Some novel nucleoside rearrangements effected by (diethylamino)sulphur trifluoride: synthesis and antiviral properties of some fluorine-containing 3′-azido-3′-deoxythymidine derivatives

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Abstract

The reaction of pyrimidine nucleoside 5′-aldehydes with (diethylamino)sulphur trifluoride (DAST) to produce 5′-deoxy-5′,5′-difluoronucleosides is reported. The preferred reaction is the production of the O^2,5′-anhydro-5′-fluoronucleoside. If this is prevented by substitution at O^4 or N-3 then, in the former case, either DAST no longer reacts or under drastic conditions the C(1′)–N(1) bond breaks and the heterocyclic base remains joined by C-5′ → O^2 to a glycosyl fluoride. In the latter case, the 5′-aldehyde of 2′,3′-*O*-isopropylideneuridine gives the 5′-deoxy-5′,5′-difluoro compound as the sole identifiable product. With the 5′-aldehyde of AZT [suitably protected at N-3] as starting material, treatment with DAST yields a diastereoisomeric mixture of glycosyl fluorides and a derivative of 5′-deoxy-5′,5′-difluoro AZT from which 3′-azido-3′,5′-dideoxy-5′,5′-difluorothymidine could be isolated. This compound is not toxic nor has it any activity against human immunodeficiency virus type-1 (HIV-1) at concentrations up to 100 μM.

Introduction

In another publication [1], we outlined our attempts to synthesize 5′-deoxy-5′,5′-difluoro derivatives of pyrimidine nucleosides by synthesis of the appropriate sugar moiety followed by condensation with a suitably protected heterocyclic base. The synthesis of the sugar moiety failed because a series of intramolecular rearrangements took place and the usual product was a glycosyl fluoride.

The CF_2H group has been proposed [2] as a reasonable isosteric and isopolar replacement for neutral oxygen. As an isopolar replacement for the hydroxy group, CF_2H is preferred to CH_2F as it more closely resembles an OH group in structure. Thus, compounds containing C–F bonds, which are relatively stable both chemically and metabolically, often have interesting medicinal properties and the electronic properties of the molecule can be

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modified by the strong electronegative character of fluorine. The CF_2H group is more likely to be involved in hydrogen bonding as a hydrogen acceptor and to a lesser extent as a hydrogen donor.

During the course of this work, a preliminary communication [3], followed by a full paper [4], described the synthesis of a 5′-deoxy-5′,5′-difluoro derivative of adenosine following treatment of the 5′-aldehyde with DAST. We describe here experiments which confirm that, unless steps are taken to prevent it, treatment of pyrimidine nucleosides (or their 5′-aldehydes) with DAST leads to O^2,5′-anhydronucleoside formation. Of course, the purine nucleosides cannot form such anhydronucleosides and so the 5′,5′-difluoro compounds could be isolated, albeit in rather poor (18%) yield [4].

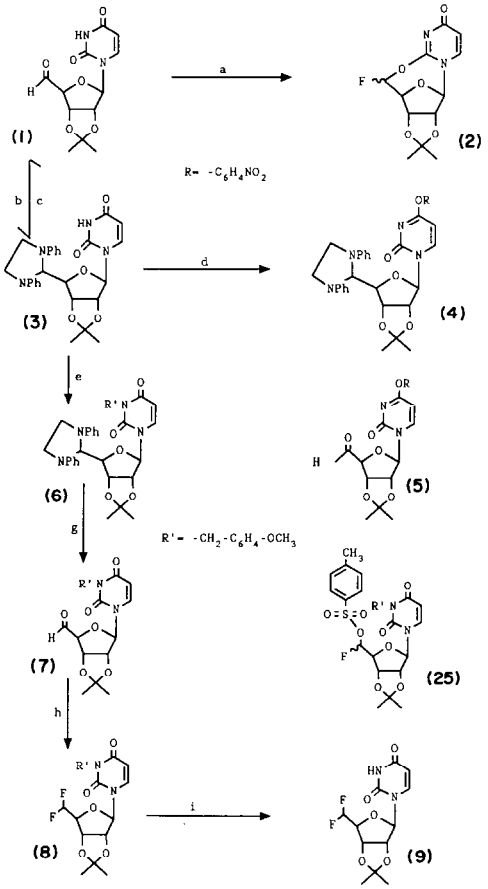
In the case of pyrimidine nucleosides, if anhydronucleoside formation is prevented by blocking the N-3- or O^4-positions, the major products found upon treatment with DAST are glycosyl fluorides with the heterocyclic base joined $O^2 \rightarrow C5'$. The 5′-deoxy-5′,5′-difluoronucleosides can also be isolated and two new derivatives of AZT have been characterized and their anti-HIV-1 activity investigated.

Chemistry

2′,3′-*O*-Isopropylideneuridine was used as a model compound (Scheme 1) as the aldehyde **1**, and its isolation, characterization and regeneration from the *N*,*N*′-diphenylethylenediamino derivative **3** are well established. We initially confirmed the result reported by Hayakawa *et al.* [5] (data not shown) that treatment of 2′,3′-*O*-isopropylideneuridine itself with DAST gave no fluorinated product and only the O^2,5′-anhydronucleoside could be isolated. In a similar reaction, treatment of the corresponding 5′-aldehyde **1** with DAST gave a diastereoisomeric mixture of the O^2,5′-anhydro-5′-fluoro derivative **2** in low yield. The two diastereoisomers which were not present in equal amounts could be distinguished easily by their ^1H and ^{19}F NMR spectra, but as the newly formed ring is seven-membered an absolute assignment of configuration at C-5′ is not possible. The observed product arises following the expected attack of DAST on the 5′-aldehyde, proton abstraction from N-3 by fluoride ion and formation of the O^2,5′-anhydro linkage which is subsequently attacked by fluoride ion.

Thus, to produce the required 5′,5′-difluoro derivatives, anhydronucleoside formation has to be prevented. This can be done in several ways and two were investigated. Firstly the 4-nitrophenyl group [6] was introduced at O^4 to give compound **4**. The corresponding 5′-aldehyde **5** was prepared and characterized but would not give any identifiable products upon reaction with DAST. The only products found but not fully characterized (data not shown) were starting material and the aldehyde formed by inversion of configuration at C-4′. When the reaction was left for a longer time, or at elevated temperatures, decomposition occurred.

The second blocking group used to prevent anhydronucleoside formation was via *p*-methoxybenzyl chloride alkylation at N-3 [7]. The corresponding



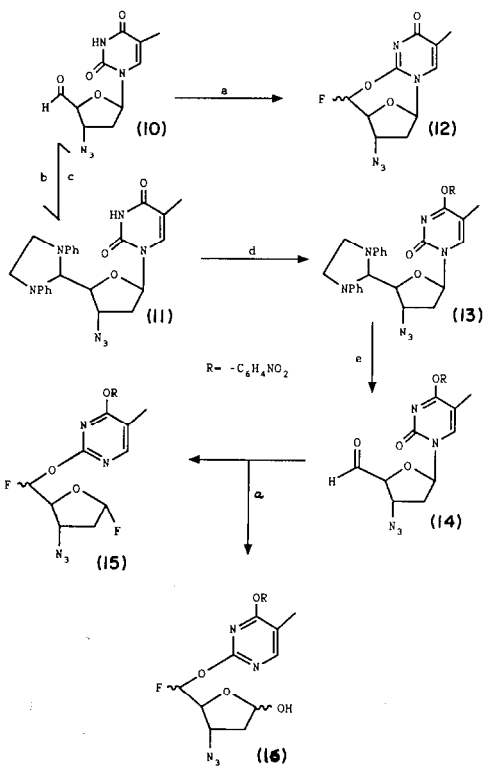
Scheme 1. Reagents: (a) DAST, CH_2Cl_2; (b) *N,N'*-diphenylethylenediamine; (c) pTsOH, CH_3COCH_3; (d) mesitylenesulphonyl chloride, DMAP, DBO, 4-NO_2–C_6H_4–OH; (e) NaH, 4-MeO–C_6H_4–CH_2Cl; (f) pTsOH; (g) pTsOH; (h) DAST, CH_2Cl_2; (i) CAN.

aldehyde **7** was again produced, characterized and treated with DAST. The reaction now proceeded smoothly to give a reasonable (52%) yield of the 5′-deoxy-5′,5′-difluoro derivative **8** from which the N-3-protecting group could be removed using ceric ammonium nitrate [8] to give the required product **9**. Compound **8** was fully characterized and in particular the ^{19}F NMR spectrum showed an AB pattern characteristic of two non-equivalent fluorine atoms which was also confirmed by the 400 MHz ^1H NMR spectrum. The necessary decoupling experiments were performed to confirm the individual resonance assignments.

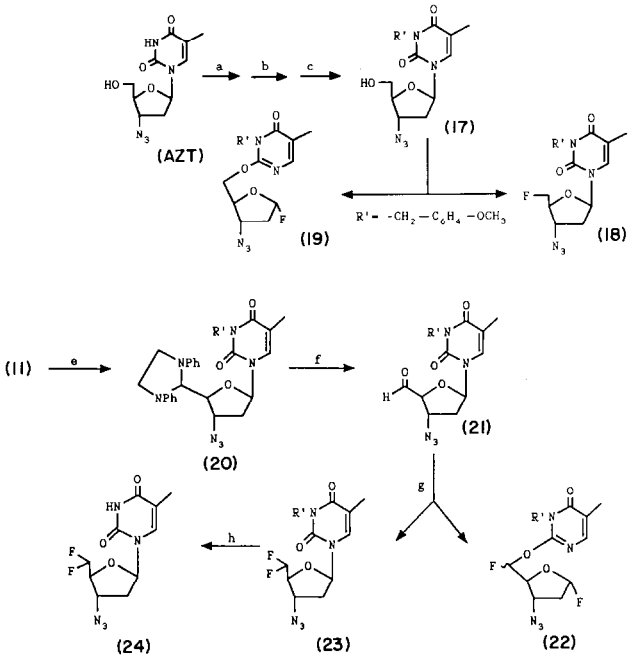
On one occasion when compound **7** was treated with DAST, in addition to the compound described above, two further compounds were isolated. These were shown to be the two diastereoisomers (**25**) formed by attack of traces of the *p*-toluenesulphonate used in the regeneration of the aldehyde **7** from its derivative **6**. The absolute configuration of the two diastereoisomers

could not be assigned but each was characterized by ^{19}F NMR, 400 MHz ^{1}H NMR and NOE difference NMR spectroscopy.

Attention was then turned to the corresponding reactions starting with 3′-azido-3′-deoxythymidine (AZT) as starting material (Schemes 2 and 3). The rationale for using AZT was two-fold. Firstly, it is a very convenient source of a stable pyrimidine nucleoside which has no functional groups which require protection. This makes the chemical synthesis, in what is already a very complex system, as simple as possible. Secondly, as AZT already has a biological activity which depends upon thymidine kinase-recognition of the 5′-hydroxy group, it is a legitimate starting material with which to investigate modification of the 5′-substituent. We would not expect to retain antiviral activity but one might expect to see toxicity if the analogues were kinase inhibitors. As O^2,5′-anhydro-3′-azido-3′-deoxythymidine [9] has been shown to have significant activity against human immunodeficiency virus (HIV), it was decided to treat the 5′-aldehyde of AZT [**10**, produced in the usual way and characterized and regenerated from the *N*,*N*′-diphenylethylenediamino derivative **11**] with DAST. The expected diastereoisomeric mixture of compounds (**12**, Scheme 2) was formed in good (70%) yield, but



Scheme 2. Reagents: (a) DAST; (b) *N*,*N*′-diphenylethylenediamine; (c) TsOH; (d) mesitylenesulphonyl chloride, DMAP, DBO, 4-NO_2–C_6H_4–OH; (e) TsOH.



Scheme 3. Reagents: (a) tBDPSCl, C_6H_5N; (b) NaH, 4-OMe$-C_6H_4-CH_2Cl$; (c) TBAF, THF; (d) DAST; (e) NaH, 4-OMe$-C_6H_4-CH_2Cl$; (f) TsOH; (g) DAST; (h) CAN.

again it was not possible to assign the specific stereochemistry to the individual isomers.

Despite the failure of the O^4-(4-nitrophenyloxy) derivative of uridine **5** to react with DAST, the corresponding derivative of AZT (**14**) was synthesized in a similar way using the *N,N'*-diphenylethylenediamino derivative **13** (Scheme 2). The 5'-aldehyde **14** was regenerated in the usual way and on treatment with DAST gave a very complex mixture which included some starting material. From this mixture, two products could be isolated and separated. Neither was the required 5',5'-difluoro compound but instead the C1'–N(1) bond had broken and the heterocyclic base was now only linked C-5' $\rightarrow O^2$. Following extensive NMR spectral analysis, the more polar compound was shown to be the glycosyl fluoride **15** which corresponds to the intramolecular rearrangement products seen previously with simple sugar derivatives [1]. The less polar compound was an anomeric mixture (**16**). In the case of both **15** and **16**, only one diastereoisomer at C-5' was present, but an absolute assignment was not possible.

Compounds with a heterocyclic base substituted at C-5' of a sugar moiety (usually at N rather than O) are called 'reversed nucleosides' [10] and several examples have been reported [11]. It is possible that with suitable conditions [12], O $\rightarrow$ N migration could be achieved with compound **15** and the fluorine

on C-1′ could then be substituted with another heterocyclic base as we have achieved previously in a simpler system [1].

In a final attempt to produce the required 5′,5′-difluoro derivative **24**, the corresponding series of reactions was performed on the *N(3)*-(4-methoxybenzyl)-substituted compound **21** (Scheme 3). A trial experiment was performed by treating the blocked nucleoside **17** itself with DAST. This reaction proceeded smoothly in high yield (> 90%) to give a separable mixture of two products (**18** and **19**), of which the former is the required 5′-fluoro compound and the latter is the corresponding glycosyl fluoride in which the base is now linked to the sugar moiety solely by C-5′ → O^2. This experiment thus suggested that treatment of the corresponding aldehyde of AZT (**21**) might indeed give the required 5′,5′-difluoro compound **23**.

Compound **20** was isolated and characterized in the usual way and used to regenerate the aldehyde **21**. Treatment of this with DAST showed (TLC) the presence of one major product which could be isolated in reasonable (51%) yield. Characterization by NMR spectroscopy, however, revealed the presence of three compounds (**22**a,b; **23**) which were inseparable. Analysis of this complex mixture by ^{19}F NMR and 400 MHz ^1H NMR spectroscopy with extensive decoupling experiments and a COSY spectrum (data not shown) confirmed the identity of the compounds in this mixture.

It was decided to deblock the mixture and attempt to separate the resulting nucleoside products. However, upon treatment with ceric ammonium nitrate, only one product could be detected and this was identified as the required difluoro compound **24**. It is likely that the products from the compounds **22** had decomposed. The product (**24**) was characterized by ^{19}F NMR and 200 MHz ^1H NMR spectroscopy, MS and elemental analysis.

Thus it is possible to produce 5′,5′-difluoro derivatives of pyrimidine nucleosides by treatment of the corresponding 5′-aldehydes with DAST. However it is necessary to prevent anhydronucleoside formation and the blocking group of choice to achieve this and also to prevent exclusive production of a reversed nucleoside is the *N(3)*-(4-methoxybenzyl) derivative.

Antiviral testing

Antiviral and cytotoxicity testing was carried out as described previously [13] on compounds **12** (mixed isomers) and compound **24**, against HIV-1. Compound **12** showed an effect of 33% protection at 100 μM. Compound **24** showed no significant activity on toxicity at 100 μM.

Hence, there is presumably very little, if any, recognition of compound **24** by the cellular thymidine kinase, as this would result in toxicity. The failure of the fluorinated anhydronucleosides **12** to show significant activity (the equivalent compound with H replacing F has an EC_{50} value of 0.56 μM[9]) is presumably a measure of their greater chemical stability. Thus the activity of the non-fluorinated analogue is almost certainly a result of its hydrolysis to AZT and is not a property of the anhydronucleoside itself.

Experimental

General procedures

Melting points were obtained on a Gallenkamp apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a JEOL FX90Q (90 MHz), JEOL GX270 (270 MHz), Bruker AC200 (200 MHz) and WH 400 (400 MHz) spectrometer in $CDCl_3$ (unless otherwise stated), relative to an internal tetramethylsilane reference. ^{19}F NMR spectra were obtained with a JEOL FX90Q instrument with trichlorofluoromethane as an internal reference. FT 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 a 30% H_2SO_4 solution in ethanol and heating. Column chromatography was performed on silica gel 60, 70–250 mesh, type 7734 or 230–400 mesh, type 9385 (Merck).

General procedure for the isolation of nucleoside-5'-aldehydes

To a solution of the 5',5'-(*N*,*N'*-diphenylethylenediamino) derivative of a nucleoside-5'-aldehyde (0.42 mmol) prepared in the usual way [14] in dichloromethane (12.5 ml) at 0 °C was added a solution of *p*-toluenesulphonic acid hydrate (1.26 mmol) in acetone (7 ml) with stirring. The solution was allowed to warm to room temperature and after 1 h the mixture was filtered and the filtrate taken to dryness under reduced pressure. Traces of solvent were removed by placing the gum so obtained under high vacuum for 2 min and the crude aldehyde was used immediately.

O^2,5'-Anhydro-5'-fluoro-2',3'-O-isopropylideneuridine (2)

To compound **1** [15], regenerated from the *N*,*N'*-diphenylethylenediamino derivative **3** as described above (0.2 g, 0.42 mmol), in dry dichloromethane (1.5 ml) at 0 °C under nitrogen, was added (diethylamino)sulphur trifluoride (DAST) (0.057 ml, 0.42 mmol) and the reaction mixture stirred at 0 °C for 5 min before allowing it to warm to room temperature. After 15 min, the reaction mixture was gently heated to 40 °C, stirred for 2 h and a further portion of DAST (0.026 ml, 0.195 mmol) added. After a further hour at 40 °C, the solution was diluted with water (5 ml), poured into aqueous sodium bicarbonate (5 ml) and the contents of the organic layer worked-up in the usual way. The material so obtained was purified by silica gel chromatography with ethyl acetate/ethanol (9:1) to give the major diastereoisomer (34 mg, 29%) as a white solid. Further fractions were combined and repurified by reverse-phase HPLC with acetonitrile/water (1:1) to give a less polar diastereoisomer (**2a**) (9.5 mg, 8.1%) as a white solid and a further 7 mg (6.5%) of the first diastereoisomer.

The more polar (major) diastereoisomer (**2b**): UV (ν_{max}) 236 nm (ϵ 13 400). ^{1}H NMR δ: 7.2 (1H, d, H-6); 6.1 (1H, d, H-5); 5.4 (1H, d, H-1′); 5.3–5.05 (1H, d, ($J_{H(5')-F(5')}$ = 50 Hz), H-5′); 5.15 (1H, d, H-2′); 4.9 (1H, d, H-3′); 4.75 (1H, s, H-4′); 1.5 (3H, s, C–CH_3); 1.4 (3H, s, C–CH_3) ppm. ^{19}F NMR (84.26 MHz) δ: −138.3 (1F, d, ($J_{F(5')-H(5')}$ = 46 Hz), F-5′) ppm. MS *m/z*: 284 $(M)^+$. Analysis: $(C_{12}H_{13}H_2O_5F)$C,H,N*.

The less polar (minor) diastereoisomer: UV (ν_{max}) 233 nm (ϵ 11 600) ^{1}H NMR δ: 7.3 (1H, d, H-6); 6.15 (1H, d, H-5); 6.1–5.85 (1H, dd ($J_{F(5')-H(5')}$ = 50 Hz), H-5′); 5.45 (1H, s, H-1′); 4.9 (2H, m, H-2′, H-3′); 4.75 (1H, s, H-4′); 1.5 (3H, s C–CH_3); 1.3 (3H, s, C–CH_3) ppm. ^{19}F NMR (84.26 MHz) δ: −140.4 (1F, d ($J_{F(5')-H(5')}$ = 46 Hz), F-5′) ppm. MS *m/z*: 285 $(M+H)^+$; found M^+ 284.0843, $C_{12}H_{13}N_2O_5F$ requires M 284.2188.

*5′-Deoxy-5′,5′-(*N,N′*-diphenylethylenediamino)-2′,3′-*O*-isopropylidene-*O*^{4}-(4-nitrophenyl)-uridine (**4**)*

To compound **3** (0.5 g, 1.05 mmol) in dry dichloromethane (5 ml) was added dry triethylamine (0.7 ml, 5.25 mmol), 2-mesitylenesulphonyl chloride (0.33 g, 1.56 mmol) and 4-(dimethylamino)pyridine (0.03 g, 0.26 mmol) with stirring and exclusion of moisture at room temperature. The reaction was complete after 30 min (TLC) and then 1,4-diazabicyclo[2.2.2]octane

TABLE 1

Elemental analyses of prepared compounds

Compound No.	Formula	Required				Found			
		C	H	N	F	C	H	N	F
2	$C_{12}H_{13}N_2O_5F$	50.8	4.6	9.8	6.7	51.1	4.7	9.5	6.9
4	$C_{32}H_{31}N_7O_5$	64.3	5.2	11.7	–	64.0	5.5	11.4	–
6	$C_{34}H_{37}N_4O_6$	68.5	6.2	9.4	–	68.3	5.9	9.5	–
8	$C_{20}H_{22}N_2O_6F_2$	56.5	5.2	6.6	9.0	56.4	5.3	6.2	9.2
9	$C_{12}H_{14}N_2O_5F_2 \cdot 0.6H_2O$	45.7	4.8	8.8	12.1	45.4	5.0	8.2	ND[a]
11	$C_{26}H_{31}N_7O_4$	62.7	5.5	21.3	–	62.9	5.4	21.1	–
12	$C_{10}H_{10}N_5O_4F$	44.7	3.8	26.1	7.1	44.5	3.8	24.5	ND
13	$C_{30}H_{28}N_8O_5$	62.0	4.8	19.3	–	62.2	5.1	19.0	–
15	$C_{16}H_{14}N_6O_5F_2 \cdot 0.3C_6H_{12}$	49.5	4.2	19.1	8.8	49.2	4.0	18.9	ND
16	$C_{16}H_{15}N_6O_6F \cdot 0.6H_2O$	46.1	3.9	20.1	4.6	46.4	3.6	19.7	ND
17	$C_{18}H_{21}N_5O_5$	55.8	5.5	18.0	–	55.8	5.9	17.6	–
19	$C_{18}H_{20}N_5O_4F$	55.5	5.2	17.9	4.9	55.7	5.6	17.4	ND
20	$C_{32}H_{33}N_7O_4$	66.3	5.7	16.9	–	66.5	6.0	16.7	–
22+23	$C_{18}H_{19}N_5O_4F_2$	53.1	4.7	17.2	9.3	53.5	5.0	16.7	ND
24	$C_{10}H_{11}N_5O_3F_2$	42.0	3.5	24.5	13.3	41.7	3.8	24.2	12.9
25	$C_{27}H_{29}N_2O_9SF$	56.3	5.2	4.8	3.3	56.1	5.2	4.7	3.7

[a]ND = not determined.

*All elemental analyses are listed in Table 1.

(0.02 g, 0.21 mmol) and 4-nitrophenol (0.28 g, 2.1 mmol) were added with stirring and exclusion of moisture. The solution was left stirring for 1 h at room temperature, when it was diluted with dichloromethane, washed with sodium bicarbonate and the organic layer worked-up in the usual way. The product was recrystallized from ethanol to give the title compound as a pale yellow crystalline solid [0.49 g, 73%, m.p. > 230 °C (d)]. ^{1}H NMR δ: 8.35 (1H, d, H-6); 7.4–6.7 (14H, m, 2×Ph, 4 ArH); 5.9–5.8 (3H, m, H-1′, H-5′); 4.9 (1H, t, H-4′); 4.7 (1H, dd, H-2′); 4.5 (1H, dd, H-3′); 3.9–3.6 (4H, m, 2×CH_2); 1.4 (3H, s, C–CH_3); 1.35 (3H, s, C–CH_3) ppm. MS *m/z*: 599 $(M+H)^+$. Analysis: ($C_{32}H_{31}O_7N_5$)C,H,N.

2′,3′-O-Isopropylidene-O^4-(4-nitrophenyl)-uridine-5′-aldehyde (5)

The title compound was isolated by the general procedure detailed above. ^{1}H NMR δ: 9.4 (1H, s, CHO); 8.4–8.1 (2H, d, ArH); 7.6 (1H, d, H-6); 7.4–7.2 (2H, d, ArH); 6.2 (1H, d, H-5); 5.6 (1H, s, H-1′); 5.2–5.1 (2H, m, H-2′, H-3′); 4.6 (1H, s, H-4′); 1.5 (3H, s, C–CH_3); 1.25 (3H, s, C–CH_3) ppm.

5′-Deoxy-5′,5′-(N,N′-diphenylethylenediamino)-2′,3′-O-isopropylidene-N(3)-(4-methoxybenzyl)-uridine (6)

To compound **3** (0.5 g, 1.05 mmol) dissolved in dry *N,N*-dimethylformamide (3 ml), was added sodium hydride (50% dispersion in oil, 0.06 g, 1.05 mmol) with stirring and exclusion of moisture. After 5 min, 4-methoxybenzyl chloride was added and the resulting yellow solution was stirred for 24 h. Methanol (5 ml) was then added and the reaction mixture poured into sodium bicarbonate solution, dichloromethane added and the organic layer worked-up in the usual way to give a product which was purified by silica gel chromatography with hexane/ethyl acetate (6:4) to give the title compound as a white foam (0.48 g, 78%). ^{1}H NMR δ: 7.5–6.5 (15H, m, H-6, 2×Ph, 4 ArH); 5.8 (2H, m, H-1′, H-5′); 5.65 (1H, d H-5); 4.9 (3H, m, H-2′, H-3′, H-4′); 3.7 (6H, s, 3×CH_2); 3.3 (3H, s, O–CH_3); 1.35 (3H, s, C–CH_3); 1.2 (3H, s, C–CH_3) ppm. MS *m/z*: 597 $(M+H)^+$; 619 $(M+Na)^+$. Analysis: ($C_{34}N_{37}N_4O_6$)C,H,N.

2′,3′-O-Isopropylidene-N(3)-(4-methoxybenzyl)-uridine-5′-aldehyde (7)

The title compound was isolated by the general procedure detailed above as an orange gum. ^{1}H NMR δ: 9.2 (1H, s, CHO); 7.8–6.8 (5H, m, H-6, ArH); 5.6 (1H, d, H-5); 5.5–4.5 (4H, m, H-1′, H-2′, H-3′, H-4′); 3.7 (3H, s, O–CH_3); 3.1–2.8 (2H, q, CH_2); 1.45 (3H, s, C–CH_3); 1.2 (3H, s, C–CH_3) ppm.

5′-Deoxy-5′,5′-difluoro-2′,3′-O-isopropylidene-N(3)-(4-methoxybenzyl)-uridine (8)

Compound **7** (0.25 g, 0.59 mmol) was dissolved in dry dichloromethane (10 ml) under dry nitrogen and (diethylamino)sulphur trifluoride (0.14 ml, 1.18 mmol) added dropwise and the reaction mixture stirred for 4 h at room temperature. The reaction mixture was then quenched with water (5 ml), stirred for 5 min and then poured into sodium bicarbonate solution. The

aqueous layer was extracted with dichloromethane and the organic layers were worked-up in the usual way to give a product which was purified by silica gel chromatography with hexane/ethyl acetate (1:1) to give the title compound as a white foam (0.13 g, 52%). ^{1}H NMR δ: 7.4 (2H, d, ArH); 7.15 (1H, d, H-6); 6.7 (2H, d, ArH); 6.05, 5.9 and 5.77 (1H, d ($J_{H(5')-H(4')}$ = 5.6 Hz) of d ($J_{H(5')-F(B)}$ = 55 Hz) of d ($J_{H(5')-F(A)}$ = 58 Hz), H-5'); 5.9 (1H, d, H-5); 5.4 (1H, m, H-2'); 5.1 (1H, m, H-3'); 5.0 (2H, s, CH_2); 4.3 (1H, m, H-4'); 3.8 (3H, s, O–CH_3); 1.6 (3H, s, C–CH_3); 1.4 (3H, s, C–CH_3) ppm. ^{19}F NMR (84.26 MHz) δ: −122 and −132 (2F, AB spectrum (J_{AB} = 302 Hz, F_A at −126.27 ppm, F_B at −128.9 ppm) with further d ($J_{F(A)-H(5)} = J_{F(B)-H(5)}$ = 56 Hz) of d ($J_{F(A)-H(4)}$ = 12 Hz, $J_{F(B)-H(4)}$ = 6 Hz), F-5') ppm. MS *m/z*: 425 $(M+H)^+$. Analysis: $(C_{20}H_{22}N_2O_6F_2)$C,H,N,F.

(R,S)-5'-Fluoro-2',3'-O-Isopropylidene-N(3)-(4-methoxybenzyl)-5'-O-(4-toluenesulphonyl)-uridine (25)

On one occasion when the previously described preparation was performed, two additional compounds were detected (TLC). Both were less polar than compound **8** and could be isolated by silica gel chromatography and identified as the two diastereoisomers of the title compound.

The more polar (minor) diastereoisomer (**25a**) (0.08 g, 10%): ^{1}H NMR δ: 7.84 (2H, d, toluoyl *ortho*-H), 7.44 (2H, d, ArH); 7.28 (2H, d, toluoyl *meta*-H); 7.32 (1H, d, H-6); 6.64 (2H, d, ArH); 6.38 and 6.22 (1H, d, ($J_{H(4')-H(5')}$ = 6 Hz) of d ($J_{H(5')-F(5')}$ = 57 Hz), H-5'); 5.73 (1H, d, H-5); 5.59 (1H, d, H-1'); 5.01 and 4.98 (2H, AB spectrum (J_{AB} = 13.5 Hz, F_A at 4.93 ppm, F_B at 5.02 ppm), CH_2-benzyl); 4.99 (1H, m, H-2'); 4.96 (1H, m, H-3'); 4.3 (1H, m, H-4'); 3.8 (3H, s, O–CH_3); 2.45 (3H, s, CH_3-toluoyl); 1.56 (3H, s, C–CH_3); 1.36 (3H, s, C–CH_3) ppm. ^{19}F NMR (84.26 MHz) δ: −133.1 and −133.8 (1F, d ($J_{F(5')-H(4')}$ = 9 Hz) of d ($J_{F(5')-H(5')}$ = 57 Hz), F-5') ppm. MS *m/z*: 577 $(M+H)^+$.

The less polar (major) diastereoisomer (**25b**) (0.28 g, 36%): ^{1}H NMR δ: 7.6 (2H, d, toluoyl *ortho*-H); 7.45 (2H, d, ArH); 7.19 (2H, d, toluoyl *meta*-H); 7.0 (1H, d, H-6); 6.85 (2H, d, ArH); 6.24 and 6.12 (1H, d ($J_{H(5')-H(4')}$ = 6 Hz) of d ($J_{H(5')-F(5')}$ = 55 Hz), H-5'); 5.71 (1H, d, H-5); 5.44 (1H, s, H-1'); 5.14 (1H, m, H-3'); 4.98 (1H, dd, H-2'); 5.03 and 5.01 and 4.98 and 4.96 (2H, AB spectrum (J_{AB} = 13 Hz, F_A at 5.00 ppm, F_B at 5.04 ppm), CH_2-benzyl); 4.25 (1H, m, H-4'); 3.78 (3H, s, O–CH_3); 2.4 (3H, s, CH_3-toluoyl); 1.51 (3H, s, C–CH_3); 1.23 (3H, s, C–CH_3) ppm. ^{19}F NMR (84.26 MHz) δ: −136.7 and −137.4 (1F, d ($J_{F(5')-H(4')}$ = 6 Hz) of d ($J_{F(5')-H(5')}$ = 55 Hz), F-5') ppm. MS *m/z*: 577 $(M+H)^+$. Analysis: $(C_{27}H_{29}N_2O_9SF)$C,H,N,F.

5'-Deoxy-5',5'-difluoro-2',3'-O-isopropylideneuridine (9)

To compound **8** (80 mg, 0.19 mmol) in acetonitrile/water (9:1, 0.8 ml) was added ceric ammonium nitrate (0.21 g, 0.38 mmol) and the reaction mixture was stirred overnight at room temperature. The reaction mixture

was then diluted with dichloromethane (30 ml), added to sodium bicarbonate solution and the organic layer worked-up in the usual way to give a product which was purified by silica gel chromatography with hexane/ethyl acetate (1:1) to give the title compound which could be further purified by reverse-phase HPLC with acetonitrile/water (85:15) (20 mg, 35%, m.p. 75–80 °C). UV (ν_{max}) 254 nm (ϵ 7450). ^{1}H NMR δ: 9.4 (1H, s, NH); 7.2 (1H, d, H-6); 6.2 and 6.0 and 5.75 (1H, d ($J_{H(5')-H(4')}=6$ Hz) of triplets ($J_{H(5')-F(B)}=J_{H(5')-F(A)}=55$ Hz), H-5'); 5.75 (1H, d, H-5); 5.6 (1H, s, H-1'); 5.1 (2H, m, H-2', H-3'); 4.3 (1H, m, H-4'); 1.55 (3H, s, C–CH_3); 1.35 (3H, s, C–CH_3) ppm. ^{19}F NMR (84.26 MHz) δ: −120 and −130 (2F, AB spectrum ($J_{AB}=302$ Hz, F_A at −122.84 ppm, F_B at −127.86 ppm) with further d ($J_{F(A)-H(5')}=J_{F(B)-H(5')}=55$ Hz) of d ($J_{F(A)-H(4')}=9$ Hz, $J_{F(B)-H(4')}=6$ Hz), F-5') ppm. MS *m/z*: 305 $(M+H)^+$; 327 $(M+Na)^+$. Analysis: $(C_{12}H_{14}N_2O_5F_2\cdot 0.6H_2O)$C,H,N,F.

*3'-Azido-3',5'-dideoxy-5',5'-(*N,N'*-diphenylethylenediamino)-thymidine (11)*

To dry 3'-azido-3'-deoxythymidine (10.0 g, 37.42 mmol), dicyclohexylcarbodiimide (23.16 g, 112.26 mmol) and dry pyridine (3.03 ml, 37.42 mmol) in dry dimethylsulphoxide (6.0 ml) at 0 °C was added trifluoroacetic acid (1.44 ml, 18.71 mmol) and the reaction mixture was stirred for 2 h at 37 °C. After quenching with oxalic acid (9.44 g, 74.84 mmol) in methanol (52.44 ml) and allowing the mixture to stand for 30 min, it was filtered and the solid washed with methanol (2×15 ml). To the filtrate was added *N,N*-diphenylethylenediamine (8.74 g, 41.16 mmol) and glacial acetic acid (4.5 ml) and the reaction kept at 22 °C for 4 h before pouring into sodium bicarbonate solution. This was extracted with chloroform and the organic layers worked-up in the usual way to give a product which could be further purified by silica gel chromatography with hexane/ethyl acetate (6:4) to give the title compound as a white foam (12.42 g, 72%). UV (μ_{max}) 245 nm (ϵ 20 100): ^{1}H NMR δ: 11.3 (1H, s, H-3); 7.3–7.1 (5H, m, Ph); 7.05 (1H, d H-6); 6.9–6.8 (5H, m, Ph); 6.1 (1H, q, H-1'); 5.8 (1H, d, H-5'); 4.5 (1H, q, H-3'); 4.1 (1H, dd, H-4'); 3.9–3.5 (4H, m, 2×CH_2); 2.4–2.2 (2H, m, H-2'); 1.6 (3H, s, CH_3) ppm. MS *m/z*: 460 $(M+H)^+$; 482 $(M+Na)^+$. Analysis: $(C_{26}H_{31}N_7O_4)$C,H,N.

3'-Azido-3'-deoxy-thymidine-5'-aldehyde (10)

Compound **11** was reacted according to the general procedure detailed above to yield the title compound as a yellow gum. ^{1}H NMR δ: 11.4 (1H, m, NH); 9.6 (1H, s, CHO); 7.6 (1H, m, H-6); 6.2 (1H, t, H-1'); 5.1 (1H, t, H-3'); 4.5 (1H, m, H-4'); 2.3 (2H, m, H-2'); 1.6 (3H, s, CH_3) ppm.

O^2,5'-Anhydro-3'-azido-3'-deoxy-5'-fluorothymidine (12)

To compound **10** (0.11 mmol) in dry dichloromethane (2 ml) at −78 °C and stirred under nitrogen was added (diethylamino)sulphur trifluoride

(0.29 ml, 1.62 mmol) and the reaction mixture was stirred for a period of 4 h while gradually warming to room temperature. The reaction was quenched by the addition of water (2 ml), stirred for 5 min, added to sodium bicarbonate (20 ml) and the organic layer worked-up in the usual way to give a product which could be further purified by silica gel chromatography with ethyl acetate/ethanol (9:1) to give separately two diastereoisomers as white foams (**12a**, 70 mg, 48%; **12b**, 32 mg, 22%).

The more polar (major) diastereoisomer (**12a**): UV (ν_{max}) 248 nm (ϵ 14 700): ^{1}H NMR δ: 7.7 (1H, s, H-6); 6.15 (1H, d, H-1′); 6.15–5.95 (1H, d ($J_{H(5')-F(5')}$ = 46 Hz), H-5′); 4.8 (1H, s, H-4′); 4.7 (1H, d, H-3′); 2.7 (1H, dd, H-2′); 2.6 (1H, dd, H-2′); 1.7 (3H, s, CH_3) ppm. ^{19}F NMR δ: −138.3 (1F, d ($J_{F(5')-H(5')}$ = 44 Hz), F-5′) ppm. MS *m/z*: 267 $(M+H)^+$. Analysis: $(C_{10}H_{10}N_5O_4F)$C,H,N.

The less polar (minor) diastereoisomer (**12b**): UV (ν_{max}) 246 nm (ϵ 12 600). ^{1}H NMR δ: 7.8 (1H, s, H-6); 6.45–6.15 (1H, d ($J_{H(5')-F(5')}$ = 48 Hz), H-5′); 6.15 (1H, m, H-1′); 4.8 (1H, s, H-4′); 4.6 (1H, d, H-3′); 2.9–2.5 (2H, m, H-2′); 1.8 (3H, s, CH_3) ppm. ^{19}F NMR δ: −134.4 (1F, d ($J_{F(5')-H(5')}$ = 46 Hz), F-5′) ppm. MS *m/z*: 267 $(M+H)^+$.

*3′-Azido-3′,5′-dideoxy-5′,5′-(*N,N′*-diphenylethylenediamino)*-O^4*-(4-nitrophenyl-thymidine (**13**)*

With compound **11** (0.5 g, 1.08 mmol) as the starting material and using the procedure described above for the preparation of compound **4**, the title compound was purified on a silica gel column with hexane/ethyl acetate (1:1) to give a yellow solid (0.5 g, 79%). ^{1}H NMR δ: 7.6–6.6 (15H, m, H-6, 2×Ph, ArH); 6.1 (1H, t, H-1′); 5.9 (1H, d, H-5′); 4.5 (1H, q, H-3′); 4.2 (1H, dd, H-4′); 3.5–3.3 (4H, m, 2×CH_2); 2.3 (2H, t, H-2′); 1.85 (3H, s, CH_3) ppm. MS *m/z*: 581 $(M+H)^+$. Analysis: $(C_{30}H_{28}N_8O_5)$C,H,N.

*3′-Azido-3′-deoxy-*O^4*-(4-nitrophenyl)-thymidine-5′-aldehyde (**14**)*

With compound **13** (0.43 g, 0.74 mmol) as the starting material, the title compound was isolated by the general procedure detailed above. ^{1}H NMR δ: 9.6 (1H, s, CHO); 8.2 (2H, d, ArH); 7.9 (1H, s, H-6); 7.3 (2H, d, ArH); 6.0 (1H, t, H-1′); 4.5 (2H, m, H-3′, H-4′); 2.2 (2H, m, H-2′); 1.5 (3H, s, CH_3) ppm.

*3-Azido-2,3-dideoxy-5-fluoro-5-*O*-[5-methyl-*O^4*-(4-nitrophenyl)-pyrimidin-2-yl]-α-*D*-ribofuranosyl fluoride (**15**) and 3-azido-2,3-dideoxy-5-fluoro-5-*O*-[5-methyl-*O^4*-(4-nitrophenyl)-pyrimidin-2-yl]-α,β-*D*-ribose (**16**)*

To compound **14** (0.74 mmol) in dry dichloromethane (10 ml) at 0 °C under dry nitrogen was added dropwise (diethylamino)sulphur trifluoride (0.26 ml, 1.42 mmol). The solution was allowed to warm to room temperature and was stirred for 3 h. More (diethylamino)sulphur trifluoride (0.1 ml, 0.55 mmol) was then added and the solution warmed to 40 °C for 1 h when it was quenched with water (10 ml), stirred for 5 min, poured into sodium

bicarbonate, extracted with dichloromethane and the organic layer worked-up in the usual way. The resulting solid was fractionated by silica gel chromatography with hexane/ethyl acetate (7:3) to give the two separate title compounds [the ribosyl fluorides **15** – the more polar compounds – (80 mg, 26%) and, after further purification by reverse-phase HPLC with acetonitrile/water (15:85), the anomeric mixture **16** – the less polar compounds – (20 mg, 7%).

The more polar compounds (**15**): ^{1}H NMR δ: 8.35 (3H, m, H-6, ArH); 7.37 (2H, m, ArH); 6.58 and 6.45 (1H, d ($J_{H(4')-H(5')}$ = 2.9 Hz) of d ($J_{H(5')-F(5')}$ = 54 Hz), H-5'); 6.01 and 6.00 and 5.85 (1H, d ($J_{H(1')-F(5')}$ = 1.2 Hz) of d ($J_{H(1')-H(2a')}$ = 3.9 Hz) of d ($J_{H(1')-F(1')}$ = 64.5 Hz), H-1'); 4.5 (1H, sextet, H-4'); 4.45 (1H, m, H-3'); 2.6–2.4 (1H, m, H-2a'); 2.4–2.3 (1H, m, H-2b'); 1.7 (3H, s, CH_3) ppm. ^{19}F NMR δ: −111.5 and −111.7 and −111.9 and −112.1 (1F, d ($J_{F(1')-H(1')}$ = 64 Hz) of d ($J_{F(1')-H(2a')}$ = 15 Hz) of d ($J_{F(1')-H(2b')}$ = 30 Hz), F-1'); −140.7 (1F, d ($J_{F(5')-H(5')}$ = 55 Hz), F-5') ppm. MS *m/z*: 409 $(M+H)^+$. Analysis: ($C_{16}H_{14}N_6O_5F_2 \cdot 0.3C_6H_{12}$)C,H,N.

The less polar compounds (**16**): the major isomer (**16a**): ^{1}H NMR δ: 8.46 (1H, s, H-6); 8.34–8.28 (2H, d, ArH); 7.54 (2H, d, ArH); 6.7 (1H, d, OH); 6.45 (1H, d ($J_{H(5')-F(5')}$ = 57.5 Hz), H-5'); 5.42 (1H, m, H-1'); 4.3 (1H, m, H-3'); 4.0 (1H, m, H-4'); 2.24 (3H, s, CH_3); 2.1 (1H, m, H-2'); 1.9 (1H, m, H-2') ppm. ^{19}F NMR δ: −134.3 and −134.8 (1F, d ($J_{F(5')-H(4')}$ = 12 Hz) of d ($J_{F(5')-H(5')}$ = 56 Hz), F-5') ppm. The minor isomer (**16b**): ^{1}H NMR δ: 8.48 (1H, s, H-6); 8.34–8.28 (2H, d, ArH); 7.54 (2H, d, ArH); 6.58 (1H, d, OH); 6.43 (1H, d ($J_{H(5')-F(5')}$ = 58 Hz), H-5'); 5.42 (1H, m, H-1'); 4.1 (2H, m, H-3', H-4'); 2.3 (1H, m, H-2'); 2.23 (3H, s, CH_3); 1.75 (1H, m, H-2') ppm. ^{19}F NMR δ: −137.5 and −138.1 (1F, d ($J_{F(5')-H(4')}$ = 12 Hz) of d ($J_{F(5')-H(5')}$ = 58 Hz), F-5') ppm. Combined diastereoisomers: MS *m/z*: 407 $(M+H)^+$. Analysis: ($C_{16}H_{15}N_6O_6F \cdot 0.6H_2O$)C,H,N.

3'-Azido-3'-deoxy-N(3)-*(4-methoxybenzyl)-thymidine (17)*

3'-Azido-5'-*O*-(t-butyldiphenylsilyl)-3'-deoxythymidine (2.5 g, 4 mmol) was dissolved in dry DMF (10 ml) and to the solution was added sodium hydride (50% dispersion in oil, 0.24 g, 4 mmol) which was stirred for 10 min. 4-Methoxybenzyl chloride (0.7 ml, 4.2 mmol) was then added and the reaction mixture allowed to stand at room temperature for 24 h before quenching with methanol (10 ml), pouring in sodium bicarbonate (100 ml) extracting with dichloromethane and working-up the organic layer in the usual way to give a dark yellow gum. This was dissolved in tetrahydrofuran (75 ml), tetrabutylammonium fluoride (1.97 g, 5.2 mmol) added, the reaction mixture stirred for 10 min, taken to dryness and the resulting gum purified by silica gel chromatography with ethyl acetate/hexane (6:4) to give the title compound as a white foam (1.25 g, 67%). ^{1}H NMR δ: 7.5–7.4 (4H, m, ArH); 6.8 (1H, s, H-6); 6.1 (1H, t, H-1'); 5.0 (2H, s, CH_2); 4.4 (1H, m, H-3'); 3.9 (3H, m, H-4', H-5'); 3.8 (3H, s, CH_3); 2.7 (1H, bs, OH); 2.4 (2H, m, H-2'); 1.7 (3H, s, CH_3) ppm. MS *m/z*: 388 $(M+H)^+$. Analysis: ($C_{18}H_{21}O_5N_5$)C,H,N.

3'-Azido-3',5'-dideoxy-5'-fluoro-N(3)-*(4-methoxybenzyl)-thymidine* (**18**) *and 3-azido-2,3-dideoxy-5*-O-*[5-methyl*-N(3)-*(4-methoxybenzyl)-pyrimidin-2-yl-α-*D-*ribofuranosyl* (**19**)

To a solution of compound **17** (0.5 g, 0.133 mmol) in dry dichloromethane (10 ml) under dry nitrogen at −78 °C was added (diethylamino)sulphur trifluoride (0.35 ml, 0.27 mmol), the solution was allowed to reach room temperature and stirred for a further 12 h. The reaction was then quenched with water (5 ml), poured in sodium bicarbonate solution (25 ml), extracted with dichloromethane and the organic layer worked-up in the usual way. The resulting gum was further purified on a silica gel column using hexane/ethyl acetate (6:4) to give the title compounds [more polar compound **18** (0.25 g, 51%); less polar compound **19** (0.23 g, 48%)].

The more polar compound: ^{1}H NMR δ: 7.5 (2H, d, ArH); 7.3 (1H, s, H-6); 6.8 (2H, d, ArH); 6.3 (1H, t, H-1'); 5.05 (2H, d, CH_2); 4.5 and 4.65 and 4.8 (2H, AB spectrum (J_{AB} = 49.56 Hz, H_A at 4.62 ppm, H_B at 4.71 ppm, with further d ($J_{H(A)-F(5')} = J_{H(b)-F(5')} = 49.9$ Hz) of d ($J_{H(5')-H(4')} = 1.9$ Hz), H-5'); 4.3 (1H, m, H-3'); 4.1 (1H, m, H-4'); 3.77 (3H, s, O−CH_3); 2.36–2.21 (2H, m, H-2'); 1.91 (3H, d, CH_3) ppm. ^{19}F NMR δ: −232.9 to −234.4 (1F, d ($J_{F(5')-H(4')} = 31$ Hz) of t ($J_{F(5')-H(5')} = 49$ Hz), F-5') ppm.

The less polar isomer (**19**): ^{1}H NMR δ: 7.5 (1H, s, H-6); 7.35–7.24 (2H, m, ArH); 6.84 (2H, m, ArH); 5.58 (1H, dd, H-1'); 5.2–5.1 (2H, m, CH_2); 4.42–4.35 (2H, m, H-5'); 4.15–4.06 (1H, m, H-3'); 3.95 (1H, m, H-4'); 3.78 (3H, s, O−CH_3); 2.45–2.41 (2H, m, H-2'); 2.0 (3H, s, CH_3) ppm. ^{19}F NMR δ: −104.98 to −106.28 (1F, d ($J_{F(1')-H(1')} = 65.9$ Hz) of d ($J_{F(1')-H(2')} = 31.73$ Hz) of d ($J_{F(1')-H(2')} = 11.59$ Hz) of d ($J_{F(1')-H(4')} = 6.1$ Hz), F-1') ppm. MS *m/z*: 390 $(M+H)^+$. Analysis: $C_{18}H_{20}N_5O_4F$)C,H,N.

3'-Azido-3',5'-dideoxy-5',5'-(N,N'-*diphenylethylenediamino)*-N(3)-*(4-methoxybenzyl)-thymidine* (**20**)

With compound **11** as the starting material (0.6 g, 1.3 mmol) and using the procedure described for the preparation of compound **17**, the title compound was recovered from the organic layer and purified by silica gel chromatography with hexane ethyl acetate (7:3) to give the product as a white foam (0.59 g, 78%). ^{1}H NMR δ: 7.4–6.7 (14H, m, 2×Ph, ArH); 6.2 (1H, t, H-1'); 5.7 (1H, s, H-5'); 5.0 (2H, m, H-3', H-4'); 4.2–4.0 (2H, m, CH_2-benzyl); 3.8 (7H, m, 2×CH_2, O−CH_3); 2.3–2.1 (2H, m, H-2'); 1.6 (3H, s, CH_3) ppm. MS *m/z*: 580 $(M+H)^+$. Analysis: ($C_{32}H_{33}N_7O_4$)C,H,N.

3'-Azido-3'-deoxy-N(3)-*(4-methoxybenzyl)-thymidine-5'-aldehyde* (**21**)

Compound **20** (0.5 g, 0.86 mmol) was reacted according to the general procedure detailed above to yield the title compound as an orange foam. ^{1}H NMR δ: 9.1 (1H, s, CHO); 7.4–6.4 (5H, m, H-6, ArH); 6.2 (1H, t, H-1'); 5.2–5.0 (2H, m, H-3', H-4'); 3.7 (5H, m, O−CH_3, CH_2); 2.4 (2H, m, H-2'); 1.8 (3H, s, CH_3) ppm.

*(5,R,S)-3-Azido-2,3-dideoxy-5-fluoro-5-*O*-[5-methyl-*N*(3)-(4-methoxybenzyl)-pyrimidin-2-yl]-α-D-ribofuranosyl fluorides (**22**) and 3'-azido-3',5'-dideoxy-5',5'-difluoro-*N*(3)-(4-methoxybenzyl)-thymidine (**23**)*

To compound **21** (0.86 mmol) in dry dichloromethane (5 ml) under dry nitrogen at −78 °C was added (diethylamino)sulphur trifluoride (0.23 ml, 1.72 mmol). The reaction mixture was stirred at −78 °C for 1 h and then for 2 h at room temperature before more (diethylamino)sulphur trifluoride was added and the reaction mixture stirred for another 2 h. It was then quenched with water (5 ml), stirred for 5 min, poured into sodium bicarbonate, extracted with dichloromethane and the organic layer worked-up in the usual way to give a gum which could be purified by silica gel chromatography with hexane/ethyl acetate (6:4). The three inseparable title compounds were isolated as a white foam (0.18 g, 51%).

Diastereoisomeric mixture (40% of the total) (**22**): Major isomer (**22a**): ^{1}H NMR δ: 7.42 (1H, s, H-6); 7.21 (2H, m, ArH); 6.78 (2H, m, ArH); 6.72 and 6.58 (1H, d ($J_{H(5')-F(5')}$ = 60 Hz) of d ($J_{H(4')-F(5')}$ = 4 Hz), H-5'); 5.90 and 5.74 (1H, d ($J_{H(1')-F(1')}$ = 60 Hz) of d ($J_{H(2')-H(1')}$ = 4 Hz), H-1'); 5.2–5.0 (2H, m, CH_2); 4.4 (1H, m, H-4'); 4.1 (1H, m, H-3'); 3.69 (3H, s, O–CH_3); 2.4–2.2 (2H, m, H-2'); 1.95 (3H, m, CH_3) ppm. ^{19}F NMR δ: −111.6 and −112.0 and −112.21 and −112.3 (1F, d ($J_{F(1')-H(1')}$ = 64.1 Hz) of d ($J_{F(1')-H(2a')}$ = 27 Hz) of d ($J_{F(1')-H(2b')}$ = 45 Hz), F-1'); −142.8 and −143.6 (1F, d ($J_{F(5')-H(5')}$ = 52 Hz) of d ($J_{F(5')-H(4')}$ = 12 Hz), F-5') ppm. Minor isomer (**22b**): ^{1}H NMR δ: 7.42 (1H, s, H-6); 7.21 (2H, m, ArH); 6.78 (2H, m, ArH); 6.62 and 6.5 (1H, d ($J_{H(5')-F(5')}$ = 60 Hz) of d ($J_{H(4')-F(5')}$ = 4 Hz), H-5'); 5.98 and 5.82 (1H, d ($J_{H(1')-F(1')}$ = 64 Hz) of d ($J_{H(2')-H(1')}$ = 4 Hz), H-1'); 5.2–5.0 (2H, m, CH_2); 4.2 (1H, m, H-3'); 4.0 (1H, m, H-4'); 3.70 (3H, s, O–CH_3); 2.4–2.2 (2H, m, H-2'); 1.95 (3H, m, CH_3) ppm. ^{19}F NMR δ: −111.6 and −112.0 and −112.21 and −112.3 (1F, d ($J_{F(1')-H(1')}$ = 64.1 Hz) of d ($J_{F(1')-H(2a')}$ = 27 Hz) of d ($J_{F(1')-H(2b')}$ = 45 Hz), F-1'); −145.6 and −146.3 (1F, d ($J_{F(5')-H(5')}$ = 55 Hz) of d ($J_{F(5')-H(4')}$ = 12 Hz), F-5') ppm.

Compound **23** (60% of the total) ^{1}H NMR δ: 7.38 (2H, d, ArH); 7.0 (1H, d, H-6); 6.7 (2H, m, ArH); 6.2 (1H, t, H-1'); 6.05 and 5.9 and 5.75 (1H, d ($J_{H(4')-5(5')}$ = 3 Hz) of d ($J_{H(5')-F(B)}$ = 52 Hz) of d ($J_{H(5')-F(A)}$ = 56 Hz), F-5'); 4.95 (2H, s, CH_2); 4.45 (1H, m, H-3'); 4.0 (1H, m, H-4'); 3.68 (3H, s, O–CH_3); 2.4–2.2 (2H, m, H-2'); 1.85 (3H, s, CH_3) ppm. ^{19}F NMR δ: −125.3 to −140 (2F, AB spectrum (J_{AB} = 295 Hz, F_A at −128.1 ppm, F_B at −132.4 ppm), F-5') ppm. Mixed isomers: MS *m/z*: 408 $(M+H)^+$. Analysis: ($C_{18}H_{19}N_5O_4F_2$)C,H,N.

*3'-Azido-3',5',5'-dideoxy-5',5'-difluoro-thymidine (**24**)*

To the mixture of compounds prepared above (**22** and **23**, 0.04 g, 0.1 mmol) dissolved in dry acetonitrile (7.3 ml) was added water (0.73 ml), ceric ammonium nitrate (0.29 g, 0.5 mmol) and the reaction mixture stirred at room temperature for 10 min and then heated under reflux for 10 min. By this time the starting materials had disappeared (TLC), the reaction mixture was allowed to cool, water (5 ml) added and extracted with ethyl acetate

(4×10 ml). The combined organic layers were worked-up in the usual way to give a residue which could be purified by silica gel chromatography using ethyl acetate/hexane (4:6) to give the title compound as a clear gum (7.1 mg, 40% based on the content of compound **23** in the mixture). ^{1}H NMR δ: 8.6 (1H, s, NH); 7.1 (1H, s, H-6); 6.2 (1H, t, H-1′); 6.2, 6.05 and 5.75 (1H, d ($J_{H(5')-H(4')}$ = 2 Hz) of d ($J_{H(5')-F(B)}$ = 58 Hz) of d ($J_{H(5')-F(A)}$ = 55 Hz), H-5′); 4.55 (1H, m, H-3′); 4.15 (1H, m, H-4′); 2.4–2.2 (1H, m, H-2′); 1.8 (3H, s, CH_3) ppm. ^{19}F NMR δ: −125 and −135 (2F, AB spectrum (J_{AB} = 295 Hz, F_A at −128.0 ppm, F_B at −132.9 ppm with further d ($J_{F(A)-H(5')}$ = 55 Hz, $J_{F(B)-H(5')}$ = 58 Hz) of d ($J_{F(A)-H(4')}$ = 9 Hz, $J_{F(B)-H(4')}$ = 19 Hz), F-5′) ppm. MS *m/z*: 287 $(M+H)^+$. Analysis: $(C_{10}H_{11}N_5O_3F_2)$C,H,N,F.

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References

1 A. E. Lloyd, P. L. Coe, R. T. Walker and O. W. Howarth, *J. Fluorine Chem.*, *60* (1993) 239.
2 D. E. Bergstrom and P. W. Shum, *J. Org. Chem.*, *53* (1988) 3953.
3 J. R. McCarthy, E. T. Jarvi, D. P. Matthews, M. L. Edwards, N. J. Prakash, T. L. Bowlin, S. Mehdi, P. S. Sunkara and P. Bey, *J. Am. Chem. Soc.*, *111* (1989) 1127.
4 E. T. Jarvi, J. R. McCarthy, S. Mehdi, D. P. Matthews, M. L. Edwards, N. J. Prakash, T. L. Bowlin, P. S. Sunkara and P. Bey, *J. Med. Chem.*, *34* (1991) 647.
5 S. Hayakawa, F. Takai, T. Tanaka, T. Miyasaka and K. Yamaguchi, *Chem. Pharm. Bull.*, *38* (1990) 1136.
6 A. Nyilas and J. Chattopadhyaya, *Acta Chem. Scand.*, *B40* (1986) 826.
7 A. Van Aerschot, L. Jie and P. Herdewijn, *Tetrahedron Lett.*, *32* (1991) 1905.
8 R. Johansson and B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1*, (1984) 2371.
9 T. S. Lin, Z. Y. Shen, E. M. August, V. Brankovan, H. K. Yang, I. Ghazzouli and W. H. Prusoff, *J. Med. Chem.*, *32* (1989) 1891.
10 N. J. Leonard and K. L. Carraway, *J. Heterocycl. Chem.*, *3* (1966) 485.
11 N. J. Leonard, F. C. Sclavolino and V. Nair, *J. Org. Chem.*, *33* (1968) 3169; S. Fukatsu, Y. Takeda and S. Umezawa, *Bull. Chem. Soc. Jpn.*, *46* (1973) 3165; T. Kanno and M. Kawazu, *Chem. Pharm. Bull.*, *22* (1974) 2851 and references cited therein; S. N. Mikhailov, L. I. Kolobushkina, A. M. Kritzyn and V. L. Florentiev, *Tetrahedron*, *32* (1976) 2409; D. Horton and C. M. Liu, *Carbohydr. Res.*, *109* (1982) 282.
12 J. J. Fox, N. Yung, J. Davoll and G. B. Brown, *J. Am. Chem. Soc.*, *78* (1956) 2117.
13 M. J. Bamford, P. L. Coe and R. T. Walker, *J. Med. Chem.*, *33* (1990) 2494.
14 R. S. Ranganathan, G. H. Jones and J. G. Moffatt, *J. Org. Chem.*, *39* (1974) 290.
15 N. P. Damodaran, G. H. Jones and J. G. Moffatt, *J. Am. Chem. Soc.*, *93* (1971) 3812.