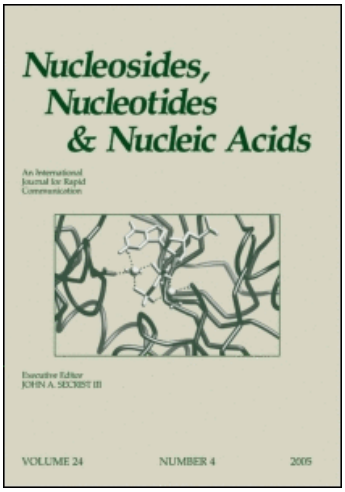

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Synthesis and Antiviral Activity of Some Fluorinated Nucleotide Derivatives

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF SOME FLUORINATED NUCLEOTIDE DERIVATIVES

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Abstract A number of 3'-fluoro-3'-deoxythymidine 5'-phosphonates and nucleoside 5'-phosphorofluoridates were prepared to study their ability to inhibit replication of HIV-1. Compounds, the 5'-phosphorofluoridates of 3'-azido-3'-deoxythymidine (**VIIIc**), 3'-fluoro-3'-deoxythymidine (**VIIId**) and 3'-deoxy-2',3'-didehydrothymidine (**VIIIe**), exhibit potent anti-HIV-1 activities.

The properties of phosphorus-containing modified nucleosides in cell cultures infected by different viruses are currently attracting considerable attention. For example, some phosphonomethyl derivatives of acyclic nucleosides **I** (Fig. 1) are highly active against several RNA viruses, DNA viruses, and retroviruses[1,2]. Some of these compounds are now undergoing clinical trials. Recently nucleoside 5'-phosphonates of general formula **II**[3,4], **III**[5,6] and **IV**[3, 7-10] with saturated or unsaturated sugar moiety and different substituents at 3'-position have been shown to possess relatively high antiviral activity.

We describe here the synthesis and antiviral properties of several fluorinated derivatives of nucleoside 5'-phosphonates and 5'-phosphorofluoridates with substitution for fluorine of a hydroxyl group in the pentosyl moiety of nucleoside and/or in the phosphate group. The introduction of the fluorine atom in a nucleotide molecule has resulted in analogues with a wide

This paper is dedicated to the memory of Professor Roland K. Robins.

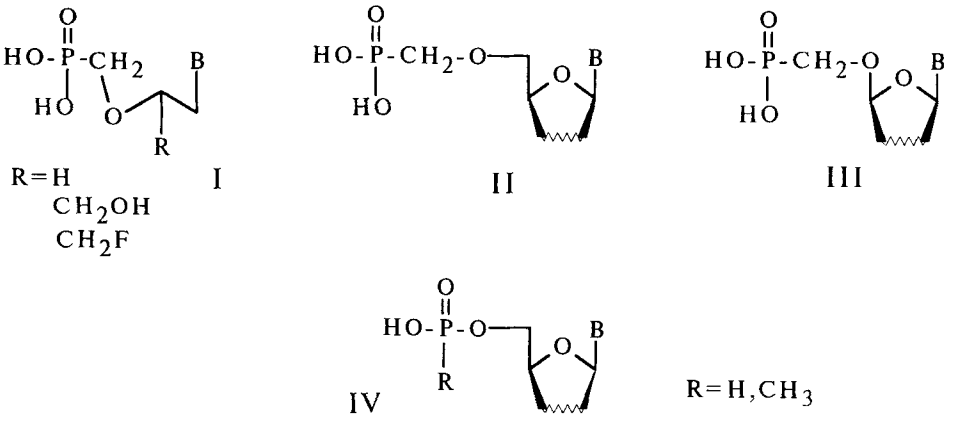
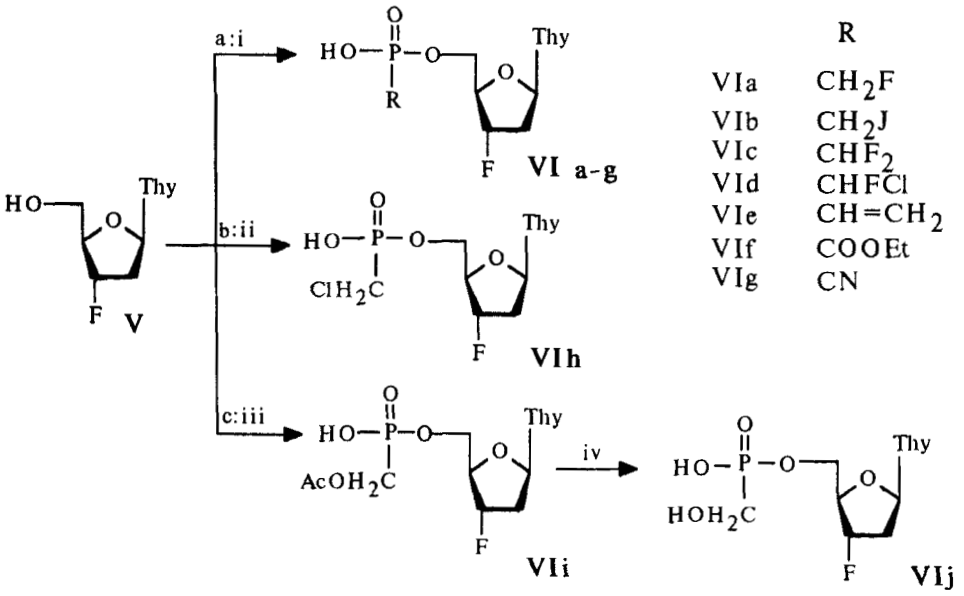


Figure 1

variety of biological activities[11]. Fluorine can be viewed as "isosteric" with hydrogen because of its size (van der Waals radii H:1.20 Å, F:1.35 Å). However, the atomic weight (18.998) and electronegativity of fluorine (4.0 [Pauling's scale], 4.000 [Sanderson's scale]) are more similar to oxygen (3.5 and 3.654, respectively) than to hydrogen (2.1 and 2.592, respectively). For example, the substitution of the 3'-hydroxy group in the molecule of thymidine for fluorine results in 3'-fluoro-3'-deoxythymidine (**V**) which possesses high antiviral properties. Its activity against HIV-1 can be compared with that of 3'-azido-3'-deoxythymidine (AZT) approved for the treatment of AIDS[1,2]. But being highly toxic nucleoside **V** can not be used for AIDS therapy. Investigations of structure-activity relationship have shown that the introduction of the second modification in the molecule of a nucleoside usually leads to the reduction of its toxicity[12]. Therefore, the synthesis and antiviral studies of 3'-fluoro-3'-deoxythymidine 5'-phosphonates **VI** seemed to be warranted.

3'-Fluoro-3'-deoxythymidine 5'-phosphonates **VIa-g** were prepared by the condensation of nucleoside **V** with the corresponding phosphonic acid in the presence of the condensing agent - N,N'-dicyclohexylcarbodiimide (DCC), 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl) or mesitylene-2-sulfonyl-3-nitro-1,2,4-triazole (MSNT). These condensing agents have similar effectivity and can be replaced by each other. DCC was found to be superior to other condensing agents only for the synthesis of phosphonate **VId** although

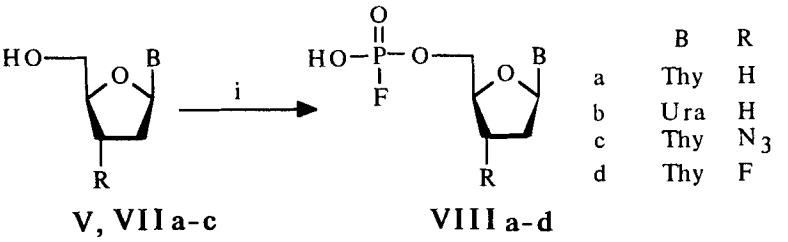


(i) phosphonic acid, Py, DCC for **VId**, TPSCl for other; (ii) $ClCH_2POCl_2$/ $PO(OEt)_3$; (iii) phosphonic acid, TPSCl/Py; (iv) $NaOH/H_2O$.

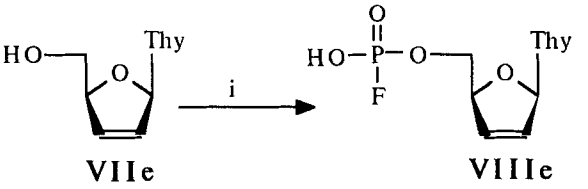
Scheme 1

it took 72h to obtain maximum yield of the product (56%) (Scheme 1a). 5'-Chloromethylphosphonate **VIh** was prepared by the treatment of nucleoside **V** with chloromethylphosphonic dichloride (Scheme 1b)[3]. The synthesis of 5'-hydroxymethylphosphonate **VIj** was carried out *via* 5'-acetoxymethyl-phosphonate **VIi** (Scheme 1c).

The other group of synthesised compounds includes modified nucleoside 5'-phosphorofluoridates **VIII a-d** (Scheme 2). Several synthetic methods for preparation of such nucleotides have been reported. Fluorination of nucleoside 5'-phosphates was carried out by 2,4-dinitrofluorobenzene[13-15] or by SO_2ClF[15-17]. Fluorine can also be introduced by the action of a fluorine ion on the P-S bond of a nucleotide[15]. Inosine 5'-phosphorofluoridate was obtained by coupling of inosine with fluorophosphate in the presence of DCC[18]. In our attempts to use the latter method for preparation of **VIIIa-d** only traces of desired nucleotides could be detected. The use of TPSCl or MSNT was found be more suitable in this case. The synthesis of 3'-deoxy-2',3'-didehydrothymidine 5'-phosphorofluoridate **VIIIe** was carried out from



Scheme 2



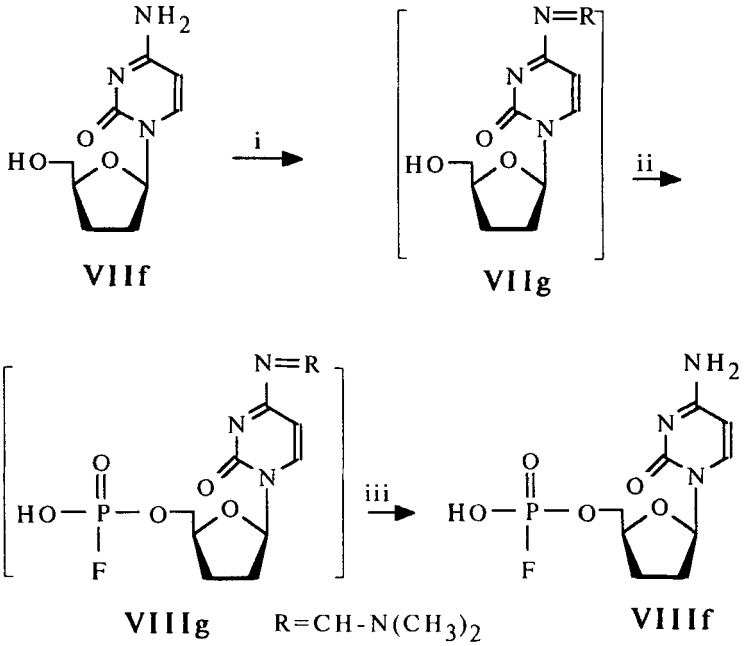
(i) Fluorophosphoric acid, MSNT or TPSCl/Py.

Scheme 3

nucleoside VIIe with analogy to Scheme 2 with TPSCl as a condensing agent (Scheme 3). The low activity of 2',3'-dideoxycytidine **VIIf** in this reaction should be mentioned. After protecting the amino group of **VIIf** (Scheme 4) with N,N-dimethylformamide dimethylacetal the activity of **VIIg** was increased up to that of thymidine derivatives **VIIa-d**. Deblocking of amino group of **VIIIg** took place during the ion-exchange chromatography of the latter and **VIIIf** was isolated with 67% yield.

Synthetic data, FAB mass and ^{1}H-NMR spectral data are presented in Tables 1, 2 and 3,4, respectively. All compounds had UV spectra typical for corresponding nucleosides. The chemical shifts and coupling constants of heterocyclic bases were also typical for corresponding units and therefore are not given in the Tables 3 and 4. The ^{31}P-NMR spectra of phosphorofluoridates **VIIIa - VIIIf** and phosphonate **VIg** are given in Table 5.

Anti-HIV activities of the synthesised phosphonates were evaluated in cell cultures H9 and in human PBL cells according to [19] (Table 6). Among 3'-fluoro-3'-deoxythymidine 5'-phosphonates **VI** only **VIc** and **VId** were shown to exhibit moderate activities, **VIa**, **VIe** and **VIf** manifested low activity and other nucleotides did not inhibit HIV reproduction at concentrations up to 100 μM.



(i) $(CH_3)_2NCH(OCH_3)_2$/DMF; (ii) fluorophosphoric acid, MSNT/Py; (iii) ion-exchange chromatography.

Scheme 4.

Table 1. Experimental conditions for the synthesis of nucleotide analogues according to the general procedure.

Compound	Condensing agent	Time (min)	Yield, %	TLC,Rf
VIa	TPSCl	30	76	0.60
VIb	TPSCl	30	76	0.61
VIc	TPSCl	30	78	0.60
VId	DCC	72h	56	0.59
VIe	TPSCl	30	72	0.60
VIf	TPSCl	20	70	0.63
VIg	TPSCl	40	63	0.64
VIi	TPSCl	20	69	0.64
VIIIa	MSNT	50	64	0.62
VIIIb	MSNT	3h	60	0.58
VIIIc	MSNT	2h	36	0.59
VIIId	TPSCl	20	62	0.58
VIIIe	TPSCl	45	44	0.61

Table 2. Mass spectral data of 5'-phosphonates and 5'-phosphorofluoridates of modified nucleosides.

Compound	Formula*	Mol. wt.	m/z**
VIa	$C_{11}H_{15}F_2N_2O_6P$	340.22	341
VIb	$C_{11}H_{15}FIN_2O_6P$	447.97	449
VIc	$C_{11}H_{14}F_3N_2O_6P$	338.05	339
VId	$C_{11}H_{14}F_2ClN_2O_6P$	374.67	375, 377
VIe	$C_{12}H_{16}FN_2O_6P$	334.07	335
VIf	$C_{13}H_{18}FN_2O_8P$	380.08	381
VIg	$C_{11}H_{13}FN_3O_6P$	333.22	334
VIh	$C_{11}H_{15}FClN_2O_6P$	356.69	357, 359
VIi	$C_{13}H_{18}FN_2O_8P$	380.08	381
VIj	$C_{11}H_{16}FN_2O_7P$	338.07	339
VIIIa	$C_{10}H_{14}FN_2O_6P$	308.06	309
VIIIb	$C_9H_{12}FN_2O_6P$	294.04	295
VIIIc	$C_{10}H_{13}FN_5O_6P$	349.06	350
VIIId	$C_{10}H_{13}F_2N_2O_6P$	326.05	327
VIIIe	$C_{10}H_{12}FN_2O_6P$	306.19	307
VIIIf	$C_9H_{13}FN_3O_5P$	293.06	294

* As free acids

** Ammonium salts. Major peak: (+)FAB ($M-NH_3+H^+$)

No phosphonate being more active than the starting nucleoside **V** can be mentioned here. Based on these data we can suppose that nucleotides **VI** do not undergo a hydrolytic dephosphorylation in cell cultures as in this case a highly active nucleoside **V** would release and suppress virus reproduction. On the other hand nucleotides **VI** apparently are not transformed to corresponding triphosphate derivatives, because such analogues would inhibit HIV reverse transcriptase, as shown *in vitro* for 5'-O-α-methylphosphonyl-β,γ-diphosphate of 3'-fluoro-3'-deoxythymidine[20], and thereby decrease virus reproduction. Besides, it was mentioned recently that 5'-fluoromethylphosphonates of modified nucleosides were not phosphorylated by cell kinases [21].

It is interesting to mark the difference in antiviral activity between nucleotides **VI** and corresponding 5'-phosphonates of AZT. 3'-Azido-3'-

Table 3. ^{1}H-NMR parameters; chemical shifts (δ, ppm).

Compounds	H-1'	H-2'a,b	H-3'	H-4'	H-5'a,b	Others
VIa	6.41dd	2.71m(2'a) 2.38m(2'b)	5.47m	4.50m	4.28-4.10m	4.64dd PCH_2F
VIb	6.40dd	2.66m(2'a) 2.43m(2'b)	5.48m	4.54m	4.23- 4.06m	2.97d PCH_2I
VIc	6.40dd	2.68m(2'a) 2.33m(2'b)	5.42m	4.50m	4.28-4.10m	6.22dt $PCHF_2$
VId*	6.40dd	2.78m(2'a) 2.35m(2'b)	5.50m	4.54m	4.32-4.20m	6.42, 6.40dd PCHFCl *
VIe	6.40dd	2.88m(2'a) 2.90m(2'b)	5.49m	4.50m	4.30-4.20m	5.65-5.98m $PCH{=}CH_2$
VIf	6.42dd	2.95-2.10m	5.50m	4.50m	4.30-4.10m	1.20dt $C\underline{H}_3CH_2$ 4.25-4.19m $CH_3C\underline{H}_2$
VIg	6.41dd	2.68m(2'a) 2.38m(2'b)	5.49m	4.50m	4.29-4.09m	
VIh	6.42dd	2.67m(2'a) 2.41m(2'b)	5.50m	4.57m	4.31-4.21m	3.58d PCH_2Cl
VIi	6.45dd	2.70-2.20m	5.52m	4.60m	4.35-4.20m	2.22c CH_3 4.28d PCH_2
VIj	6.44дд	2.66м(2'a) 2.42м(2'b)	5.49м	5.55м	4.28-4.10м	3.79д PCH_2OH
VIIIa	5.04dd	2.40- 1.90m		4.25m	4.08-3.92m	
VIIIb	5.26m	2.40- 1.90m		4.28m	4.07-3.93m	
VIIIc	6.50t	2.50-2.40m	5.53m	4.80m	4.20-4.15m	
VIIId	6.48dd	2.74m(2'a) 2.48m(2'b)	5.48dd	4.60m	4.18-4.12m	
VIIIe	6.85m	6.22-6.39m	5.88m	5.84m	4.33-4.47m	
VIIIf	5.98m	2.49- 1.90m		4.30m	4.07-3.93m	

* R- and S-diastereomers in the ratio 1:1.

Table 4. ^{1}H-NMR parameters, coupling constants (J, Hz).

N	1',2'a	1',2'b	2'a,2'b	2'a,3'*	2'a,b,F	3',F	4',F	Others
VIa	5.5	9.5	15.0	5.0	21.5 41.5	53.0	28.0	4.5 (CH_2,P); 48.0 (F,P)
VIb	5.5	9.5	15.0	5.5	21.5 41.5	53.0	28.0	9.5 (CH_2,P)
VIc	5.0	8.5	14.0	5.0	21.5 38.0	54.0		21.0 (CH,P); 48.0 (F,P)
VId	5.5	9.5	15.0	5.0	22.0 38.0	53.0	28.0	6.05 (CH,P); 46.0 (F,P)
VIe	6.0	8.0	14.0	5.0	20.0 38.0	52.5	28.0	
VIf	5.5	8.5	15.0	5.0	20.0 39.0	52.0	28.0	0.8 (CH_2,P) 7.5 (CH_3,CH_2)
VIg	5.0	9.0	14.5	5.0	21.0 38.0	53.0	28.0	
VIh	5.5	9.5	15.0	5.0	21.5 41.5	54.0	28.0	9.5 (CH_2,P)
VIi	5.2	9.8	15.0	5.0	22.0 40.0	54.0	28.0	7.8(CH_2,P)
VIj	5.0	9.0	13.5	5.0	19.5 37.5	48.5	25.0	7.5 (CH_2,P)
VIIIa	4.0	6.0						
VIIIc	6.0	6.0	12.0					
VIIId	5.0	9.0	15.0	5.0		52.5	25.0	

* $J_{2'b,3'}$<0.5 Hz

Table 5. ^{31}P-NMR parameters for nucleotide analogues **VIg** and **VIIIa-VIIIf** in D_2O.

Compounds	Chemical shifts ppm (δ)	Coupling constant $J_{P,F}$ (Hz)
VIg	-9,79	-
VIIIa	-7,00	932
VIIIb	-6,98	933
VIIIc	-6,91	932
VIIId	-6,88	934
VIIIe	-6,90	935
VIIIf	-6,88	934

deoxythymidine 5'-ethoxycarbonylphosphonate (analogue of **VIf**)[7,22], 5'-chloromethylphosphonate (analogue of **VIh**)[22] and 5'-hydroxymethyl-phosphonate (analogue of **VIj**)[22] were shown to possess high antiviral activity Some other phosphonates of AZT also demonstrated antiviral properties[22].

5'-Phosphorofluoridates **VIII** were shown to be more potent antiviral agents. Phosphorofluoridate **VIIIc** exhibit anti-HIV activity higher than that of the nucleoside **VIIc**. The activities of nucleotide analogues **VIIId, VIIIe** and **VIIIf** were nearly similar and **VIIIa** was lower in comparison with those of parent nucleosides. The toxicities of synthesised nucleotides did not change dramatically in comparison with those of parent nucleotides. For example, inhibition of PBL cell growth for 50% was found to be 0.58 mM for the phosphorofluoridate **VIIIa** (4.3 mM for **VIIa**), more than 1 mM for **VIIIf** (3.5 mM for **VIIf**) and 0.63 mM for **VIIId** (0.775 mM for **V**).

Metabolic conversion of phosphorofluoridates may take a number of alternative courses. (i) Hydrolysis in intercellular media or in cells to the corresponding nucleosides. However the high activity of **VIIIc** can not be explained by this version. (ii) Hydrolysis of the P-F bond with intracellular formation of corresponding monophosphates. But until now there is no evidence supporting this pathway. (iii) Phosphorylation of phosphoro-

Table 6. Anti-HIV effect of synthesised nucleotide analogues.

Compounds	Cells	Anti-HIV activity EC_{50}* (μM)	Anti-cell growth activity IC_{50}** (μM)	Selectivity index SI IC_{50}/EC_{50}
VIa	H9	10-100	nt*** at 100	
VIc	H9	8	nt at 100	
VId	H9	2-5	nt at 100	
VIe	H9	24	nt at 100	
VIf	H9	30	nt at 100	
VIIIa	PBL	100	580	5.8
VIIIb	PBL	100	nd****	
VIIIc	PBL	0.0001-0.001	578	578000
VIIIc	H9	0.1	nt at 100	
VIIId	PBL	0.004	630	157500
VIIId	H9	0.3	nt at 100	
VIIIe	PBL	0.05	571	11420
VIIIf	PBL	<0.08	>1000	>12500
V	PBL	0.002	775	387500
V	H9	0.2	nt at 100	
VIIa	PBL	1.4	4300	3070
VIIb	PBL	100	nd	
VIIc	PBL	0.0047	>1000	>212766
VIIc	H9	0.23	>100	>435
VIIe	PBL	0.05	349	6980
VIIf	PBL	0.008	3500	437500

* 50% effective concentration of inhibiting HIV-1 replication, based on P24-ELISA.[10,19] ** 50% inhibitory concentration of cell growth, based on trypan-blue test for H9 cells and XTT test for PBL.[23] ***non-toxic. ****no data.

fluoridates to di- and triphosphate analogues. In this last version several further transformations are possible. No final decision between these alternatives is possible at present.

Phosphonates **VI** and phosphorofluoridates **VIII** did not inhibit HSV-1 and CMV reproduction. The tests were performed as in [19].

Experimental Section

TLC was performed on Kieselgel 60 F_{254} (Merck) in 2-propanol: NH_4OH:water 7:1:2 (v/v). For column chromatography 650 M DEAE Toyopearl from Toyosoda (Japan) and LiChroprep RP-18 (25-40μ) from Merck were used. UV spectra were registered on a Specord-M10 spectrophotometer, ^{1}H-NMR spectra - on a Varian XL 100 and a Bruker 250 spectrometers in D_2O with *t*-BuOH as an internal standard. ^{31}P-NMR spectra were recorded at 101.26 MHz on a Bruker 250 spectrometer in D_2O with 85% H_3PO_4 as an external standard. FAB mass spectra were determined with Kratos MS 50TC mass spectrometer. The yields were estimated spectrophotometrically using molar extinction coefficients (ε) of the parent nucleosides.

General procedure for synthesis of 5'-phosphonates VIa-g, VIi and 5'-phosphorofluoridates VIIIa-e

The nucleosides **V, VII** (0.3 mmol) were dissolved in dry pyridine (5ml) and the solution of tri-*n*-butylammonium salt of corresponding phosphonic or fluorophosphoric acid (0.5 mmol) in DMF (1ml) and then a condensing agent (0.8 mmol) were added. The reaction mixture was allowed to stand at room temperature till the starting nucleoside disappeared (TLC control in $CHCl_3$:MeOH 9:1, v/v). Water was added (30ml) and the mixture was stirred for 15 min and filtered. The filtrate was diluted with water (300 ml) and it was put on a Toyopearl DEAE (HCO_3^-) column (5x40 cm). The column was washed with 300 ml of water and then with a linear gradient of ammonium bicarbonate buffer (0-->0.2 M, pH 7.5), total volume 600 ml. The product was eluted at ~0.15M NH_4HCO_3. The appropriate fractions were combined, evaporated to dryness and reevaporated with water (3x15 ml). The residue was dissolved in water (2 ml) and applied onto a LiChroprep RP-18 column (2.5x15 cm). Elution with water followed by freeze-drying yielded nucleotides **VIa-g, VIi, VIIIa-e** as NH_4^+ salts.

3'-Fluoro-3'-deoxythymidine 5'-hydroxymethylphosphonate VIj

The nucleotide **VIi** obtained according to the general procedure was dissolved in 0.3 M solution of NaOH (10 ml) and stored overnight at room temperature. The solution was neutralized with Dowex 50 (H^+), filtered, evaporated to dryness and reevaporated with 3 ml of NH_4OH. The residue was dissolved in water (1 ml) and applied onto a LiChroprep RP-18 column (2.5x15 cm). Elution with water followed by freeze-drying yielded **VIj** as NH_4^+ salt (80%, 58 mg).

3'-Fluoro-3'-deoxythymidine 5'-chloromethylphosphonate VIh

The nucleoside **V** (49 mg, 0.2 mmol) was dissolved in trimethylphosphate (1 ml) and chloromethylphosphonic dichloride (0.026ml, 0.25 mmol) was added. The mixture was stirred at 0°C overnight and then reaction was stopped by adding of 1 ml of pyridine-water mixture (1:1, v/v). After 20 min solvents were evaporated from the reaction mixture, nucleotide **VIh** was isolated by ion-exchange and reversed phase chromatography as described in general procedure. After freeze-drying compound **VIh** was obtained as NH_4^+ salt in 76% yield (56 mg).

2',3'-Dideoxycytidine 5'-phosphorofluoridate VIIIf

2',3'-Dideoxycytidine **VIIf** (73 mg, 0.3 mmol) and N,N-dimethylformamide dimethyl acetal (0.24 ml, 6.0 mmol) were dissolved in 3 ml of DMF and the solution was set aside overnight at room temperature. To the mixture concentrated to dryness in vacuo 2ml of 0.5 M solution of fluorophosphate tri-*n*-butylammonium salt in pyridine and MSNT (148 mg, 0.5 mmol) were added. After 30 min the reaction was quenched by 5 ml of water. Further isolation was performed as described above. Compound **VIIIf** was obtained as NH_4^+ salt in 67% yield (62 mg).

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