl–$CH_3$); 4.2–4.8 (3H, m ($J_{H5-F5}$ = 49.2 Hz); H-4, H-5); 5.3–5.5 (2H, m, H-2, H-3); 6.1 (1H, s, H-1) ppm. $^{19}$F NMR (90 MHz) δ: −231; −232 (1F, d ($J_{F5-H4}$ = 25.9 Hz) of t ($J_{F5-H5}$ = 46.5 Hz), F-5) ppm. MS *m/z*: 279 $(M+H)^+$. Anal.: Found: C, 47.0; H, 5.4; F, 6.8%. $C_{11}H_{15}O_7F$ requires: C, 47.4; H, 5.4; F, 6.8%. For compound **13b** (β-anomer, the less polar isomer): $^1$H NMR (90 MHz) δ: 2.1 (9H, 35, 3×O−$CH_3$); 4.2–4.5 (3H, m ($J_{H5-F5}$ = 46 Hz); H-4, H-5); 5.2 (1H, m, H-2); 5.3 (1H, d–d, H-3); 6.4 (1H, d ($J_{H1-H2}$ = 4.5 Hz), H-1) ppm. $^{19}$F NMR δ: −233, −234 (1F, d ($J_{F5-H4}$ = 30.5 Hz) of t ($J_{F5-H5}$ = 47.3 Hz), F-5) ppm. MS *m/z*: 259 (M − F). $[\alpha]_D^{22}$ + 66.6 (*c* 2.0, ethanol). Anal.: Found: C, 47.1; H, 5.6; F, 6.5%. $C_{11}H_{15}O_7F$ requires: C, 47.4; H, 5.4; F, 6.8%.

*Acetyl 5-O-(t-butyldiphenylsilyl)-2,3-O-isopropylidene-β-D-ribofuranose (**10a**)*

To compound **2c** (3 g, 6.79 mmol) [which was made by the treatment of compound **2a** with t-butylchlorodiphenylsilane under standard conditions] in freshly dried dichloromethane (18.75 ml) and acetic acid (18.75 ml) at 0 °C was added with stirring redistilled acetic anhydride (5.63 ml) and 8 drops of conc. sulphuric acid. The reaction mixture was stirred at 0 °C for 1 h and then poured on to ice, the organic layer separated, the aqueous

layer extracted with dichloromethane, the organic layers combined and worked-up in the usual way to give a yellow oil. This was purified on a silica column using ethyl acetate/hexane (9:1) to give a clear oil (2.1 g, 66%) $[\alpha]_D^{22}$ −15.4 (*c*, 2.0, ethanol). $^1$H NMR (90 MHz) $\delta$: 1.0 (9H, s, $(CH_3)_3$); 1.3 (3H, s, C−$CH_3$); 1.4 (3H, s, C−$CH_3$); 1.8 (3H, s, acetyl−$CH_3$); 3.6 (2H, m, H-5); 4.3 (1H, t, H-4); 4.6 (1H, d, H-3); 4.2 (1H, d, H-2); 6.1 (1H, s, H-1); 7.1–7.6 (10H, m, 2×Ph) ppm. MS *m/z*: 471 $(M+H)^+$; 493 $(M+Na)^+$. Anal.: Calc. for $C_{26}H_{34}O_6Si$: C, 66.4; H, 7.2%. Found: C, 66.4, H, 7.3%.

*Acetyl 2,3-O-isopropylidene-α,β-D-ribofuranose (**10b**)*

Compound **10a** (0.5 g, 1.06 mmol) was dissolved in dry THF (25 ml) and tetrabutylammonium fluoride (4.3 mmol, 0.67 g) added and the mixture stirred with exclusion of moisture for 10 min until the reaction was complete (TLC). Solvent was removed and the oil obtained was purified on a silica column using hexane/ethyl acetate (7:3) to give the product as a clear oil (0.2 g, 80%, $\alpha$:$\beta$ ratio = 1:3.5). $^1$H NMR (270 MHz) major isomer $\delta$: 1.3 (3H, s, C−$CH_3$); 1.5 (3H, s, C−$CH_3$); 2.1 (3H, s, acetyl–$CH_3$); 3.3 (1H, bs, OH); 4.1–4.8 (5H, m, H-2, H-3, H-4, H-5); 5.1 (1H, s, H-1) ppm: minor isomer $\delta$: 1.4 (3H, s, C−$CH_3$); 1.6 (3H, s, C−$CH_3$); 2.08 (3H, s, O−$CH_3$); 3.3 (1H, bs, OH); 4.1–4.8 (5H, m, H-2, H-3, H-4, H-5); 5.4 (1H, d, H-1) ppm. MS *m/z*: 233 $(M+H)^+$; 215 (M−OH). Anal.: Calc. for $C_{10}H_{16}O_6$: C, 51.7; H, 6.9%. Found: C, 51.6; H, 7.0%.

*5-O-Acetyl-2,3-O-isopropylidene-α-(**11a**)- and β-(**11b**)-D-ribofuranosyl fluoride (**11**)*

Compound **10b** (0.4 g, 2.13 mmol) was dissolved in dry dichloromethane (8 ml) under dry nitrogen at room temperature and DAST (2.55 mmol, 0.25 ml) added dropwise to the stirred solution which was then left at room temperature overnight. Water (5 ml) was then added and the reaction stirred for 10 min before pouring into saturated sodium hydrogen carbonate solution. The aqueous layer was extracted with dichloromethane and the organic layer worked-up in the usual way to give a yellow oil which could be purified by silica gel chromatography using hexane/ethyl acetate (7:3). The products were obtained as clear oils (**11a**, $\alpha$-isomer, 0.1 g, 25%; **11b**, $\beta$-isomer, 0.25 g, 62.5%). For compound **11a**: $^1$H NMR (200 MHz) $\delta$: 1.3 (3H, s, C−$CH_3$); 1.4 (3H, s, C−$CH_3$); 2.1 (3H, s, acetyl−$CH_3$); 4.0–4.2 (2H, m, H-5); 4.5 (1H, m, H-4); 4.7–4.8 (2H, m, H-2, H-3); 5.6 and 5.9 (1H, d ($J_{H1-F1}$ = 64 Hz), H-1) ppm. $^{19}$F NMR (84.67 MHz) $\delta$: −116.3 (1F, d ($J_{F1-H1}$ = 61 Hz), F-1) ppm. MS *m/z*: 219 (M-15) $[\alpha]_D^{22}$ +15.4° (*c*, 2.0, ethanol). Anal.: Found: C, 51.3; H, 6.4%. $C_{10}H_{15}O_5F$ requires: C, 51.2; H, 6.4%. For compound **11b**, the less polar isomer: $^1$H NMR (200 MHz) $\delta$: 1.4 (3H, s, C−$CH_3$); 1.6 (3H, s, C−$CH_3$); 2.1 (3H, s, O–$CH_3$); 4.1–4.3 (2H, dq, H-5); 4.5–4.7 (3H, m, H-2, H-3, H-4); 5.8 and 5.45 (1H, d ($J_{H1-H2}$ = 5 Hz) of d ($J_{H1-F1}$ = 66 Hz), H-1) ppm. $^{19}$F NMR (90 MHz) $\delta$: −130.29 and −131.06 (1F, d ($J_{F1-H2}$ = 15 Hz) of d ($J_{F1-H1}$ = 65.5 Hz), F-1) ppm. MS *m/z*: 219 (M−15). $[\alpha]_D^{22}$ +36°

(*c*, 2.0, ethanol). Anal.: Found: C, 51.3; H, 6.2%. $C_{10}H_{15}O_5F$ requires: C, 51.2; H, 6.4%.

*5'-Deoxy-2',3'-O-isopropylidene-5'-O-methyl-ribothymidine (**18a**)*

To a suspension of thymine (0.125 g, 0.99 mmol) in hexamethyldisilazane (0.79 ml) was added trimethylchlorosilane (0.19 ml) and the reaction mixture heated under reflux until complete solution was obtained (24 h). The excess of hexamethyldisilazane was removed under reduced pressure to leave an oil (**14**) which was dissolved in dry acetonitrile. This was then added to compound **9a** (0.12 g, 0.58 mmol) dissolved in dry acetonitrile to which was then added a solution of acetonitrile (1 ml) saturated with tetrafluorosilane. The resulting cloudy solution was stirred for 10 min at room temperature, a further aliquot of acetonitrile (3 ml) saturated with tetrafluorosilane added and, after stirring for 3.5 h at room temperature, the reaction was poured into saturated sodium hydrogen carbonate solution (100 ml) and the organic-soluble (ethyl acetate) material isolated in the usual way to give a white foam which could be further purified by silica gel chromatography using hexane/ethyl acetate (8:2) to give the product (60 mg, 33%). $^1$H NMR (270 MHz) $\delta$: 1.35 (3H, s, C$-$CH$_3$); 1.6 (3H, s, C$-$CH$_3$); 1.95 (3H, s, thymine$-$CH$_3$); 3.4 (3H, s, O$-$CH$_3$); 3.3–3.6 (2H, m, H-5'); 4.35 (1H, m, H-4'); 4.55 (1H, d–d, H-3'); 4.7 (1H, d–d, H-2'); 5.4 (1H, s, H-1'); 7.65 (1H, s, H-6); 8.1 (1H, s, NH) ppm. IR $\lambda_{max}$ (ethanol): 261 nm ($\epsilon$ = 10 400). MS *m/z*: 313 $(M+H)^+$. Anal.: Found: C, 54.0; H, 6.4; N, 10.5%. $C_{14}H_{20}N_2O_6 \cdot 0.5CH_3CN$ requires: C, 54.1; H, 6.4; N, 10.5%.

*(5',R,S)-5'-Deoxy-5'-fluoro-2',3'-isopropylidene-5'-O-methylribothymidine (**18**)*

Compound **17** was made as previously described from thymine (0.25 g, 1.98 mmol). A solution of the resulting syrup in dry acetonitrile (2 ml) was added to a solution of compound 5 (0.25 g, 1.12 mmol) in dry acetonitrile (2 ml) and the reaction cooled to 0 °C. To this solution was added a solution of dry acetonitrile saturated with tetrafluorosilane (3 ml) and the cooling bath removed. The reaction was quenched after 2 min by pouring into saturated sodium hydrogen carbonate solution (200 ml) and the organic-soluble (ethyl acetate) material was worked-up in the usual way to give a white foam which could be further purified on silica gel using hexane acetate (1:1) to give the product as a diastereoisomeric mixture (0.15 g, 40%). Major diastereoisomer: $^1$H NMR (300 MHz) $\delta$: 1.35 (3H, s, C$-$CH$_3$); 1.45 (3H, s, C$-$CH$_3$); 1.55 (3H, s, thymine$-$CH$_3$); 3.5 (3H, s, O$-$CH$_3$); 4.6 (1H, m, H-4'); 4.3–5.0 (2H, m, H-2', H-3'); 5.1 (1H, m, H-1'); 5.9 (1H, d ($J_{H5'-F5'}$ = 63 Hz), H-5'); 7.4 (1H, s, H-6); 9.2 (1H, s, NH) ppm. $^{19}$F NMR (90 Hz) $\delta$: $-117.8$ (1F, d ($J_{F5'-H5'}$ = 64 Hz), F-5') ppm. Minor diastereoisomer: $^1$H NMR (300 MHz) $\delta$: 1.3 (3H, s, C$-$CH$_3$); 1.45 (3H, s, C$-$CH$_3$); 1.55 (3H, s, thymine–CH$_3$); 3.4 (3H, s, O$-$CH$_3$); 4.4 (1H, m, H-4'); 4.3–5.0 (2H, m, H-2', H-3'); 5.25 (1H, m, H-1'); 6.0 (1H, d ($J_{H5'-F5'}$ = 64 Hz), H-5'); 7.3 (1H, s, H-6); 9.3 (1H, s, NH) ppm. $^{19}$F NMR (84.67 MHz) $\delta$: $-112.7$ and $-113.5$

(1F, d $J_{F5'-H4'}=6$ Hz) of d ($J_{F5'-H5'}=64$ Hz), F-5') ppm. IR $\lambda_{max}$ (ethanol): 264 nm ($\epsilon=10\,200$). MS *m/z*: 331 $(M+H)^+$. Anal.: Found: C, 51.3; H, 6.2; N, 10.0%. $C_{14}H_{19}N_2O_6F \cdot 0.5CH_3CN$: C, 51.4; H, 5.9; N, 10.0%.

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