The synthesis of difluoro and trifluoro analogues of pyrimidine deoxyribonucleosides: a novel approach using elemental fluorine

Paul L. Coe*, Ratnakar R. Talekar and Richard T. Walker
School of Chemistry, The University of Birmingham, Edgbaston, Birmingham B15 2TT (UK)

(Received May 12, 1993; accepted January 24, 1994)

Abstract

The preparation of some novel fluorodeoxy nucleosides in good yields by the fluorination of unsaturated intact nucleosides with elemental fluorine at −78 °C in mixtures of chloroform, ethanol and fluorotrichloromethane is described. This is the first example of the fluorination of an intact nucleoside by elemental fluorine and represents a considerable step forward in the use of the element in the synthesis of bioactive species. Thus, we were able to obtain 1-(2′,3′-didehydro-2′,3′-dideoxy-β-D-ribofuranosyl)-5-fluorouracil (**6**), 1-(2′,3′-didehydro-2′,3′-dideoxy-2′,3′-difluoro-β-D-ribofuranosyl)-5-fluorouracil (**7**), 1-(2′,3′-didehydro-2′,3′-dideoxy-2-fluoro-β-D-ribofuranosyl)-5-fluorouracil (**8**), 1-(2′,3′-dideoxy-2′,3′-difluoro-β-D-ribofuranosyl)-5-fluorocytosine (**10**), 2′,3′-dideoxy-5-fluorouridine (**11**), 1-(2′,3′-dideoxy-2′-fluoro-β-D-arabinofuranosyl)-5-fluorouracil (**12**), 1-(2′,3′,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5-fluorouracil (**13**), 1-(2-deoxy-3,5-di-*O*-acetyl-β-D-ribofuranosyl)-5-fluorouracil (**14**) and (5*R*,6*S*)- and (5*S*,6*R*)-1-(3′,5′-anhydro-2-deoxy-β-D-*threo*-pentofuranosyl)-difluoro-5,6-dihydro-5-methyluracil (**16** and **17**) by a series of fluorinations and deprotections. From the products we have obtained, it is clear that (at least in these fluorinations) the addition of the fluorine is in a *cis* mode.

1. Introduction

The synthesis of 2′,3′-didehydro-2′,3′-dideoxy- and 2′,3′-dideoxy-nucleosides has attracted considerable attention recently because of their potential as anti-HIV agents. These nucleoside analogues include 3′-azido-3′-deoxythymidine (AZT) [1], 2′,3′-dideoxy-2′,3′-didehydrocytidine (D4C) [2, 3], 2′,3′-didehydro-2′,3′-dideoxythymidine (D4T) [4], 2′,3′-dideoxyinosine (ddI) [5] and 2′,3′-dideoxycytidine (ddC) [6]. The above nucleoside analogues are all at different stages of clinical trial; AZT, ddI and ddC are currently approved for AIDS therapy [7]. A remarkable feature of these nucleosides is the absence of the 3′-hydroxy group in the carbohydrate portion of the molecule.

These compounds are all thought to act as chain terminators in the DNA polymerisation process, since after conversion to the 5′-triphosphates by cellular kinases, they become incorporated into the growing chain. However, the absence of the 3′-hydroxy group then prevents further chain extension and hence replication of the HIV [8]. Based on current knowledge of the structure–activity relationships of nucleoside analogues, it is known that all active species have a free 5′-hydroxy group in the furanose moiety [9].

As the 2′-deoxynucleosides are natural substrates for reverse transcriptase, we decided to try to prepare some fluorinated derivatives based on the following rationale. The fluorine atom is strongly electronegative and a good steric replacement for hydrogen at the molecular level [10–12]. As the dideoxynucleosides, in particular pyrinidine purine nucleosides, are rapidly degraded by phosphorylases [13], introduction of a fluorine atom in the carbohydrate moiety might render them more stable towards enzymatic degradation. There have been many reports of fluorinated compounds being prepared with this aim and some are quite active against viruses [14–23]. Of these compounds, 2′,3′-dideoxy-3′-fluoro-5-chlorouridine has been found to be the most active and selective against HIV and is comparable with AZT, although its toxicity is not yet reported. However, since most of the methods used are multistep and often low yielding, we decided to investigate the preparation of fluoropyrimidine nucleosides by the reaction of elemental fluorine with readily available unsaturated nucleosides.

2. Results and discussion

The reported methods of synthesis of fluorinated nucleosides as indicated above are often complex and

*Corresponding author.

SSDI 0022-1139(94)03070-G

usually start from either the condensation of fluorinated sugars with suitable bases, with consequent problems of anomer formation and separation [15, 16, 18], or the fluorination of suitably protected nucleosides with DAST [22–24], or the ring-opening of anhydronucleosides [25].

Recently, Rozen et al. [26] have discovered the direct electrophilic *syn*-addition of elemental fluorine to olefins using alcohol as a proton donor in a polar solvent system by working at low temperature. Earlier investigations of the direct fluorination of the uracil moiety of pyrimidine nucleosides, using elemental fluorine, resulted in glycosyl linkage cleavage [27, 28]. Herein, we report smooth fluorination of a range of pyrimidine nucleosides with elemental fluorine.

Treatment of 5′-*O*-acetyl-2′,3′-didehydro-2′,3′-dideoxyuridine (**1**) [29] in a mixture of chloroform, ethanol and fluorotrichloromethane containing molecular sieves (4 Å) at −78 °C with a dilute stream of fluorine in nitrogen (10% fluorine) gave, after brief treatment with triethylamine, compounds **4** and **5**. We were unable to isolate the fluorine adducts **2** and **3**, even when the reaction mixture was not pretreated with triethylamine. Thin layer chromatography showed only the presence of compounds **4** and **5**. Presumably, facile elimination of HF occurred on thin layer silica gel plates without addition of triethylamine. Working-up the fluorination mixture with aqueous bicarbonate solution resulted in the degradation of products.

The ^{1}H NMR spectrum of compound **4** showed a one-proton doublet at δ 8.0 ppm, indicating the presence of one proton in the heterocyclic moiety. This is further confirmed by the ^{19}F NMR spectra which showed one fluorine signal at δ −125 ppm typical of 5-fluorouridine [30]. The ^{1}H and ^{19}F NMR spectra of compound **5** showed one fluorine in the uracil moiety and two fluorines in the sugar moiety. The stereochemistry of the fluorine atoms in the sugar moiety in **5** was established by ^{1}H–^{1}H NOE experiments as follows. The distinction between 2′-H and 3′-H was made using spin decoupling experiments by irradiating the 1′-H signal. An observed NOE at 3′-H on irradiation of the 5′-CH_2 established the 3′-H to be on the β-face of the sugar moiety. A significant NOE at 2′ on irradiation of 6-H and a lack of a significant NOE at 2′ on irradiation of the 1′-H established 2′-H to be on the β-face of the ribose moiety. Hence, stereochemically, the fluorine atoms are *cis* and thus in the ribo configuration.

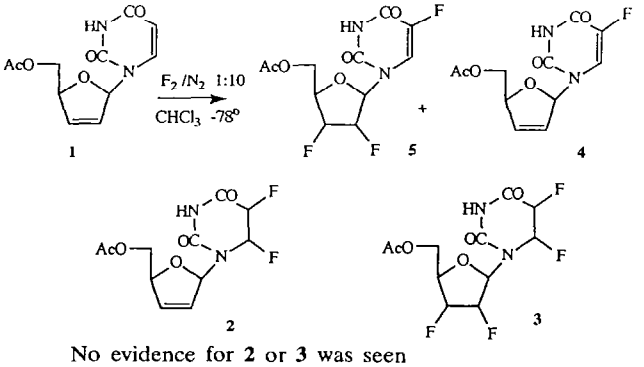
This is, we believe, the first time that elemental fluorine has been used to fluorinate a pyrimidine nucleoside without any significant accompanying degradation of the glycoside linkage. Further, to our knowledge, this is the first time that elemental fluorine has been used to add across a double bond on the sugar moiety of a nucleoside in high yield to give stereospecific *cis* addition in the ribo configuration. The rate of electrophilic addition of fluorine at the 5,6-double bond in the base moiety is faster than at the 2′,3′-double bond as revealed by an analysis of the reaction mixture with time. However, we did not detect any products arising from the β-elimination of hydrofluoric acid by treatment of compound **5** with methanolic ammonia. These results are shown in Scheme 1.

The facile β-elimination of hydrofluoric acid from compound **5** was achieved by treatment with potassium t-butoxide in dimethylformamide to give compound **8** exclusively by selective abstraction of 2′-H by the base. We did not detect any of the other regioisomeric elimination product (**9**) formed by abstraction of the 3′-proton of compound **5**. The position of the fluorine in compound **8** at the 2′-position was confirmed by ^{1}H–^{1}H NOE experiments. A positive NOE was observed between the olefinic proton and 4′-H in compound **8** but not between 1′-H and the olefinic proton. To our knowledge, this is the first example of a 2′,3′-difluoropyrimidine nucleoside with a ribo configuration which undergoes regioselective β-elimination.

Hydrogenation of compound **4** using palladium/carbon as the catalyst in ethyl acetate, followed by deblocking of the acetate group with saturated methanolic ammonia, gave compound **11**. Similarly, catalytic hydrogenation of **8** gave compound **12**. These results are summarised in Scheme 2.

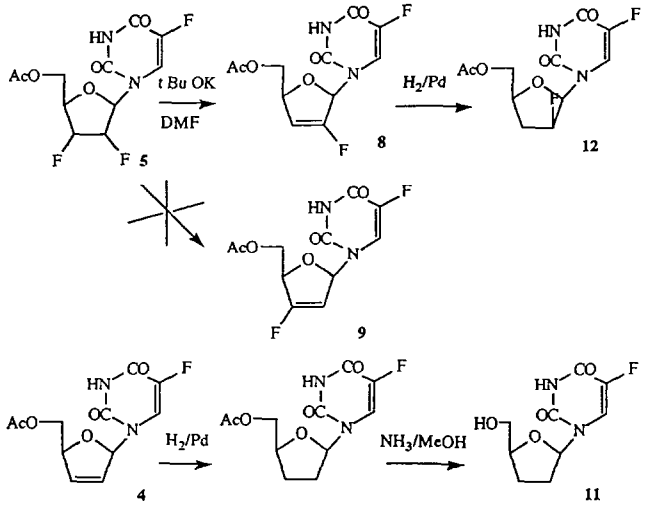
Treatment of compound **5** with trifluoromethane sulphonic anhydride in a mixture of dichloromethane and pyridine, followed by reaction with saturated methanolic ammonia, gave compound **10**. Reaction of **4** and **5** with saturated methanolic ammonia afforded the nucleosides **6** and **7**. These results are shown in Scheme 3.

In order to test the generality of electrophile fluorination with elemental fluorine on uridine nucleosides, reactions with 2′,3′,5′-tri-*O*-acetyluridine and 3′,5′-di-*O*-acetyl-2′-deoxyuridine were investigated. The exposure of the above compounds to elemental fluorine gave products **13** and **14** in good yield without appre-

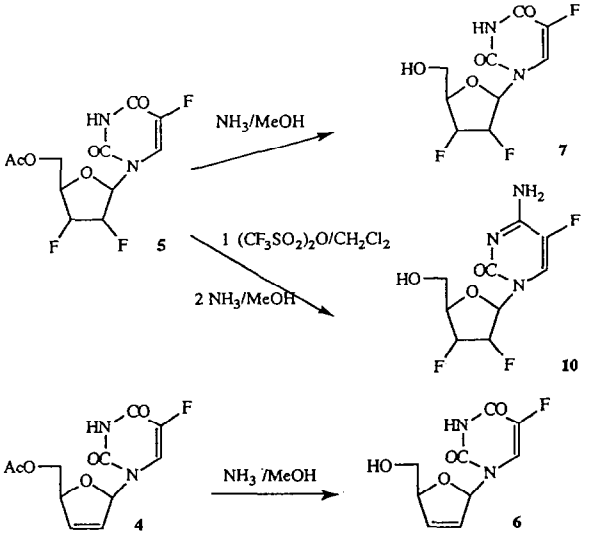


No evidence for **2** or **3** was seen

Scheme 1.



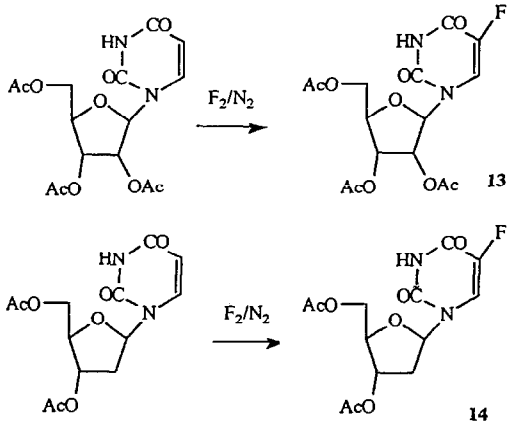
Scheme 2.



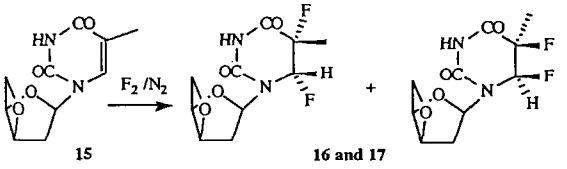
Scheme 3.

ciable degradation or glycosidic cleavage. The compounds **13** and **14** have been synthesised previously by treatment of 2',3',5'-tri-*O*-acetyluridine and 3,5'-di-*O*-acetyl-2'-deoxyuridine with trifluoromethyl hypofluorite [30]. These fluorinations are shown in Scheme 4.

We were unable to isolate the 5,6-difluoro electrophilic *syn*-addition products from the reaction of fluorine with the base portion of uridine nucleosides. Therefore, we decided to investigate the fluorination of compound **15** with elemental fluorine in the hope that we would be able to isolate a stable difluoro adduct. The reaction of **15** with elemental fluorine gave two *syn*-addition products, **16** and **17**. The ^{19}F NMR spectra of compounds **16** and **17** showed identical fluorine signals consisting of a double doublet for the 6-F and double quartet for 5-F, indicating *syn*-addition of fluorine to the 5,6-double bond. We were unable to determine which was



Scheme 4.



Scheme 5.

which of the products **16** and **17** by ^1H and ^{19}F NMR spectroscopy and we failed in all attempts to dehydrofluorinate the products to give the corresponding 6-fluorothymidine analogues. This chemistry is shown in Scheme 5.

These compounds are all in the process of biological assay as potential antivirals and the results will be published later.

3. Experimental details

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Thin layer chromatography was performed on precoated Merck silica gel (60 F 25H) plates and the spots were examined with UV light (254 nm) and *p*-anisaldehyde spray. Column chromatography was performed using Kieselgel 60, 230–400 mesh ASTM, type 9385, supplied by E. Merck A.G., Darmstadt, Germany. ^1H NMR spectra were recorded either on a JEOL GX270 (270 MHz) or a Bruker 200 (200 MHz) spectrometer. The spin decoupling and NOE measurements were carried out on a Bruker 360 (360 MHz) NMR spectrometer. ^1H NMR spectra were run in deuterated dimethyl sulphoxide solution using tetramethylsilane as internal reference, unless otherwise stated. ^1F NMR spectra were recorded on a JEOL FX90Q (90 MHz) spectrometer using fluorotrichloromethane as reference standard.

Ethanol and methanol were dried over magnesium turnings and distilled. Chloroform was dried over P_2O_5 and distilled. Dimethylformamide and pyridine were dried over calcium hydride and distilled under vacuum. Molecular sieves (4 Å) were dried at 110 °C under high vacuum prior to use.

3.1. 1-(5'-O-Acetyl-2',3'-dideoxy-2',3'-difluoro-β-D-ribofuranosyl)-5-fluorouracil (5) and 1-(5'-O-acetyl-2',3'-didehydro-2',3'-dideoxy-β-D-ribofuranosyl)-5-fluorouracil (4)

A five-necked flask equipped with a vibro stirrer, thermometer, gas inlet, calcium chloride drying tube and a stopper was charged with a solution of **1** (2.0 g, 7.93 mmol) in chloroform (50 cm^3), fluorotrichloromethane (75 cm^3) and ethanol (15 cm^3), and dried 4 Å molecular sieves (10 g). The mixture was cooled to −78 °C under nitrogen. A stream of fluorine gas (10% in nitrogen) was then passed through the reaction mixture at the rate of 1 $dm^3\ h^{-1}$ for 5 h. The mixture was purged with dry nitrogen for 0.5 h to remove any excess of fluorine gas and quenched with dry triethylamine (10 cm^3), allowed to warm up to room temperature and filtered through a Celite pad. The filtrate was evaporated to dryness. The residue was chromatographed (silica gel eluted with ethyl acetate and n-hexane (3:7)) to give compound **5** (0.356 g, 14.56%), m.p. 98–100 °C (ethyl acetate/hexane) {Analysis: Found: C, 41.77; H, 3.94; N, 8.84%. $C_{11}H_{11}F_3N_2O_5 \cdot 0.5H_2O$ requires: C, 41.64; H, 3.78; N, 8.83%. FAB-MS *m/z*: 309 $(M+H^+)$; 131 $(B+2H)^+$; 179 $(sugar)^+$. ^1H NMR (360 MHz) δ: 2.05 (s, 3H, CH_3); 4.3 (m, 2H, 5-CH_2); 4.41 (dt, $J=18$ Hz, 5 Hz, 1H); 5.25–5.45 (ddt, $J=52$ Hz, 8 Hz, 4 Hz, 1H, 3-H); 5.45–5.65 (ddt, $J=52$ Hz, 8 Hz, 4 Hz, 1H, 2-H); 5.95 (dt, $J=18$ Hz, 4 Hz, 1H, 1-H); 8.0 (d, $J=8.0$ Hz, 6-H) ppm. ^{19}F NMR δ: −124.64 (1F, d, $J=4.4$ Hz); −13.03 (1F, m); −154.2 to −158.6 (1F, m) ppm} and a more polar product (**4**) (0.69 g, 32.1%), m.p. 146–148 °C (ethyl acetate/hexane) {Analysis: Found: C, 48.9; H, 4.3; F, 7.1; N, 9.6%. $C_{11}H_{11}FN_2O_5$ requires: C, 48.9; H, 4.1; F, 7.1; N, 10.3%. FAB-MS *m/z*: 271 $(M+H)^+$; 131 $(B+2H)^+$. ^1H NMR (200 Mz) ($CDCl_3$) δ: 2.12 (s, 3H); 4.25 (dd, $J=14$ Hz, 4 Hz, 1H, 5'-H); 4.45 (dd, $J=14$ Hz, 4 Hz, 1H, 5'-H); 5.05 (m, 1H, 4'-H); 5.92 (d, $J=6.6$ Hz, 1H, 3'-H); 6.35 (d, $J=6.6$ Hz, 1H, 2'-H); 7.12 (m, 1H, 1'-H); 7.7 (d, $J=8.0$ Hz, 1H, 6-H); 8.7 (b s, 1H, NH) ppm. ^{19}F NMR δ: −125.39 (1F, d, $J=6.1$ Hz) ppm}.

3.2. 1-(2',3'-Didehydro-2',3'-dideoxy-β-D-ribofuranosyl)-5-fluorouracil (6)

A solution of compound **4** (0.115 g, 0.42 mmol) in methanolic ammonia (8 M, 15 cm^3) was stirred at room temperature overnight. The mixture was concentrated in vacuo and the residue chromatographed (silica gel, dichloromethane/methanol (98:2)) to give compound **6** (0.07 g, 72.0%), m.p. 142–144 °C (ethyl acetate/hexane). Analysis: Found: C, 47.33; H, 4.05; N, 12.11%. $C_9H_9FN_2O_4$ requires: C, 47.37; H, 3.97; N, 12.27%. ^1H NMR (200 MHz) δ: 4.8 (m, 2H, 5'-CH_2); 5.15 (b s, 1H, OH); 5.9 (dt, $J=6$ Hz, 1.5 Hz, 1H, 3'-H); 6.4 (dt, $J=6.0$ Hz, 1.5 Hz, 1H, 2'-H); 6.8 (b s, 1H, 1'-H); 8.2 (d, $J=7.5$ Hz, 1H, 6-H); 11.85 (b s, 1H, NH) ppm.

3.3. 1-(2,3-Dideoxy-2,3-difluoro-β-D-ribofuranosyl)-5-fluorouracil (7)

A solution of compound **5** (0.075 g, 0.24 mmol) in methanolic ammonia (8 M, 15 cm^3) was stirred at room temperature overnight. The mixture was concentrated to dryness in vacuo. The residue was chromatographed (silica gel, dichloromethane methanol (98:2)) to give compound **7** (0.046 g, 71%), m.p. 116–118 °C (ethyl acetate/hexane). Analysis: Found: C, 41.57; H, 3.83; N, 9.35%. $C_9H_9F_3N_2O_4 \cdot 0.25$ ethyl acetate (by NMR) requires: C, 41.66; H, 3.82; N, 9.72%. ^1H NMR (200 MHz) δ: 3.65 (m, 2H, 5'-CH_2); 4.35 (dt, $J=18$ Hz, 2.5 Hz, 1H, 4'-H); 5.1–5.6 (m, 3H, 2',3'-H and OH exchangeable); 6.05 (dd, $J=15$ Hz, 5 Hz, 1H, 1'-H); 8.2 (d, $J=7.5$ Hz, 1H, 6-H); 12.0 (b s, 1H, NH) ppm.

3.4. 1-(2',3'-Didehydro-2',3'-dideoxy-2'-fluoro-β-D-ribofuranosyl)-5-fluorouracil (8)

To a solution of compound **5** (0.092 g, 0.3 mmol) in dry dimethylformamide (15 cm^3) was added potassium t-butoxide (0.11 g, 0.9 mmol). The mixture was stirred at room temperature overnight, then diluted with methanol (15 cm^3) and neutralised with an ion-exchange resin (IRA-120(H)). The reaction mixture was filtered and the resin washed with methanol (15 cm^3). The filtrate was evaporated to dryness and the residue chromatographed (silica gel, chloroform/methanol (98:2)) to give compound **8** (50 mg, 67.75%). Analysis: Found: C, 43.86; H, 3.32; N, 10.87%. $C_9H_8F_2N_2O_4$ requires: C, 43.9; H, 3.25; N, 11.38%. ^1H NMR (200 MHz) δ: 3.65 (b s, 2H, 5'-CH_2); 4.85 (m, 1H, 4'-H); 5.25 (b s, 1H, OH, exchangeable); 6.0 (t, $J=1.5$ Hz, 1H, 1-H); 6.75 (m, 1H, 3'-H); 8.45 (d, $J=7.5$ Hz, 1H, 6-H); 11.95 (b s, 1H, NH) ppm.

3.5. 1-(2',3'-Dideoxy-2',3'-difluoro-β-D-ribofuranosyl)-5-fluorocytosine (10)

A solution of compound **5** (0.308 g, 1 mmol) in pyridine/dichloromethane (1:3, 15 cm^3) was cooled to 0 °C. To this solution was added trifluoromethane sulphonic anhydride solution in dichloromethane (4.8 mmol, 4 cm^3) dropwise. The mixture was stirred at room temperature for 8 h, and then poured into saturated methanolic ammonia solution (50 cm^3) and

stirred overnight at room temperature. The reaction mixture was concentrated to dryness in vacuo. The residue was chromatographed (silica gel, eluant dichloromethane/methanol (95.5)) to give compound **10** as a white powder (110 mg). FAB-MS *m/z*: 288 $(H+Na)^+$; 266 $(M+H)^+$; 130 $(B+2H)^+$. ^1H NMR (200 MHz) δ: 3.55–3.75 (m, 2H, 5'-CH_2); 4.25 (dd, $J=18$ Hz, 3.0 Hz, 1H, 1'-H); 5.2 (m, 1H, 3'-H); 5.4 (m, 2H, 2'-H and OH); 6.05 (dd, $J=15.0$ Hz, 2.5 Hz, 1H, 1'-H); 7.65 (b s, 1H, NH); 7.9 (b s, 1H, NH); 8.1 (d, $J=7.0$ Hz, 1H, 6-H) ppm. ^{19}F NMR (DMSO) δ; −208.3 (m, 1F); 207.1 (m, 1F); −166.2 (s, 1F) ppm.

3.6. 2',3'-Dideoxy-5-fluorouridine (11)

A solution of compound **4** (0.17 g, 0.63 mmol) in ethyl acetate (30 cm^3) was hydrogenated at ambient pressure over palladium/carbon (10%, 200 mg) until no more absorption of hydrogen took place. The mixture was filtered through a Celite pad and the catalyst washed with ethyl acetate (10 cm^3). The filtrate was concentrated in vacuo. The residue was directly treated with methanolic ammonia (8 M, 20 cm^3) and stirred at room temperature overnight. The solvents were evaporated to dryness. The residue was chromatographed (silica gel, ethyl acetate) to give compound **11** (0.05 g, 33.5%). MS-EI *m/z*: 230 $(M)^+$; 131 $(B+2H)^+$; 101 $(sugar)^+$. ^1H NMR (200 MHz) δ: 1.8–2.4 (m, 4H, 2' and 3'-CH_2); 3.55 (dt, $J=12$ Hz, 5 Hz, 1H, 5'-H); 4.5 (m, 1H, 4'−H); 5.15 (b t, 1H, OH); 5.9 (m, 1H, 1'-H); 8.35 (d, $J=7.5$ Hz, 1H, 6-H); 11.75 (b s, 1H, NH) ppm.

3.7. 1-(2',3'-Dideoxy-2'-fluoro-β-D-arabinofuranosyl)-5-fluorouracil (12)

A solution of compound **8** (79 mg, 0.31 mmol) in ethyl acetate (20 cm^3) was hydrogenated over palladium/carbon (10%, 200 mg). The mixture was filtered through a Celite pad and the filtrate evaporated to dryness. The residue was chromatographed (silica gel, ethyl acetate) to give compound **12** (40 mg, 50.0%). MS-EI *m/z*: 248 $(M)^+$; 130 $(B+H)^+$; 119 $(sugar)^+$.

3.8. 1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-5-fluorouracil (13)

A solution of 2',3',5'-tri-*O*-acetyl uridine (0.8 g, 2.16 mmol) in chloroform (60 cm^3), fluorotrichloromethane (75 cm^3) and ethanol (15 cm^3) containing 4 Å molecular sieves (10 g) was fluorinated at −78 °C as described above. The reaction mixture was quenched with triethylamine (30 cm^3) and left at room temperature overnight. The mixture was filtered and evaporated to dryness and the residue chromatographed (silica gel, ethyl acetate/hexane 7:3) to give compound **13** as a foam (0.61 g, 72.7%). Analysis: Found: C, 46.14; H, 4.80; N, 6.52; F, 4.59%. $C_{15}H_{17}N_2O_9F$ requires: C, 46.39; H, 4.41; N, 7.21; F, 4.89%. FAB-MS *m/z*: 389 $(M+H)^+$. ^1H NMR (270 MHz) δ: 2.05, 2.06, 20.7 (3s, 9H, $3CH_3$); 4.2–4.38 (m, 3H, 4'-H and 5'-CH_2); 5.31 (t, $J=6.5$ Hz, 1H, 3'-H); 5.44 (t, $J=6.4$ Hz, 1H, 2'-H); 5.89 (d, $J=5.2$ Hz, 1H, 1'-H); 8.1 (d, $J=7.0$ Hz, 1H, 6-H); 12.0 (s, 1H, NH) ppm. ^{19}F NMR (DMSO) δ: −163.7 (d, $J=4.5$ Hz) ppm.

3.9. 1-(2'-Deoxy-3',5'-di-O-acetyl-β-D-ribofuranosyl)-5-fluorouracil (14)

A solution of 2'-deoxy-3',5'-di-*O*-acetyl uridine (1.0 g, 3.2 mmol) was fluorinated in chloroform (60 cm^3), fluorotrichloromethane (75 cm^3) and ethanol (15 cm^3) containing 4 Å molecular sieves (15 g) at −78 °C until no starting material remained. The reaction mixture was quenched with dry triethylamine (30 cm^3) and left at room temperature overnight. The mixture was filtered and the filtrate evaporated to dryness. The residue was chromatographed (silica gel, ethyl acetate/hexane (7:3)) to give compound **14** as a white powder (0.79 g, 74.7%). Analysis: Found: C, 47.11; H, 4.60; N, 8.22; F, 5.57%. $C_{13}H_{15}N_2O_7F$ requires: C, 47.27; H, 4.57; N, 4.84; F, 5.75%. FAB-MS *m/z*: 353 $(M+Na)^+$; 331 $(M+H)^+$; 131 $(B+2H)^+$. ^1H NMR (270 MHz) δ: 2.02 (s, 3H, CH_3); 2.05 (s, 3H, CH_3); 2.2–2.5 (m, 2H, 2-CH_2); 4.1–4.3 (m, 3H, 4'-H and 5'-CH_2); 5.2 (m, 1H, 3'-H); 6.15 (t, $J=4.0$ Hz, 1H, 1'-H); 7.98 (d, $J=7.0$ Hz, 1H, 6-H); 11.92 (b s, NH) ppm. ^{19}F NMR δ: −164.05 (dd, $J=1.7$ Hz, 6.1 Hz) ppm.

3.10. 1-(3,5-Anhydro-2-deoxy-β-D-threo-pentofuranosyl)(5R,6S)-difluoro-5,6-dihydro-5-methyluracil (16) or (17) and 1-(3,5-anhydro-2-deoxy-β-D-threo-pentofuranosyl)(5S,6R)-difluoro-5,6-dihydro-5-methyluracil (16) or (17)

A solution of compound **15** (1.68 g, 7.5 mmol) in chloroform (60 cm^3), fluorotrichloromethane (75 cm^3) and ethanol (15 cm^3) containing 4 Å molecular sieves (15 g) was fluorinated at −78 °C as above. The mixture was quenched with triethylamine (15 cm^3) and left at room temperature overnight. The mixture was washed as usual and the residue chromatographed (silica gel, ethyl acetate) to give **16** or **17** (0.44 g, 22.4%), m.p. 185–86 °C (ethyl acetate/hexane) {Analysis: Found: C, 46.36; H, 4.80; N, 10.4%. $C_{10}H_{12}N_2O_4F_2$ requires: C, 45.80; H, 4.58; N, 10.62%. FAB-MS *m/z*: 263 $(M+H)^+$; 165 $(B+2H)^+$; 99 $(sugar)^+$. ^1H NMR (200 MHz) δ: 1.65 (d, $J=22.5$ Hz, 3H, CH_3); 2.2–2.6 (m, 2H, 2'-CH_2); 4.15 (d, $J=75$ Hz, 1H, 4'-H); 4.7 (dd, $J=7.5$ Hz, 1H, 5'-H); 4.8 (t, $J=2.5$ Hz, 1H, 5'-H); 5.45 (t, $J=4.5$ Hz, 1H, 3'-H); 6.35 (dd, $J=7.5$ Hz, 2.5 Hz, 1H, 1'-H); 6.4 (dd, $J=52.5$ Hz, 2 Hz, 1H, 6-H) ppm. ^{19}F NMR δ: −150.57 (dd, $J=55.0$ Hz, 16.94 Hz, 1F); −174.2 (dt, $J=21.1$ Hz, 18.8 Hz, 1F) ppm} and a second fraction (**16** or **17**) (0.71 g, 36.1%), m.p. 175–176 °C (ethyl acetate/hexane) {Analysis: Found: C, 45.38; H, 4.57; N, 10.37%. $C_{10}H_{12}F_2N_2O_4$ requires: C, 45.8; H, 4.58;

N, 10.62%. FAB-MS *m/z*: 263 $(M+H)^+$; 165 $(B+2H)^+$; 99 $(sugar)^+$. ^1H NMR (200 MHz) δ; 1.65 (d, $J=22.5$ Hz, 3H, CH_3); 2.25–2.6 (m, 2H, 2′-CH_2); 4.15 (d, $J=7.5$ Hz, 1H, 4′-H); 4.65 (dd, $J=8.0$ Hz, 1H, 5′-H); 4.85 (t, $J=2.5$ Hz, 1H, 5′-H); 5.45 (t, $J=4.0$ Hz, 1H, 3′-H); 6.35 (m, 1H, 1′-H); 6.45 (dd, $J=52$ Hz, 2.5 Hz, 1H, 6-H) ppm. ^{19}F NMR ($CDCl_3$) δ; −149.56 (dd, $J=53.6$ Hz, 18.65 Hz, 1F); −173.67 (dt, $J=21.46$ Hz, 19.9 Hz, 1F) ppm.

References

1 H. Mitsuya, K.J. Weinhold, P.A. Furman, M.H. St. Clair, S.N. Lehrman, R.C. Gallo, D. Bolognesi, D.W. Barry and S. Broder, *Proc. Natl. Acad. Sci. USA, 82* (1985) 7096.

2 J. Balzarini, R. Pauwels, P. Herdewijn, E. De Clercq, D.A. Cooney, G.J. Kang, M. Dalal, D.G. Johns and S. Broder, *Biochem. Biophys. Res. Commun., 140* (1986) 735.

3 T.S. Lin, R.F. Schinazi, M.S. Chen, E. Kinney-Thomas and W.H. Prusoff, *Biochem. Pharmacol., 36* (1987) 311.

4 M.M. Mansuri, J.E. Starrett, Jr., I. Ghazzouli, M.J.M. Hitchcock, R.Z. Sterzycki, V. Brankovan, T.S. Lin, E.M. August, W.H. Prusoff, J.-P. Sommadossi and J.C. Martin, *J. Med. Chem., 32* (1989) 461.

5 R. Yarchoan, H. Mitsuya, R.V. Thomas, J.M. Pluda, N.R. Hartman, C.-F. Perno, K.S. Marczyk, J.-P. Allain, D.G. Johns and S. Broder, *Science, 245* (1989) 412.

6 R. Yarchoan, C.-F. Perno, R.V. Thomas, R.W. Klecker, J.-P. Allain, R.J. Willis, N. McAtee, M.A. Fischl, R. Dubinsky, M.C. McNeely, H. Mitsuya, J.M. Pluda, T.J. Lawley, M. Leuther, B. Safai, J.M. Collins, C.E. Myers and S. Broder, *Lancet,* (1988) 76.

7 M.A. Fischl, D.D. Richman, M.H. Grieco, M.S. Gotlieb, P.A. Volberding, O.L. Laskin, J.M. Leedom, J.E. Groopman, D. Mildvan, R.T. Schooley, G.G. Jackson, D.T. Durack and D. King, *N. Engl. J. Med., 317* (1987) 185.

8 P.A. Furman, J.A. Fyfe, M.H. St. Clair, K. Wienhold, J.L. Rideout, G.A. Freeman, S.N. Lehrman, D.P. Bolognesi, S. Broder, H. Mitsuya and D.W. Barry, *Proc. Natl. Acad. Sci. USA, 83* (1986) 8333.

9 E.W. Taylor, P. Van Roey, R.F. Schinazi and C.K. Chu, *Antiviral Chem. Chemotherap., 1* (1990) 163.

10 C. Walsh, in A. Meister (ed.), *Advances in Enzymology,* Interscience, New York, 1985, Vol. 55, p. 197.

11 J.T. Welch, *Tetrahedron, 43* (1987) 3123.

12 J. Mann, *Chem. Soc. Rev., 16* (1987) 381.

13 H. Mitsuya and S. Broder, *Proc. Natl. Acad. Sci. USA, 83* (1986) 1911.

14 K.A. Watanabe, K. Harada, J. Zeidler, J. Matulic-Adamic, K. Takahashi, W.-Y. Ren, L.-C. Cheng, J.J. Fox, T.-C. Chou, Q.-Y. Zhu, B. Polsky, J.W.M. Gold and D. Armstrong, *J. Med. Chem., 33* (1990) 2145, and reference therein.

15 R.Z. Sterzyaki, I. Ghazzouli, V. Brankovan, J.C. Martin and M.M. Mansuri, *J. Med. Chem., 33* (1990) 2150.

16 J.A. Martin, D.J. Bushnell, I.B. Duncan, S.J. Dunsdon, M.J. Hall, P.J. Machin, J.H. Merrett, K.E.B. Parkes, N.A. Roberts, G.J. Thomas, S.A. Galpin and D. Kinchington, *J. Med. Chem., 33* (1990) 2137.

17 D.F. Smee, M. Chernow, M. Kraft, P.M. Okamoto and E.J. Prisbe, *Nucleosides Nucleotides, 7* (1988) 155.

18 L.W. Hertel, J.S. Kroin, J.W. Misner and J.M. Tustin, *J. Org. Chem., 53* (1988) 2406.

19 K. Biggadike, A.D. Borthwick, A.M. Exall, B.E. Kirk and R.A. Ward, *J. Chem. Soc., Chem. Commun.,* (1988) 898.

20 K. Harada, J. Matulic-Adamic, R.W. Price, R.F. Schinazi, K.A. Watanabe and J.J. Fox, *J. Med. Chem., 30* (1987) 226.

21 M.M. Mansuri, I. Ghazzouli, M.S. Chen, H.G. Howell, P.R. Brodfuehrer, D.A. Benigni and J.C. Martin, *J. Med. Chem., 30* (1987) 867.

22 A. Van Aerschot and P. Herdewijn, *Bull. Soc. Chim. Belg., 98* (1989) 931.

23 P. Herdewijn and A. Van Aerschot, *Bull. Soc. Chim. Belg., 98* (1989) 943.

24 A. Van Aerschot, P. Herdewijn, J. Balzarin, R. Pauwels and E. De Clercq, *J. Med. Chem., 32* (1989) 1743.

25 K. Green and D.M. Blum, *Tetrahedron Lett., 32* (1991) 2091.

26 See S. Rozen, *Acc. Chem. Res., 21* (1988) 307, and reference therein.

27 H. Meinert and D. Cech, *Z. Chem., 12* (1972) 292.

28 D. Cech, H. Meinert, G. Etzold and P. Langen, *J. Prakt. Chem., 315* (1973) 149.

29 R.R. Talekar, University of Birmingham, unpublished results.

30 M.J. Robins, M. MacCoss, S.R. Naik and G. Ramani, *J. Am. Chem. Soc., 98* (1976) 7381.