54. Syntheses of Pyrrolo[2,3-*d*]pyrimidine 2′,3′-Dideoxyribonucleosides Related to 2′,3′-Dideoxyadenosine and 2′,3′-Dideoxyguanosine and Inhibitory Activity of 5′-Triphosphates on HIV-1 Reverse Transcriptase

by **Frank Seela***, **Heinz-Peter Muth**, and **Angelika Röling**

Laboratorium für Organische und Bioorganische Chemie, Fachbereich Biologie/Chemie, Universität Osnabrück, Barbarastr. 7, D-4500 Osnabrück

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The synthesis of 4-chloropyrrolo[2,3-*d*]pyrimidine and 2-amino-4-chloropyrrolo[2,3-*d*]pyrimidine α-D- and β-D-2′,3′-dideoxyribonucleosides **6a**, **b** and **7a**, **b** is described (*Scheme 1*). Glycosylation of the pyrrolo[2,3-*d*]-pyrimidinyl anions of **1a**, **b** with *in situ* prepared 2,3-dideoxy-α/β-D-*glycero*-pentofuranosyl chloride (**2**) was regioselective but afforded anomeric mixtures of the 2′,3′-dideoxyribonucleosides **3a**/**4a** and **3b**/**4b**, respectively. The glycosylation products were deprotected and subjected to nucleophilic displacement yielding various pyrrolo[2,3-*d*]pyrimidine 2′,3′-deoxyribonucleosides related to 2′,3′-dideoxyadenosine and 2′,3′-dideoxyguanosine. One-pot phosphorylation gave the corresponding triphosphates. Some of them are strong inhibitors of HIV-1 reverse transcriptase, similar to corresponding purine 2′,3′-dideoxynucleotides, but exhibit a better selectivity index in comparison to DNA polymerases. According to that, the N(7) of the purine moiety is not an essential binding position of ddATP or ddGTP at the active centre of HIV-1 reverse transcriptase.

Introduction. – The rational design of drugs to inhibit HIV reverse transcriptase has already yielded promising compounds which selectively inhibit the viral target (HIV) [1]. The first drug shown to be effective in anti-HIV cell culture discovered by random testing was 3′-azido-3′-deoxythymidine (AZT[1])) [2], originally synthesized by *Horwitz et al.* [3]. In the mean time, other nucleosides such as 2′,3′-dideoxynosine ($I_{d_2^{2',3'}}$), 2′,3′-dideoxycytidine ($C_{d_2^{2',3'}}$), or 3′-azido-2′,3′-dideoxyuridine ($U_{d_2^{2',3'}}$ az) have shown antiviral activity and are now considered for clinical use (phase I or phase II) [4]. The majority of the 2′,3′-dideoxyribonucleosides that have been tested for anti-HIV activity are pyrimidine or purine dideoxynucleosides.

Theoretically, the purine ring system can be modified so that 63 isomers with a different N-pattern are generated. The situation is similar in the series of monodeazapurines: 42 isomeric structures can be calculated, however, not all of them are accessible by chemical synthesis. Among deazapurine dideoxyribonucleosides, the 7-deaza compounds are of particular interest [5]. Their structure mimics the parent purines very closely, and they possess an intact pyrimidine moiety, responsible for *Watson-Crick* base pairing. Various ribonucleosides [6] and 2′-deoxyribonucleosides [7] have been synthesized, as our laboratory has developed stereoselective glycosylation techniques employing the nucleobase anion [8–10]. Moreover, triphosphates such as 7-deaza-2′-deoxyguanosine triphosphate have been prepared which are commonly used in DNA sequencing [11].

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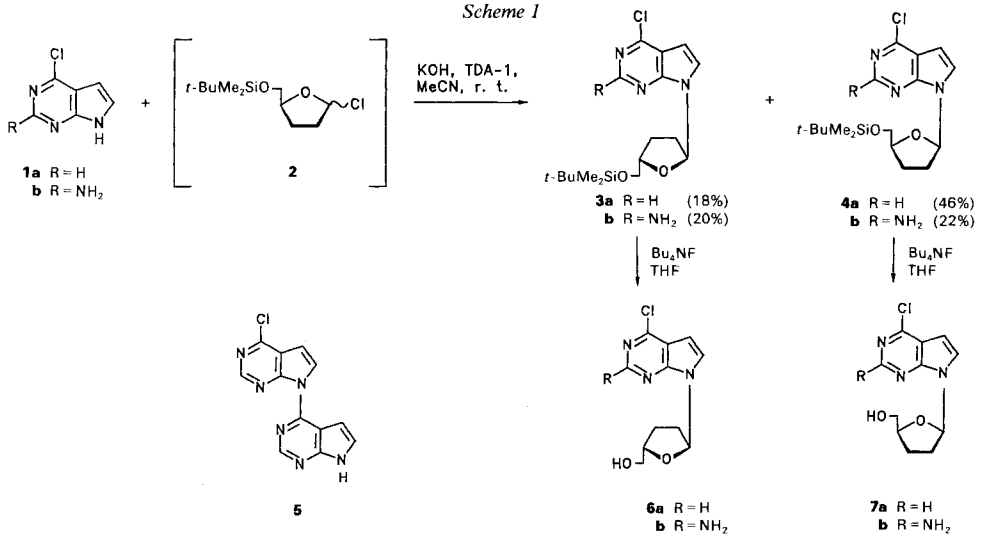
[1]) The IUPAC-IUB-recommended abbreviation of this compound is $T_{d_2^{2',3'}}$ az (T = ribosylthymine and not thymidine, which is 2′-deoxyribosylthymine, hence T_d).

In the following, we describe the direct glycosylation of pyrrolo[2,3-*d*]pyrimidinyl anions with an appropriately protected 2,3-dideoxyribofuranosyl halide and the conversion of the glycosylation products into pyrrolo[2,3-*d*]pyrimidine 2′,3′-dideoxyribonucleoside 5′-triphosphates as well as their inhibitory activity on HIV-1 reverse transcriptase (RT).

Results and Discussion. – *2′,3′-Dideoxyribonucleosides.* Some 7-deazapurine 2′,3′-dideoxyribonucleosides have already been synthesized from the corresponding 2′- or 3′-deoxyribonucleosides by the radical-mediated deoxygenation of a 3′- or the 2′-thiocarbonyloxy group [12–14] as well as by elimination of a 3′-mesyloxy group yielding unsaturated compounds which were subjected to catalytic hydrogenation [15]. Also the deoxygenation of ribonucleosides has been employed [16–18]. As all these protocols ask for sufficient amounts of the starting, ribo- or 2′-deoxyribonucleosides, they are laborious. Therefore, the direct glycosylation of pyrrolo[2,3-*d*]pyrimidinyl anions with an appropriately protected 2,3-dideoxyglycosyl halide was considered [19]. This technique has also been applied to 3-deazapurines [20] and 3,7-dideazapurines [19].

Thus, 4-chloropyrrolo[2,3-*d*]pyrimidine (**1a**) [21] [22] as well as 2-amino-4-chloropyrrolo[2,3-*d*]pyrimidine (**1b**) [23] were chosen for such a glycosylation, giving suitable precursors for pyrrolo[2,3-*d*]pyrimidine 2′,3′-dideoxyribonucleosides related to 2′,3′-dideoxyadenosine ($A_{d2'3'}$) or 2′,3′-dideoxyguanosine ($G_{d2'3'}$). The anions of **1a** or **1b** were generated under solid-liquid phase-transfer conditions [9] using powdered KOH and the cryptand tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) in MeCN. The α/β-D halogenose **2** necessary for the glycosylation of **1a** or **1b** was prepared at −78° *in situ* from the corresponding lactol [24] by *Appel* chlorination [25] (see *Scheme 1* and *Exper. Part*). Although the chlorination was stereoselective, the use of an anomeric mixture of the lactol resulted in an anomeric mixture **2** [19]. Attempts to employ the glycosyl bromide as already described for the glycosylation of silylated purines or pyrimidines [26] failed. Glycosylation was also studied with anomeric acetates [24], but due to their low reactivity, the displacement of AcO–C(1) by the nucleobase anion was not observed.

Scheme 1



When equimolar amounts of **1a** and **2** were used, the glycosylation gave a 1:1 mixture **3a**/**4a** in 28% yield. With a 2:1 excess of the nucleobase, the yield of **3a**/**4a** was 22% (based on **1**) or 44% (based on **2**), and a side product **5** was formed (41% yield). The structure of **5** was established by ^{1}H- and ^{13}C-NMR spectroscopy. A similar compound carrying a ribofuranosyl residue was isolated recently [6]. The formation of **5** from 2 molecules of the anions of **1a** is unlikely as the nucleophilic displacement of the 4-Cl substituent on the anion of **1a** is extremely difficult. This was proven by a glycosylation experiment in which the halogenose **2** was omitted: no **5** was formed. As a consequence, **5** could arise from the nucleosides **3a** or **4a** *via* displacement of their 4-Cl groups by the anion of **1a**. But in an analytical-scale experiment using **4a** and a threefold excess of **1a** in the presence of MeCN, KOH, and TDA-1, no 5′-protected 2′,3′-dideoxyribofuranoside of **5** could be detected (TLC). Thus, the formation of **5** is more complicated. Apparently, other components of the glycosylation mixture of the *in situ* formed halogenose **2** facilitate the formation of **5**, including N-glycosylic bond hydrolyses. For all these reasons, it is not suitable to use an excess of the nucleobase for glycosylation.

When the amount of the glycosyl halide **2** was increased over **1a**, the glycosylation products were deprotected during workup. To avoid this, the reaction mixture was poured into $NaHCO_3$ solution, which increased the total glycosylation yield to 64% (**4a**/**3a** 2.6:1). Under similar conditions, **1b** was glycosylated to **4b**/**3b** (*ca.* 1:1) in 44% yield.

The protected anomers **3a**, **b** and **4a**, **b** were separated by flash chromatography (α-D-anomers less polar) and deprotected with 1M Bu_4NF in THF affording **6a**, **b** or **7a**, **b**. It is worth mentioning that the silylated anomers show an extremely good separation on silica gel, which is not found for the deprotected materials. Nucleophilic displacement reactions of the chloro nucleosides **7a** and **7b** have already been described [12] [13]. Assignment of the anomeric structures was made on the basis of NOE-difference spectroscopy, and of ^{1}H-NMR chemical-shift differences. *Table 1* summarizes the ^{13}C-NMR data.

Scheme 2

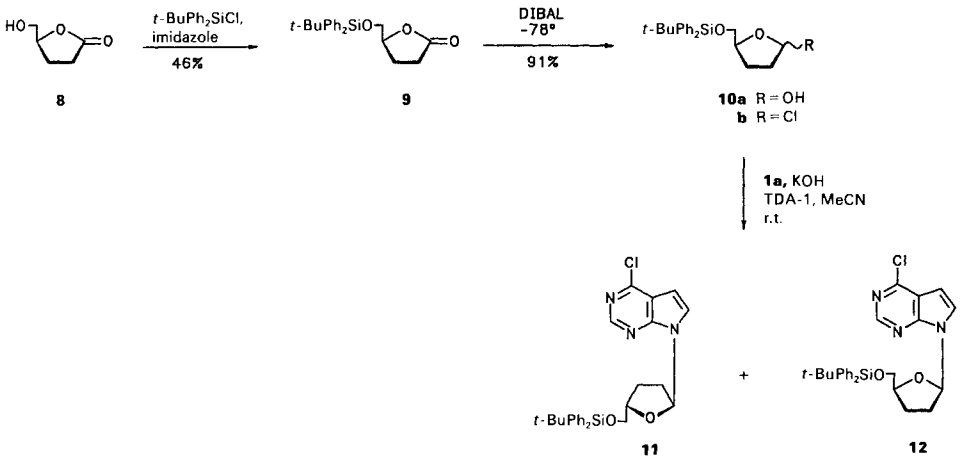


Table 1. *^{13}C-NMR Chemical Shifts of Pyrrolo[2,3-d]pyrimidine 2′,3′-Dideoxyribonucleosides in (D_6)DMSO at 23°*

	C(2)	C(4)	C(4a)	(C(5)	C(6)	C(7a)
3a	150.3[a])	150.4[a])	117.2	99.3	128.5	150.7[a])
3b	159.2	151.1	108.8	99.5	123.3	153.3
4a	150.4[a])	150.2[a])	117.2	99.1	128.2	150.6[a])
4b	159.3	151.0	108.8	99.3	122.9	w153.3
11	150.42[a])	150.36[a])	117.3	99.4	128.6	150.7[a])
12	150.4[a])	150.6	117.2	99.2	128.2	150.3[a])
5	150.4	150.6	118.6	101.67	130.4	151.4
	147.0	153.9	110.2	101.72	127.3	151.1
6a	150.4[a])	150.7[a])	117.2	99.3	128.6	150.7[a])
6b	159.2	151.1	108.8	99.5	123.3	153.4
	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)	
3a	84.8	31.4	26.2	80.4	65.1	
3b	83.8	31.0	26.4	80.0	65.1	
4a	84.2	31.7	25.6	81.0	64.5	
4b	83.2	31.3	25.8	80.3	64.7	
9[b])	177.7	28.6	22.8	80.1	65.5	
10a	98.6, 99.0	34.8, 32.9	25.3, 23.9	80.3, 79.0	66.3, 66.1	
11	84.8	31.4	26.2	80.2	65.9	
12	84.2	31.4	25.7	80.9	64.4	
6a	84.7	31.3	26.4	81.0	63.4	
6b	83.5	30.9	26.5	80.4	63.5	
	$(CH_3)_3C$	$(CH_3)_3C$	CH_3Si	CH_3O	C=S	
3a	25.8	17.9	−5.37, −5.41	–	–	
3b	25.8	18.0	−5.3, −5.4	–	–	
4a	25.7	18.0	−5.5	–	–	
4b	25.8	18.0	−5.5	–	–	
9[b])	26.8	19.2	–	–	–	
10a	26.7, 26.6	19.3, 19.2	–	–	–	
11	26.6	18.8	–	–	–	
12	26.6	18.7	–	–	–	

[a]) Tentative assignment. [b]) Measured in $CDCl_3$.

In the case of the β-D-anomer **4a**, saturation of H–C(1′) gave an NOE of 1.6% on H–C(4′), clearly indicating β-D-configuration [27]. In the case of the α-D-anomer **3a**, this NOE was not observed. The same results were found for the deprotected anomers **6a** and **7a**. Whereas **7a** showed an NOE value of 1.5% for H–C(4′) upon irradiation of H–C(1′), no NOE was observed for **6a**. In the case of compounds **6b** and **7b**, the α-D-anomer gave no NOE at H–C(4′) upon irradiation of H–C(1′); compound **7b** was compared with an authentic sample [13].

A comparison of the ^{1}H-NMR chemical shifts of several anomeric 2′,3′-dideoxyribonucleosides shows significant differences of the chemical shifts of H–C(4′) and H–C(5′) ($\Delta[\delta(\text{H–C(4′)}) - \delta(\text{H–C(5′)})]$), as also described for anomeric toluoylated 2′-deoxyribonucleosides [29]. In the case of the silylated α-D-anomers, $\Delta\delta$ was 0.8 ppm, and in the case of the β-D-anomers only 0.4 ppm. After deprotection, the $\Delta\delta$s were 0.9 and 0.5 ppm, respectively.

The ^{13}C-NMR chemical shifts of the nucleobases were assigned in analogy to corresponding 2′-deoxyribonucleosides; assignment of the glycosyl moieties was based on earlier work done with compound **15b** (β-D-anomers) [28] or 3-deazapurine 2′,3′-dideoxy-α-D-ribofuranosides [20].

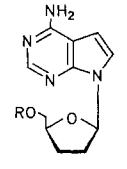
If a (*t*-Bu)Ph_2Si residue was used for silylation of the glycosyl precursor **8** instead of the (*t*-Bu)Me_2Si group, and after reduction of the resulting lacton **9** [30] (TLC: detection by UV light) with DIBAL [31], the crystalline anomeric lactols **10a** were obtained (*Scheme 2*). The ^{1}H-NMR data ($CDCl_3$) of **10a** show a pseudo-*t* at 5.57 and *dd* at 5.44 ppm for the

anomeric protons; anomeric ratio 1.6:1. Chlorination of **10a** in the usual way yielded **10b** which was used directly for glycosylation experiments. Thus, as described above for the glycosylation with **2**, **1a** and **10b** yielded the anomeric nucleosides **11** and **12**.

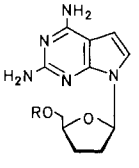
Recently, *Chu et al.* reported the stereoselective synthesis of 2′,3′-dideoxyribonucleosides using a 1-*O*-acetyl 2,3-dideoxyribose with a phenylselenyl residue in the 2-position [32]. We have also considered this protocol for the syntheses of pyrrolo[2,3-*d*]-pyrimidine 2′,3′-dideoxyribonucleosides. However, the additional steps for the introduction and removal of the 2′-substituent including a separation step of diastereoisomeric phenylselenyl-sugars makes this approach laborious and time consuming and results in overall yields of the β-D-anomers being not better than those obtained by direct glycosylation with the dideoxyglycosyl halide **2**.

5′-Triphosphates and Inhibitory Activity on HIV-1 Reverse Transcriptase. The synthesis of 2′,3′-dideoxyribonucleoside triphosphates **13a–16a**, **16d**, **17a–20a**, and **20b** was carried out in a one-pot reaction following a protocol originally developed for phosphorylation of purine and pyrimidine 2′-deoxynucleosides [33]. The nucleosides were dissolved in $PO(MeO)_3$ and cooled to 0°. Two equiv. of $POCl_3$ were added resulting in the formation of an activated dichlorophosphate which was directly condensed with tetrabutylammonium diphosphate ($[Bu_4N]_4P_2O_7$). After neutralisation with $(Et_3NH)HCO_3$ buffer, the triphosphates were purified by *DEAE* cellulose column chromatography and isolated as solid triethylammonium salts (for yields, see *Table 3* in the *Exper. Part*).

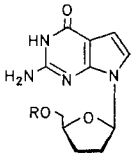
In some phosphorylations the 2′,3′-dideoxyribonucleoside monophosphates were obtained (**13b**, **14b**, **16b**, **18b**, **19b**) besides the triphosphates. This has to be attributed to partial hydrolysis of the dichlorophosphates. In order to avoid hydrolyses of acid-sensitive nucleosides caused by the formation of HCl, some phosphorylations were carried out



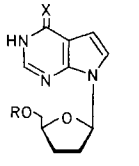
13	**a**	**b**	**c**
R	p_3	p	H



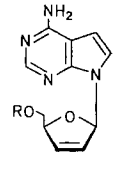
14	**a**	**b**	**c**
R	p_3	p	H



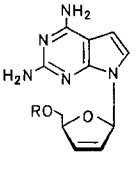
15a R = p_3
b R = H



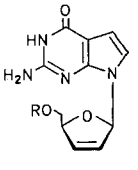
16	**a**	**b**	**c**	**d**	**e**
X	O	O	O	S	S
R	p_3	p	H	p_3	H



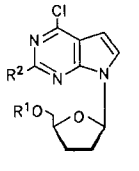
17a R = p_3
b R = H



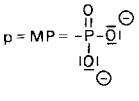
18	**a**	**b**	**c**
R	p_3	p	H



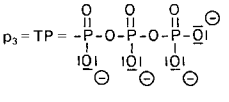
19	**a**	**b**	**c**
R	p_3	p	H



20	**a**	**b**	**c**
R^1	p_3	p_3	H
R^2	H	Cl	Cl



p = MP = $-P(=O)(-O^{\ominus})-O^{\ominus}$



p_3 = TP = $-P(=O)(-O^{\ominus})-O-P(=O)(-O^{\ominus})-O-P(=O)(-O^{\ominus})-O^{\ominus}$

in the presence of 1,8-bis(dimethylamino)naphthalene (proton sponge). This base was first introduced by *Kovács et al.* for the synthesis of acid-sensitive pyrimidine nucleoside triphosphates [34]. This proton sponge has a stabilizing influence on the N-glycosylic bond hydrolysis of highly acid-sensitive nucleosides and thus improves the triphosphate yields. Moreover, it improves the formation of the intermediate nucleoside dichlorophosphates, which are difficult to obtain in some cases [34].

Recombinant HIV-1 reserve transcriptase has been overproduced as a soluble protein in *E. coli* [35] [36]. It was active as both a homodimer of 66000 Dalton subunits and a heterodimer of 66000 and 51000. Crystals were obtained from the heterodimer. The 66000 subunit shows RNAse H activity. A number of 2′,3′-dideoxynucleoside triphosphates, including AZTTP (= $p_3T_{d2'3'}$ az) have been used as inhibitors of the enzyme. As poly(rA)$_n$ oligo $(dT)_{12-18}$ templates were employed in most cases, only inhibitors structurally related to ddTTP (= $p_3T_{d2'3'}$) could be studied. In order to assay other inhibitors, the template was changed [37]. In our studies, a piece of HIV-1 RNA was used together with the recombinant enzyme. *Table 2* summarizes data of 50% inhibition by several pyrrolo[2,3-*d*]pyrimidine triphosphates compared to ddATP (= $p_3A_{d2'3'}$), ddGTP (= $p_3G_{d2'3'}$), and AZTTP. It can be seen, that the 7-deaza derivatives **13a** and **15a** of 2′,3′-dideoxyadenosine and 2′,3′-dideoxyguanosine, respectively, are as active inhibitors as the parent purine nucleoside triphosphates ddATP or ddGTP. Similar values were

Table 2. *Inhibition of HIV-1 Reverse Transcriptase* (RT) *by Pyrrolo[2,3-*d*]pyrimidine and Purine 2′,3′-Dideoxyribonucleoside Triphosphates*[a])

IC_{50} [μM]		IC_{50} [μM]		IC_{50} [μM]		IC_{50} [μM]	
13a	0.39	**16d**	1680.0	**19a**	0.09	AZTTP[b])	0.5
14a	0.5	**17a**	0.53	**20a**	102.0	ddATP[b])	0.45
15a	0.12	**18a**	0.39	**20b**	> 100.0	ddGTP[b])	0.2
16a	20.0						

[a]) The RT inhibitory tests were performed in the Laboratories of *Boehringer Mannheim GmbH.*

[b]) AZTTP = 3′-azido-3′-deoxythymidine 5′-triphosphate; ddATP = 2′,3′-dideoxyadenosine 5′-triphosphate; ddGTP = 2′,3′-dideoxyguanosine 5′-triphosphate.

measured for the 2′,3′-dideoxy-2′,3′-didehydro compounds [5]. Also the 2,6-diamino derivatives **14a** and **18a** are highly active. Contrary to these observations, the ddI derivatives **16a** or its thio analogue **16d** show only marginal activity. Synthetic precursor molecules such as the 6-chloro- or the 2,6-dichloro compound **20a** and **20b**, respectively, show activities being two magnitudes lower than that of the other 2′,3′-dideoxyribonucleosides. The IC_{50} value of AZTTP as shown in *Table 2* (0.5 μM) is about one magnitude higher than that reported by others [37]. This difference is due to the use of a random template (HIV-LTR-RNA) used in our experiments instead of poly(rA) [38].

From the results discussed above, it can be seen that pyrrolo[2,3-*d*]pyrimidine 2′,3′-dideoxyribonucleoside triphosphates are as strong inhibitors of HIV reverse transcriptase as the parent purine compounds. Therefore, we conclude that N(7) is not a proton acceptor position during the binding of ddATP or ddGTP on the active centre of HIV-1 reverse transcriptase. Moreover, changes in the electronic properties of the nucleobase, at least in the five-membered ring, seem also of less importance.

From the NOE spectra of purine and 7-deazapurine 2′,3′-dideoxyribonucleosides, the conformation around the N-glycosylic bond as well as the sugar puckering can be estimated [39]. According to this, only minor differences are observed between purine and pyrrolo[2,3-*d*]pyrimidine nucleosides. The conformation of the nucleobases at the N-glycosylic bond is preferentially '*anti*' and the *N*–*S* equilibrium of the sugar puckering is biased towards the *N*-type while 2′-deoxy-D-ribonucleosides exhibit preferentially an *S*-type sugar pucker.

Apart from the inhibitory activity on HIV-1 reverse transcriptase, the inhibition of DNA-polymerase α and DNA-polymerase$_\gamma$ was assayed in case of compound **15a**. Compound **15a** shows an IC_{50} of 0.1 μM for HIV reverse transcriptase and values of 680 μM for DNA-Pol$_\alpha$ and 1216 μM for DNA-Pol$_\gamma$. According to that, the cellular polymerases are much more sensitive to modifications within the five-membered ring than reverse transcriptase. In terms of selectivity index numbers (*SI*), it is 5600 for DNA-Pol$_\alpha$ and 12300 for DNA-Pol$_\gamma$. The increased selectivity index of pyrrolo[2,3-*d*]pyrimidine 2′,3′-dideoxyribonucleosides over that of the corresponding purines implies lower toxicity. However, the situation is more complicated in the cellular system infected with HIV-1 [40]. Factors such as phosphorylation or interaction with other metabolic enzymes have to be considered. *In vitro* inhibitory data of the pyrrolo[2,3-*d*]pyrimidine 2′,3′-dideoxynucleosides **13c** and **17b** determined in virus-infected MT-4 cell cultures have already been reported [41] [42], others will be published elsewhere.

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Experimental Part

General. TLC silica gel *Sil G-25 UV$_{254}$* plates (*Macherey & Nagel*). Column chromatography: silica gel *60* (⩽ 230 mesh, *Merck*); FC = flash chromatography. Ion-exchange chromatography: *DEAE-Sephadex A25* (HCO_3^- form) from *Pharmacia Fine Chemicals* (Sweden). HPLC: *Merck-Hitachi*, model *655A-12*, with proportioning valve, model *655A* variable-wavelength UV monitor, model *L-5000* controller, and *D-2000* integrator; 250 × 4 mm (7 μm) *RP-18 LiChrosorb* column with *RP-18* 25 × 4 mm precolumn (*Merck*). M.p.: *Büchi SM-20* apparatus. UV spectra: *150-20 Hitachi* spectrophotometer; λ_{max} (ε) in nm. NMR spectra: ^{1}H at 250.1, ^{13}C at 62.9, and ^{31}P at 101.3 MHz; *Bruker-AC-250* spectrometer; chemical shifts δ in ppm with TMS as internal standard (^{1}H and ^{13}C) or with 85% phosphoric acid as external standard (^{31}P). Elemental analyses were performed by *Mikroanalytisches Laboratorium Beller* Göttingen, Germany.

*4-Chloro-7-{2,3-dideoxy-5-O-[(1,1-dimethylethyl)dimethylsilyl]-α-*D*-glycero-pentofuranosyl}-7H-pyrrolo[2,3-d]pyrimidine* (**3a**). Compound **1a** [21] [22] (500 mg, 3.3 mmol) was dissolved in anh. MeCN (30 ml). Powdered KOH (550 mg, 9.8 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1; 50 μl, 0.16 mmol) were added. After 10 min, the cold THF soln. of **2** [20] (prepared *in situ* from the corresponding lactol [24] (1.5 g, 6.45 mmol)) was added in five portions (5 ml each) within 15 min. Stirring was continued for 10 min, the insoluble material filtered off, and the filtrate poured into 5% aq. $NaHCO_3$ soln. (100 ml). The aq. layer was extracted with AcOEt (3 × 100 ml) and the combined org. layer washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was applied to FC (column 2.5 × 30 cm, CH_2Cl_2/MeOH 98:2), affording two zones. From the first zone, **3a** (220 mg, 18%) was isolated as a colorless oil which crystallized upon storing. TLC (light petroleum ether/AcOEt 9:1): R_f 0.34. UV (MeOH): 225 (25500), 273 (4800). ^{1}H-NMR ((D$_6$)DMSO): 0.05, 0.07 (2*s*, Me_2Si); 0.88 (*s*, *t*-Bu); 1.86, 2.33 (2*m*, CH_2(2′), CH_2(3′)); 3.64 (*m*, CH_2(5′)); 4.44 (*m*, H–C(4′)); 6.55 (*dd*, *J* = 6.6, 4.2, H–C(1′)); 6.71 (*d*, *J* = 3.8, H–C(5)); 7.91 (*d*, *J* = 3.8, H–C(6)); 8.66 (*s*, H–C(2)). Anal. calc. for $C_{17}H_{26}ClN_3O_2Si$ (368.0): C 55.49, H 7.12, Cl 9.64, N 11.42; found: C 55.68, H 7.13, Cl 9.83, N 11.35.

*4-Chloro-7-{2,3-dideoxy-5-O-[(1,1-dimethylethyl)dimethylsilyl]-β-*D*-glycero-pentofuranosyl}-7H-pyrrolo[2,3-d]pyrimidine* (**4a**). From the second zone (see FC above), **4a** (550 mg, 46%) was isolated. Colorless oil. TLC

(light petroleum ether/AcOEt 9:1): R_f 0.19. UV (MeOH): 225 (25200), 273 (4800). ^{1}H-MNR ((D$_6$)DMSO): −0.01, 0.00 (2*s*, Me_2Si); 0.84 (*s*, *t*-Bu); 2.06 (*m*, CH_2(3′)); 2.30, 2.45 (2*m*, CH_2(2′)); 3.67 (*dd*, *J* = 4.5, 11.2, 1 H, CH_2(5′)); 3.81 (*dd*, *J* = 3.8, 11.2, 1 H, CH_2(5′)); 4.14 (*m*, H–C(4′)); 6.52 (*dd*, *J* = 3.5, 6.9, H–C(1′)); 6.66 (*d*, *J* = 3.8, H–C(5)); 7.94 (*d*, *J* = 3.8, H–C(6)); 8.64 (*s*, H–C(2)). Anal. calc. for $C_{17}H_{26}ClN_3O_2Si$ (368.0): C 55.49, H 7.12, Cl 9.64, N 11.42; found: C 55.69, H 7.18, Cl 9.97, N 11.38.

*2-Amino-4-chloro-7-{2,3-dideoxy-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-α-*D*-glycero-pentofuranosyl}-7H-pyrrolo[2,3-d]pyrimidine* (**3b**). Compound **3b** and **4b** were prepared from **1b** [21] [23] (1.0 g, 5.93 mmol), MeCN (100 ml), KOH (1.0 g, 17.8 mmol), TDA-1 (0.1 ml, 0.31 mmol), and a THF soln. of **2** (12.9 mmol) as described for **3a**/**4a**. In order to dissolve **1b**, DMF (10 ml) was added to MeCN prior to addition of KOH. After removal of insoluble material, the filtrate was poured into 5% aq. $NaHCO_3$ soln. (200 ml) and extracted with AcOEt (3 × 200 ml). The combined org. layers were washed with H_2O and brine, dried (Na_2SO_4), filtered, and evaporated. The residue was applied to FC (column 4.5 × 25 cm, light petroleum ether/AcOEt 9:1). From the first zone, **3b** (460 mg, 20%) was isolated. Colorless oil. TLC (light petroleum ether/AcOEt 7:3): R_f 0.8. UV (MeOH): 235 (27700), 260 (4200), 317 (5800). ^{1}H-NMR ((D$_6$)DMSO): 0.04, 0.05 (2*s*, Me_2Si); 0.87 (*s*, *t*-Bu); 1.84, 2.23, 2.43 (3*m*, CH_2(2′), CH_2(3′)); 3.60 (*m*, CH_2(5′)); 4.35 (*m*, H–C(4′)); 6.30 (*dd*, *J* = 4.0, 6.8, H–C(1′)); 6.33 (*d*, *J* = 3.8, H–C(5)); 6.65 (*s*, NH_2); 7.28 (*d*, *J* = 3.8, H–C(6)). Anal. calc. for $C_{17}H_{27}ClN_4O_2Si$ (383.0): C 53.32, H 7.11, Cl 9.26, N 14.63; found: C 53.58, H 7.19, Cl 9.00, N 14.63.

*2-Amino-4-chloro-7-{2,3-dideoxy-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-β-*D*-glycero-pentofuranosyl}-7H-pyrrolo[2,3-d]pyrimidine* (**4b**). The second zone (see FC above) afforded **4b** (500 mg, 22%). Colorless oil. TLC (light petroleum ether/AcOEt 7:3): R_f 0.45. UV (MeOH): 235 (25700), 260 (3900), 317 (5200). ^{1}H-NMR ((D$_6$)DMSO): 0.00 (*s*, Me_2Si); 0.84 (*s*, *t*-Bu); 1.98 (*m*, CH_2(3′)); 2.15, 2.33 (2*m*, CH_2(2′)); 3.64 (*dd*, *J* = 4.6, 11.1, 1 H, CH_2(5′)); 3.75 (*dd*, *J* = 3.9, 11.1, 1 H, CH_2(5′)); 4.05 (*m*, H–C(4′)); 6.23 (*dd*, *J* = 4.0, 6.8, H–C(1′)); 6.29 (*d*, *J* = 3.8, H–C(5)); 6.66 (*s*, NH_2); 7.33 (*d*, *J* = 3.8, H–C(6)). Anal. calc. for $C_{17}H_{27}ClN_4O_2Si$ (383.0): C 53.32, H 7.11, Cl 9.26, N 14.63; found: C 53.25, H 7.28, Cl 9.40, N 14.40.

(5S)-5-{{[(1,1-Dimethylethyl)diphenylsilyl]oxy}methyl}tetrahydrofuran-2-ol (**10a**) [31]. Compound **9** [30] (7.8 g, 22 mmol) was reduced with DIBAL as described in [31]. After stirring for 5 min, the mixture was quenched with MeOH (5 ml) and allowed to warm up to r.t. AcOEt (30 ml) and sat. aq. $NaHCO_3$ soln. (4 ml) were added, and stirring was continued for 2 h. Powdered Na_2SO_4 (20 g) was then added and the mixture stirred overnight. The solid material was filtered off and washed with AcOEt. The combined liquid phase was evaporated and the residue purified by column chromatography (silica gel, column 5 × 15 cm, CH_2Cl_2) and crystallization from light petroleum ether: **10a** (7.2 g, 92%). TLC (CH_2Cl_2): R_f 0.14. Colorless crystals. M.p. 60–64°. ^{1}H-NMR ((D$_6$)DMSO): 1.00, 1.01 (2*s*, *t*-Bu); 1.66–2.07 (*m*, CH_2(2), CH_2(3)); 3.58–3.77 (*m*, CH_2(5)); 4.04, 4.21 (2*m*, H–C(4)); 5.33, 5.41 (2*m*, H–C(1)); 5.97, 6.00 (2*d*, *J* = 4.8, 4.5, OH–C(1)); 7.43, 7.66 (2*m*, arom. H).

*2,3-Dideoxy-5-*O*-[(1,1-dimethylethyl)diphenylsilyl]-*D*-glycero-pentofuranosyl Chloride* (**10b**) *in THF Solution.* To a stirred soln. of **10a** (0.72 g, 2 mmol) in anh. THF (8 ml), CCl_4 (0.3 ml, 3.1 mmol) was added with a syringe under Ar. The soln. was cooled to −80° and tris(dimethylamino)phosphane (0.48 ml, 2.6 mmol) added dropwise within 20 min. Stirring was continued for 4 h at −80°. The cold soln. was immediately used for the glycosylation.

*4-Chloro-7-{2,3-dideoxy-5-*O*-[(1,1-dimethylethyl)diphenylsilyl]-α-*D*-glycero-pentofuranosyl}-7H-pyrrolo-[2,3-d]pyrimidine* (**11**). To a soln. of **1a** (620 mg, 4 mmol) in MeCN (50 ml), powdered KOH (1.0 g, 18 mmol) and TDA-1 (0,1 ml, 0.31 mmol) were added. After 10 min, the cold THF soln. of **10b** (2 mmol; prepared *in situ*) was added. Upon stirring for 30 min, the insoluble material was filtered off and the filtrate evaporated. The residue was applied to FC (column 3 × 30 cm, light petroleum ether/AcOEt 9:1). Isolation of the material of the first zone gave 200 mg (20%) of **11**. Oil. TLC (light petroleum ether/AcOEt 9:1): R_f 0.38. UV (MeOH): 222 (31900), 271 (4900). ^{1}H-NMR ((D$_6$)DMSO): 1.01 (*s*, *t*-Bu); 2.01, 2.38 (2*m*, CH_2(2′), CH_2(3′)); 3.70 (*m*, CH_2(5′)); 4.54 (*m*, H–C(4′)); 6.60 (*dd*, *J* = 4.6, 6.6, H–C(1′)); 6.71 (*d*, *J* = 3.8, H–C(5)); 7.39–7.44, 7.63–7.68 (2*m* arom. H); 7.91 (*d*, *J* = 3.8, H–C(6)); 8.66 (*s*, H–C(2)). Anal. calc. for $C_{27}H_{30}ClN_3O_2Si$ (492.1): C 65.90, H 6.14, Cl 7.20, N 8.54; found: C 66.00, H 6.23, Cl 7.16, N 8.54.

*4-Chloro-7-{2,3-dideoxy-5-*O*-[(1,1-dimethylethyl)diphenylsilyl]-β-*D*-glycero-pentofuransoyl}-7H-pyrrolo-[2,3-d]pyrimidine* (**12**). The second zone (see FC above) yielded **12** (290 mg, 29%). Colorless oil which crystallized upon storing. TLC (light petroleum ether/AcOEt 9:1): R_f 0.21. UV (MeOH): 222 (31300), 271 (4600). ^{1}H-NMR ((D$_6$)DMSO): 0.96 (*s*, *t*-Bu); 2.12 (*m*, CH_2(3′)); 2.36 (*m*, CH_2(2′)); 3.72 (*dd*, *J* = 4.3, 11.1, 1 H, CH_2(5′)); 3.86 (*dd*, *J* = 3.6, 11.1, 1 H, CH_2(5′)); 4.23 (*m*, H–C(4′)); 6.54 (*m*, H–C(1′)); 6.55 (*d*, *J* = 3.7, H–C(5)); 7.28–7.65 (*m*, arom. H); 7.84 (*d*, *J* = 3.7, H–C(6)); 8.64 (*s*, H–C(2)). Anal. calc. for $C_{27}H_{30}ClN_3O_2Si$ (492.1): C 65.90, H 6.14, Cl 7.20, N 8.54; found: C 65.81, H 6.01, Cl 7.28, N 8.59.

4′-Chloro-4,7′-bi[7H-pyrrolo[2,3-d]pyrimidine] (**5**). To a soln. of **1a** (1.2 g, 8.0 mmol) in MeCN (60 ml), powdered KOH (1.4 g, 25 mmol) and TDA-1 (0.1 ml, 0.31 mmol) were added. After 10 min, the soln. of **2** (prepared

in situ from 930 mg (4 mmol) of lactol) was added. Stirring was continued for 60 min, then the insoluble material filtered off, and the filtrate evaporated. The residue was applied to FC (column 2.5 × 30 cm, light petroleum ether/AcOEt 9:1). From the first zone, **3a** (290 mg, 10%) was isolated, from the second zone, **4a** (360 mg, 12%). A mixture of CH_2Cl_2/MeOH 95:5 eluted **1a** (200 mg, 17%) at first, then **5** (490 mg, 41%) as colorless solid. TLC of **5** (CH_2Cl_2/MeOH 9:1): R_f 0.65. UV (MeOH): 222 (37700), 301 (9100). ^{1}H-NMR ((D_6)DMSO): 6.77 (*d*, *J* = 3.4, H–C(5)); 7.00 (*d*, *J* = 3.9, H–C(5′)); 7.68 (*d*, *J* = 3.4, H–C(6)); 8.32 (*d*, *J* = 3.9, H–C(6′)); 8.78 (*s*, H–C(2)); 8.80 (*s*, H–C(2′)); 12.59 (*s*, NH). Anal. calc. for $C_{12}H_7ClN_6$ (270.7): C 53.25, H 2.61, N 31.05; found: C 53.35, H 2.80, N 30.70.

General Desilylation Procedure. The protected nucleoside **3a,b**, **4a,b**, **11** or **12**, dissolved in THF (5 ml), was stirred with 1M Bu_4NF in THF (5 ml) at r.t. for 30 min, the soln. evaporated, and the residue applied to FC yielding one main zone.

4-Chloro-7-(2,3-dideoxy-α-D-glycero-*pentofuranosyl)-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**6a**). From **11** (400 mg, 0.81 mmol), after FC (silica gel, column 3 × 20 cm, CH_2Cl_2/MeOH 98:2), **6a** (170 mg, 82%).

From **3a** (350 mg, 0.95 mmol), after FC (silica gel, column 3 × 20 cm, CH_2Cl_2/MeOH 98:2), **6a** (160 mg, 66%). Colorless oil, which crystallized upon storing. TLC (CH_2Cl_2/MeOH 95:5): R_f 0.37. UV (MeOH): 224 (22000), 273 (4100), 287 (sh, 3600). ^{1}H-NMR ((D_6)DMSO): 1.92, 2.25, 2.50 (3*m*, CH_2(2′), CH_2(3′)); 3.47 (*m*, CH_2(5′)); 4.39 (*m*, H–C(4′)); 4.82 (*t*, *J* = 5.7, OH–C(5′)); 6.58 (*dd*, *J* = 4.6, 6.8, H–C(1′)); 6.72 (*d*, *J* = 3.7, H–C(5)); 7.92 (*d*, *J* = 3.7, H–C(6)); 8.67 (*s*, H–C(2)). Anal. calc. for $C_{11}H_{12}ClN_3O_2$ (253.7): C 52.08, H 4.77, Cl 13.98, N 16.56; found: C 52.19, H 4.83, Cl 13.58, N 16.35.

2-Amino-4-chloro-7-(2,3-dideoxy-α-D-glycero-*pentofuranosyl)-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**6b**). From **3b** (180 mg, 0.47 mmol), after FC (column 3 × 28 cm, CH_2Cl_2/MeOH 98:2), **6b** (100 mg, 79%). Colorless oil which crystallized upon storing. TLC (CH_2Cl_2/MeOH 95:5): R_f 0.22. UV (MeOH): 203 (13700), 234 (29500), 260 (4100), 316 (5500). ^{1}H-NMR ((D_6)DMSO): 1.82, 2.22, 2.41 (3*m*, CH_2(2′), CH_2(3′)); 3.38 (*m*, CH_2(5′)); 4.28 (*m*, H–C(4′)); 4.77 (*t*, *J* = 5.7, OH–C(5′)); 6.31 (*dd*, *J* = 4.6, 6.8, H–C(1′)); 6.34 (*d*, *J* = 3.8, H–C(5)); 6.66 (*s*, NH_2); 7.29 (*d*, *J* = 3.8, H–C(6)). Anal. calc. for $C_{11}H_{13}ClN_4O_2$ (268.7): C 49.17, H 4.88, Cl 13.19, N 20.85; found: C 49.44, H 5.10, Cl 13.36, N 20.76.

4-Chloro-7-(2,3-dideoxy-β-D-glycero-*pentofuranosyl)-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**7a**). From **4a** (500 mg, 1.4 mmol), after FC (column 4.5 × 23 cm, CH_2Cl_2/MeOH 98:2), **7a** (230 mg, 67%). Identical with an authentic sample [12]. TLC (CH_2Cl_2/MeOH 95:5): R_f 0.5 ([12]: R_f 0.5).

From **12** (900 mg, 1.8 mmol) after FC (column 4.5 × 20 cm, CH_2Cl_2/MeOH 98:2), **7a** (250 mg, 54%). Colorless solid.

Table 3. *Pyrrolo[2,3-*d*]pyrimidine Nucleoside 5′-Mono- and 5′-Triphosphates*

Product[a])	Educt	Yield	UV (H_2O)	^{31}P-NMR[c]) (*J* [Hz])		
		$OD_{\lambda max}$ (%)	λ_{max} (ε)[b])	δ(P(α))	δ(P(β))	δ(P(γ))
13a	**13c**[d])	627 (55)	271 (11400)	−10.17 (*d*, *J* = 20)	−21.65 (*t*, *J* = 20)	−7.53 (*d*, *J* = 20)
13b		205 (18)		3.75 (*s*)		
14a	**14c**[f])	469 (46)	262 (10200)	−10.06 (*d*, *J* = 19)	−21.59 (*t*, *J* = 19)	−7.52 (*d*, *J* = 19)
14b		132 (13)		4.01 (*s*)		
15a	**15b**[f])	412 (31)	261 (13100)	−10.25 (*d*, *J* = 19)	−21.76 (*t*, *J* = 19)	−6.31 (*d*, *J* = 19)
16a	**16c**[h])	294 (31)	261 (9500)	−10.30 (*d*, *J* = 19)	−22.14 (*t*, *J* = 19)	−9.26 (*d*, *J* = 19)
16b		104 (11)		3.73 (*s*)		
16d	**16e**[h])	184 (42)	267 (4500)	−10.25 (*d*, *J* = 19)	−21.71 (*t*, *J* = 19)	−6.14 (*d*, *J* = 19)
17a	**17b**[e])	462 (35)	271 (12200)	−10.57 (*d*, *J* = 19)	−22.19 (*t*, *J* = 19)	−8.39 (*d*, *J* = 19)
18a	**18c**[g])	265 (26)	263 (10200)	−10.30 (*d*, *J* = 19)	−21.40 (*t*, *J* = 19)	−6.54 (*d*, *J* = 19)
18b		255 (25)		3.99 (*s*)		
19a	**19c**[g])	746 (57)	259 (13100)	−10.40 (*d*, *J* = 19)	−21.57 (*t*, *J* = 19)	−6.99 (*d*, *J* = 19)
19b		196 (15)		2.98 (*s*)		
20a	**6a**	242 (55)	274 (4500)	−10.22 (*d*, *J* = 19)	−21.60 (*t*, *J* = 19)	−6.05 (*d*, *J* = 19)
20b	**20c**[i])	335 (78)	278 (4300)	−10.40 (*d*, *J* = 19)	−22.30 (*t*, *J* = 19)	−9.40 (*d*, *J* = 19)

[a]) Isolated as triethylammonium salt. [b]) ε-Values from the corresponding nucleosides. [c]) Measured in D_2O/*Tris*-HCl buffer pH 8.0 1:1, 0.1M Na_4EDTA. [d]) [16]. [e]) [15]. [f]) [13]. [g]) [44]. [h]) [12]. [i]) [45].

*2-Amino-4-chloro-7-(2,3-dideoxy-β-*D*-glycero-pentofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine* (**7b**). From **4b** (900 mg, 2.35 mmol), after FC (column 3 × 24 cm, CH_2Cl_2/MeOH 97:3), **7b** (540 mg, 85%). Colorless solid. Identical with an authentic sample [13]. TLC (CH_2Cl_2/MeOH 95:5): R_f 0.34 ([13]: R_f 0.34).

2',3'-Dideoxyribonucleoside Triethylammonium 5'-Triphosphates: General Procedure. The 2',3'-dideoxyribonucleoside (0.1 mmol) and 1.8-bis(dimethylamino)naphthalene (32 mg, 0.15 mmol) were dissolved in $PO(MeO)_3$ (0.5 ml), cooled to 0° (ice-bath), and treated with $POCl_3$ (20 µl, 0.21 mmol). The mixture was stored at 4° for 3 h (refrigerator). $Bu_4NP_2O_7$ [43] in anh. DMF (0.5M, 1 ml) and Bu_3N (100 µl, 0.42 mmol) were added. After stirring for 1 min at 0°, aq. $(Et_3NH)HCO_3$ (pH 7–8; 10 ml) was poured into the soln. and the solvent evaporated. The residue was dissolved in H_2O (100 ml), applied to an ion-exchange column (*DEAE-Sephadex*, HCO_3^- form, column 32 × 2 cm), and chromatographed using a linear gradient of $(Et_3NH)HCO_3$ (0.1M (1.0 l) to 0.7M (1.0 l)). The 5'-monophosphates were eluted at 0.3M, the 5'-triphosphates at 0.5M $(Et_3NH)HCO_3$. The phosphate-containing fractions were lyophilized. Compound **16a** was further purified by HPLC (*LiChrosorb RP-18*, 0.1M $(Et_3NH)OAc$/5% MeCN).

The phosphates **14a**, **15a**, **16d**, **17a**, **20a**, and **20c** were prepared without the addition of 1,8-bis(dimethylamino)naphthalene. The yields and physical properties of all phosphates are summarized in *Table 3*.

HIV-1 Reverse Transcriptase Inhibition Test. A heterodimer of HIV-1 reverse transcriptase, expressed from *E. coli*, was used. The reactions were carried out in buffer (50 mM *Tris*-HCl, pH 7.9; 50 mM KCl; 5 mM $MgCl_2$; 1 mM DTT), containing HIV-LTR template and a 18mer primer. (*methyl*-^{3}H)Thymidine 5'-triphosphate was used for radioactive labeling. The test compounds were added in DMSO soln. After incubation, DNA was precipitated with CCl_3COOH and dried, and incorporated radioactivity was measured. A detailed description of the test procedure is available upon request.

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