146. 8-Azaadenine 2′,3′-Dideoxyribonucleosides: Synthesis *via* 1,2,3-Triazolo[4,5-*d*]pyrimidinyl Anions

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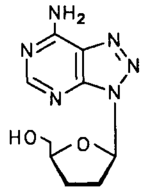
The 8-azaadenine 2′,3′-dideoxyribonucleosides **1**–**3** were synthesized *via* glycosylation of the 7-methoxy- or 7-amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidinyl anion with 5-*O*-[(*tert*-butyl)dimethylsilyl]-2,3-dideoxy-D-*glycero*-pentofuranosyl choride (**6**). As **6** was an anomeric mixture, anomeric glycosylation products were formed. Moreover, three regioisomers (N^1, N^2, and N^3) were obtained in the case of the methoxy compound, but only two (N^1 and N^2) using 8-azaadenine. They were characterized by ^{13}C-NMR and CD spectra. The N-glycosylic bond of 8-aza-2′,3′-dideoxyadenosine (**1**) was *ca.* 10 times more stable against acid than that of 2′,3′-dideoxyadenosine. Compound **1** was deaminated by adenosine deaminase and showed inhibitory activity on HIV reverse transcriptase in form of its *O*-5′-triphosphate.

Introduction. – The 8-azaadenine nucleosides received considerable attention as purine antagonists in biological systems including viruses and cancer [1–3]. Analogs of the bases of common nucleosides were prepared [4]. The first azapurine, which was synthesized by *Traube*, was 1,3-dimethyl-7*H*-8-azapurine-2,6(1*H*,3*H*)-dione [5]. The chemistry of 8-azapurines (= 1*H*-1,2,3-triazolo[4,5-*d*]pyrimidines) is reviewed by *Albert* [6]. Whithin the series of 8-azaadenine derivatives, ribonucleosides [7–10], arabinonucleosides [11] [12] and 2′-deoxyribonucleosides [13] [14] were synthesized by common glycosylation techniques. Recently, we reported on the synthesis of 8-aza-2′-deoxyadenosine and related 2′-deoxyribonucleosides *via* nucleobase-anion glycosylation [15].

Purine 2′,3′-dideoxy-*β*-D-ribonucleosides are highly active compounds against the human immunodeficiency virus (HIV), thereby inhibiting the HIV reverse transcriptase in form of their triphosphates [16]. Recently, we synthesized various deazapurine 2′,3′-dideoxyribonucleosides and tested their activity [17–19]. We now focussed our interest on 8-azapurine 2′,3′-dideoxyribonucleosides. In the following, we report on the synthesis, stability, and activity of the regioisomeric 8-azaadenine 2′,3′-dideoxyribonucleosides **1**–**3** [20] related to $\mathrm{A}_{\mathrm{d}}^{2',3'}$ (**4**).



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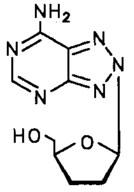

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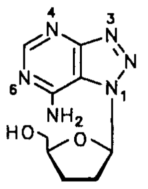

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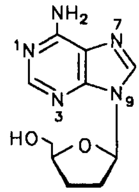
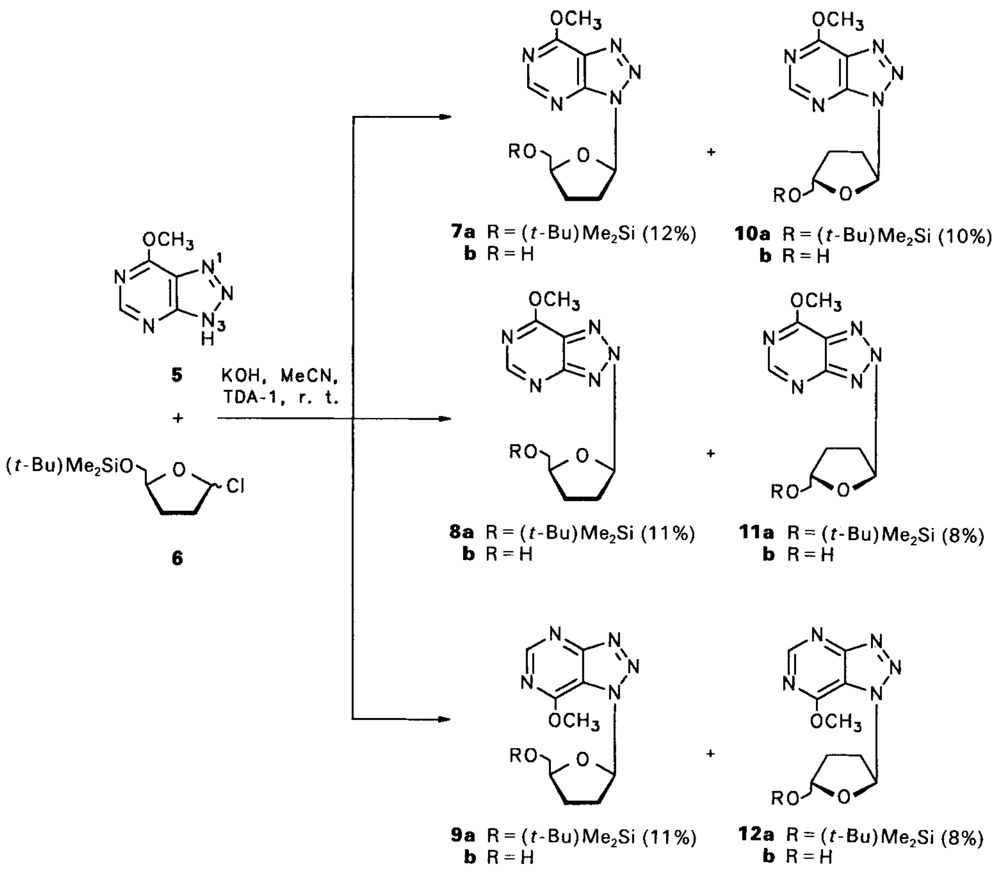


4 (purine numbering)

Results and Discussion. – In 1974, the preparation of 8-azaadenine 2′,3′-dideoxyribonucleoside (**1**) from the corresponding ribonucleoside was reported without substance characterization [21]. Compound **1** was also mentioned in another patent, again without any characterization [22]. Microbial preparation from 8-azaadenine and 2′,3′-dideoxypyrimidine nucleosides was reported *via* transglycosylation [23] [24]. As the chemical synthesis of base-modified 2′,3′-dideoxyribonucleosides from corresponding ribo-, or 2′-deoxyribonucleosides is laborious, we decided to use the direct glycosylation of the 8-azapurinyl anion, carrying a 6-amino or 6-methoxy group, by the halogenose **6**. According to the nucleophilicity of the triazole moiety, *N*-regioisomers were expected, as found in the case of 2′-deoxyribonucleosides [15].

The glycosylation of 7-methoxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**5**) with 5-*O*-[(*tert*-butyl)dimethylsilyl]-2,3-dideoxy-D-*glycero*-pentofuranosyl chloride (**6**) was carried out in MeCN in the presence of a three-fold excess of powdered KOH and the cryptand tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1), as described for the synthesis of 3-deazapurine and other base-modified 2′,3′-dideoxyribonucleosides [17] [18]. The halogenose **6**

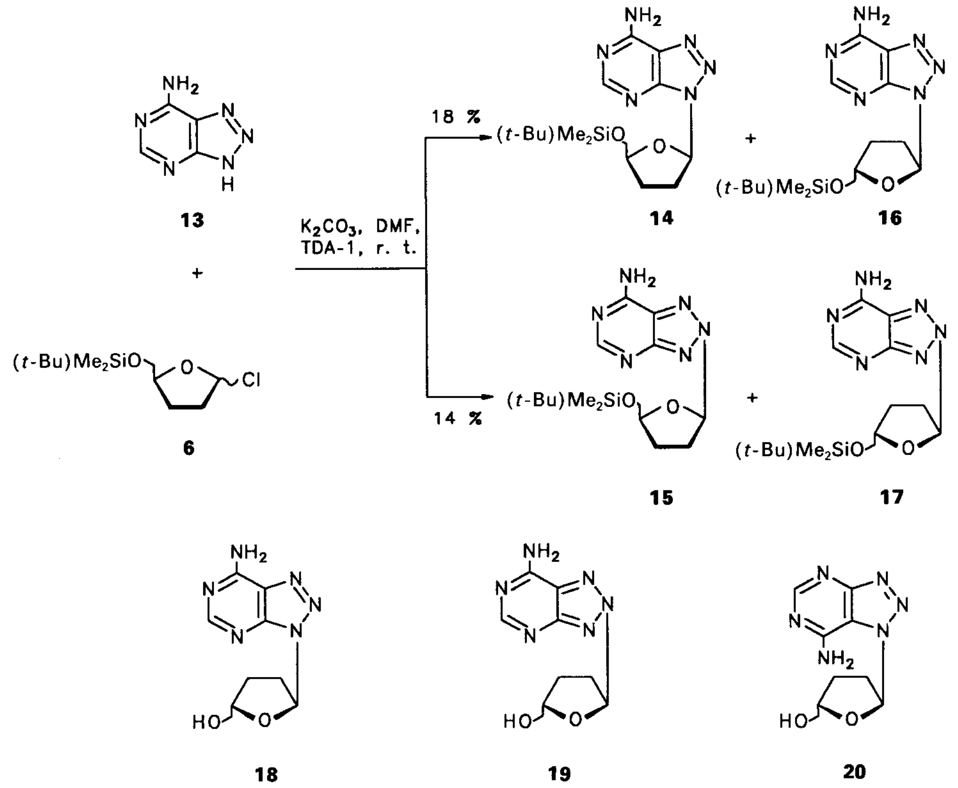
Scheme 1



was prepared from the corresponding lactol [25]. After workup, the reaction mixture was separated by repeated flash chromatography (FC; see *Exper. Part*), giving the six glycosylation products **7a**–**12a** in 60% overall yield. The ratio of the regioisomers was *ca.* 1:1:1, comparable with that of the corresponding 2′-deoxyribonucleosides [15]. A small excess of the β-D-anomers **7a**–**9a** was formed. Compounds **7a**–**12a** were desilylated with Bu_4NF in THF ($\rightarrow$ **7b**–**12b**) and then treated with $MeOH/NH_3$ to yield the crystalline β-D-anomers **1**–**3** and the corresponding α-D-anomers (see below **18**–**20**). Structural assignment of the glycosylation products are discussed below.

As the sugar halide **6** was an anomeric mixture, anomeric glycosylation products were formed under conditions (MeCN) which proceeded stereoselectively in the case of 2′-deoxyribonulecosides [15]. Therefore, non-stereoselective conditions (DMF) could be used as well. This allowed the use of 8-azaadenine (**13**) as base, thus circumventing the MeO/NH_2 displacement of the former reaction route (*Scheme 1*) and reducing the number of regioisomers to only two. The reaction of **13** with **6** was carried out in the presence of K_2CO_3 and TDA-1 (*Scheme 2*). After chromatographic workup (see *Exper. Part*; 32% overall yield), only **14** (faster migrating), **16** (slower migrating), and the anomers **15**/**17** (slowest migrating; not separated) were isolated. Neither an N^1- nor an N^4-isomer was obtained. Deprotection with Bu_4NF in THF afforded compounds **1**, **18**,

Scheme 2



and **2**/**19**, respectively, in 80–90% yield. Contrary to **15**/**17**, the deprotected nucleosides **2**/**19** could be separated. The anomeric ratios of the amino derivatives were about the same as those found for the methoxy compounds. In opposition to the synthesis of 8-aza-2′-deoxyadenosine [15] which makes use of 7-methoxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**5**), the synthesis of 8-aza-2′,3′-dideoxyadenosine (**1**) gives better results with 8-azaadenine (**13**) because of a shorter synthetic sequence and less regioisomers formed, even if the total glycosylation yield is lower.

During the work on 8-azapurine 2′-deoxyribonucleosides, the ^{13}C-NMR chemical shifts of the nucleobase moieties were already assigned [15]. We now measured gated-decoupled spectra of all 2′,3′-dideoxyribonucleosides described above (*Table 1*). Moreover,

Table 1. *^{13}C-NMR Chemical Shifts of 8-Aza-2′,3′-dideoxyadenosine* (**1**) *and Related 1,2,3-Triazolo[4,5-*d*]pyrimidine 2′,3′-Dideoxyribofuranosides in (D_6)DMSO at 23°*

	C(3a)[a]	C(5)	C(7a)	C(7)	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)
1	148.5	156.8	123.9	156.2	85.9	30.6	27.0	82.7	63.8
2	157.5	157.1	125.5	156.9	94.4	31.9	26.5	83.8	63.9
3	160.9	154.5	113.6	151.9	89.5	29.4	25.3	81.8	63.0
7a	150.3	156.4	125.3	161.4	86.6	30.8	26.5	82.7	65.0
b	150.3	156.4	125.3	161.4	86.5	30.9	27.0	83.2	63.7
8a	159.2	155.9	126.1	162.3	95.2	32.0	25.8	83.7	65.0
b	159.1	155.9	126.1	162.3	95.3	32.4	26.4	84.3	63.8
9a[b]	161.7	153.7	114.5	157.3	89.3	30.9	26.2	82.9	65.0
b[b]	161.7	153.8	114.7	157.4	89.3	31.4	26.6	83.5	63.6
10a	150.2	156.4	125.4	161.4	87.2	30.6	26.2	81.5	64.9
b[c]	150.2	156.2	125.4	161.4	87.2	30.4	26.4	82.1	63.2
11a	159.2	155.9	126.2	162.3	95.7	31.8	25.3	82.2	64.8
b[c]	159.2	155.9	126.2	162.3	95.7	31.7	25.5	82.8	63.1
12a[b]	161.6	153.7	114.3	157.2	89.9	30.8	25.8	81.3	64.8
b[b]	161.7	153.9	114.4	157.5	90.0	31.0	26.1	81.9	63.2
14	148.6[d]	156.8	123.9	156.1[d]	85.7	30.4	26.6	82.2	65.1
15[e]	157.5[d]	157.1	125.5	156.9[d]	94.3	31.6	25.9	83.2	65.2
16	148.5[d]	156.9	124.0	156.1[d]	86.3	30.2	26.3	81.1	64.8
17[e]	157.5[d]	157.1	125.5	156.9[d]	94.7	31.4	25.4	81.7	64.7
18[c]	148.5[d]	156.9	124.0	156.1[d]	86.3	30.1	26.5	81.7	63.1
19[c]	157.5[d]	157.1	125.5	156.7[d]	94.7	31.3	25.6	82.3	63.1
20[c]	160.9[d]	154.5	113.7	151.9[d]	89.1	30.2	25.4	83.3	63.0

[a] Systematic 1,2,3-triazolo[4,5-*d*]pyrimidine numbering. [b] Aglycone signals according to the gated-decoupled spectra of 7-methoxy-1-[2′-deoxy-3′,5′-di-*O*-(4-toluoyl)-*β*-D-*erythro*-pentofuranosyl]-1*H*-1,2,3-triazolo[4,5-*d*]pyrimidine [12]. [c] According to gated-decoupled ^{13}C-NMR spectra. [d] Tentative. [e] Taken from the anomeric mixture **15**/**17**.

the ^{13}C,^{1}H-coupling constants were obtained from the gated-decoupled spectra of a set regioisomeric 7-amino- and 7-methoxy-1,2,3-triazolo[4,5-*d*]pyrimidine 2′,3′-dideoxyribonulecosides (*Table 2*). It became apparent that in all cases, the coupling between C(3a) to the anomeric proton is low or not detectable. This is different to purine nucleosides, indicating that 8-azapurine 2′-3′-dideoxyribonucleosides prefer a high-*anti* conformation around the N-gylcosylic bond, similar to other 8-azapurine nucleosides [26]. The lack of *J*(C(3a),*H*–C(1′)) makes the assignment of C(3a) *vs.* C(7) difficult in the

Table 2. *J(C,H) Values* [Hz] *of 1,2,3-Triazolo[4,5-*d*]pyrimidine 2′,3′-Dideoxyribofuranosides*[a])

	10b	**11b**	**18**	**19**	**20**
J(C(3a),H–C(5))	13	13	13	13	12
J(C(3a),H–C(1′))	1	–	–	–	–
J(C(5),H–C(5))	209	207	201	199	200
J(C(7),H–C(5))	11	11	11	11	12
J(C(7),MeO)	4	3	–	–	–
J(C(7a),NH_2)	–	–	4	*m*	*m*
J(C(1′),H–C(1′))	171	174	169	172	175
J(C(2′),H–C(2′))	135	135	135	139	135
J(C(3′),H–C(3′))	133	134	133	131	133
J(C(4′),H–C(4′))	147	148	148	147	147
J(C(5′),H–C(5′))	140	140	140	142	138

[a]) Systematic numbering.

case of the NH_2 compounds; the MeO compounds, however, allow the assignment as two *q* appear for C(7). If the chemical shifts of C(7) of the N^1-, N^2-, and N^3-regioisomers of the 7-NH_2 compounds are compared with those of the 7-MeO derivatives, almost the same chemical-shift differences are observed within the series of regioisomers. However, the NH_2 compounds resonate at higher field (5 ppm), which is in line with the change of *ipso*-substituents (*Table 1*). According to this, the chemical shifts of C(3a) *vs.* C(7) for the 8-azaadenine N^1-(2′,3′-deoxyribofuranosides) have to be reversed in [15].

The assignments of the anomeric configuration of the 2′,3′-dideoxyribonucleosides are based on data summarized in *Table 3*. The NOE of H–C(4′) upon irradiation of H–C(1′) can be used for the assignment of the β-D-configuration [27]. In the case of 2′,3′-dideoxynucleosides, this NOE is observed, apart from a smaller NOE in the case of the α-D-isomers. The small NOE of the α-D-anomers is due to the three-spin effect [28]. In the case of the amino nucleoside **3**, an additional NOE at the NH_2 group (2.4%) is detected upon irradiation of H–C(1′). This confirms N^1 as the glycosylation site (systematic numbering). The N^3-glycosylation site is deduced from the typical up- and downfield shifts (10 ppm) of C(3a) and C(7a) induced by the substitution of the N-atom in α-position [29]. The assignment of the N^2-isomers resulted from the absence of NOE's at H–C(5), which should be present if the sugar is attached to N^4 or N^6. The anomeric

Table 3. *Spectroscopic Data of Anomeric 8-Azaadenine 2′,3′-Dideoxyribonucleosides*

	NOE [%] at H–C(4′)[a])[b])	δ(C(4′))	R_f[c])		δ(C(4′))	$\Delta\delta$(CH_3Si)
1 (N^3,β-D)	1.5	82.7	0.55	**7a** (N^3,β-D)	82.7	0.044
2 (N^2,β-D)	1.6	83.8	0.30	**8a** (N^2,β-D)	83.7	0.052
3 (N^1,β-D)	2.0	83.3	0.25	**9a** (N^1,β-D)	82.9	0.040
18 (N^3,α-D)	0.8	81.7	0.40	**10a** (N^3,α-D)	81.5	0.016
19 (N^2,α-D)	0.9	82.3	0.25	**11a** (N^2,α-D)	82.2	0.017
20 (N^1,α-D)	0.9	81.8	0.25	**12a** (N^1,α-D)	81.3	0.015

[a]) Upon irradiation of H–C(1′). [b]) Measured in (D_6)DMSO. [c]) TLC (silica gel, CH_2Cl_2/MeOH 9:1).

assignments are also supported by other data summarized in *Table 3*, *e.g.* the chemical shifts of C(4′) of the protected MeO compounds being always 1–1.5 ppm upfield shifted in the case of the α-D-anomers compared to the β-D-compounds. Furthermore, the ^{1}H-NMR chemical-shift differences of the Me signals of the (*t*-Bu)Me$_2$Si groups was 0.04 for the β-D-anomers and 0.02 for the α-D-anomers. Moreover, the deprotected MeO compounds were converted into the corresponding NH$_2$ nucleosides confirming these assignments. From the 8-azapurine 2′,3′-dideoxyribonucleosides, only compound **1** can be converted into the corresponding inosine derivative (data not shown), which is an additional structural proof, at least within the series of the N^3-regioisomers.

Ulbricht and coworkers [30] proposed that the anomeric configuration of nucleosides can be correlated to the CD spectra. Pyrimidine β-D-nucleosides should have a positive *Cotton* effect at 260 nm, while the α-D-anomers show the opposite behaviour. For purine nucleosides, the situation is different; β-D-purine nucleosides exhibit negative *Cotton* effects in the region of 260 nm and *vice versa*. However, it was already recognized that this rule depends on the electronic state and the torsion angle of the nucleobases [31]. We measured the CD spectra of compounds **1**–**3** and **18**–**20**. The *Figure* shows that the empirical CD rules cannot be transferred from purine to 8-azapurine nucleosides. Opposite CD spectra are observed in the anomeric pair of **3** and **20**. The situation becomes more difficult in the case of **1** and **18**. Assignment of the anomers **2** and **19** does not follow these rules.

Ribo- and 2′-deoxyribonucleosides can be cleaved at the N-glycosylic bond within cells by the action phosphorylases thereby loosing their activity. Hydrolysis depends on the activity of the enzyme but also on the chemical stability of the N-glycosylic bond. In particular, 2′,3′-dideoxyribonucleosides are extremely labile [32]. It was shown that 8-azaadenine 2′-deoxyribonculeosides undergo acid-catalysed hydrolysis *via* cyclic glycosyl oxocarbenium ions as rate-limiting step with the N^1-regioisomers (systematic numbering) as the most labile and the N^3-isomers as the most stable compounds [33]. *Table 4* summarizes the stability of the regioisomeric 8-azaadenine 2′,3′-dideoxyribonucleosides. Again, the N^1-isomers are the most labile compounds, whereas the N^2- and the N^3-isomers are comparably stable. The β-D-anomers are hydrolysed slightly faster than the α-D-compounds by a factor of *ca.* 1.5 which is opposite to the 8-azaadenine 2′-deoxyribonucleosides [15] as well as to parent 2′-deoxyadenosine and its α-D-anomer [32]. In comparison to $\mathrm{A}_{\mathrm{d}_2^{2',3'}}$ (**4**), compound **1** is approximately ten-fold more stable (*Table 4*).

Table 4. *Kinetic Data of N-Glycosylic-Bond Hydrolysis of Adenine and 8-Azaadenine 2′,3′-Dideoxy-*D*-ribofuranosides*

	T [°C]	$t_{1/2}$ [min]	c_{HCl} [mol l^{-1}]		T [°C]	$t_{1/2}$ [min]	c_{HCl} [mol l^{-1}]
1 (N^3,β-D)	25	12.3	0.1	**3** (N^1,β-D)	25	5.4	0.0005
18 (N^3,α-D)	25	19.7	0.1	**20** (N^1,α-D)	25	8.5	0.0005
2 (N^2,β-D)	25	11.8	0.1	**4** (N^3,β-D)	25	1.6	0.1
19 (N^2,α-D)	25	16.4	0.1				

Next, compounds **1** and **2** were phosphorylated in a one-pot reaction following a protocol originally developed for phosphorylation of purine nucleosides [34]. The nu-

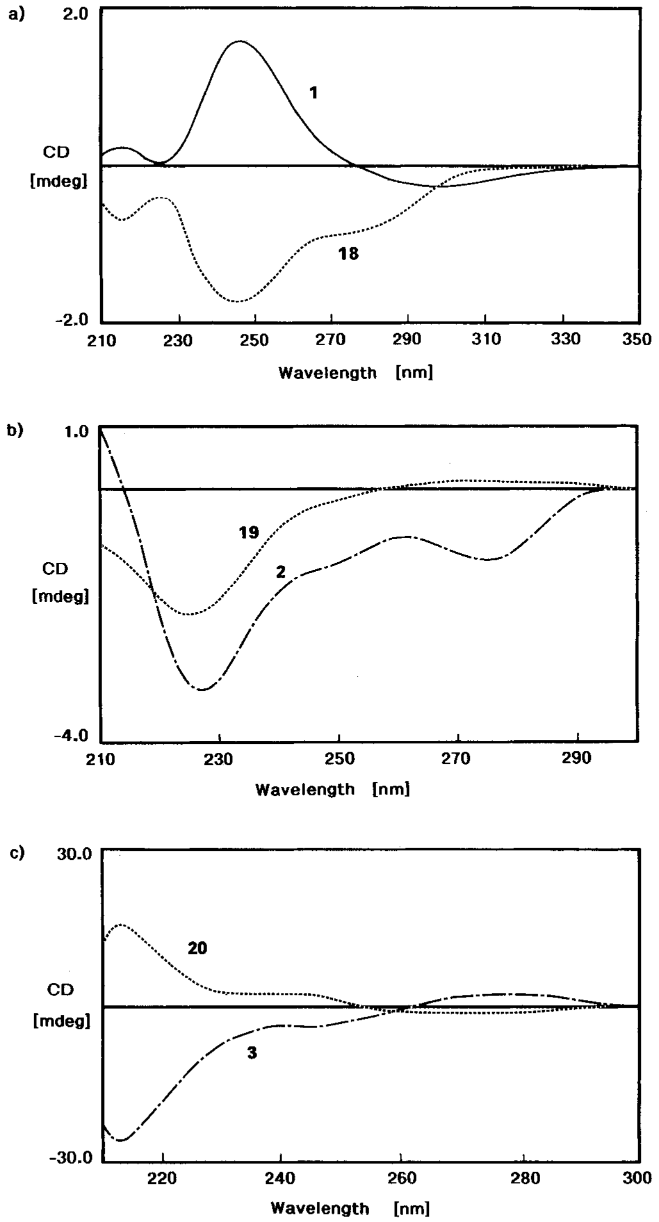
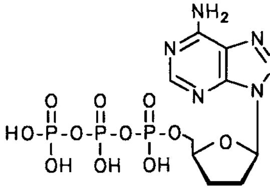


Figure. *CD Spectra of 8-Azaadenine 2′,3′-dideoxyribonucleosides* **1**–**3** *and* **18**–**20** *measured at 5° in 0.06* M *Na-cacodylate*, pH 7.0

cleosides were dissolved in $PO(MeO)_3$ and treated at 0° with 2.7 equiv. of $POCl_3$ resulting in the formation of an activated dichlorophosphate which was directly condensed with $[Bu_4N]_4P_2O_7$. The triphosphates **21** and **22** were purified by *DEAE*-cellulose column chromatography and isolated as solid triethylammonium salts. Their inhibitory activity



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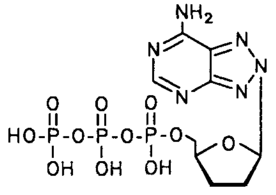

22

was tested against HIV reverse transcriptase [35]: dideoxyadenosine analogue **21** showed an IC_{50} value of 42 µM against HIV reverse transcriptase, whereas the regioisomeric **22** was inactive (> 100 µM). Compared to the parent $\mathrm{pppA}_{\mathrm{d}2',3'}$ [18], the *in vitro* activity of **21** is *ca.* 2 magnitudes lower, but it is in the range of the activity of 3-deaza-2',3'-dideoxyadenosine triphosphate (IC_{50} = 79 µM) [35].

We thank Dr. *B. König* from the *Boehringer Mannheim GmbH* for the inhibitory studies on HIV-reverse transcriptase and Dr. *H. Rosemeyer* for the discussion of the NMR spectra.

Experimental Part

General. See [15]. CD Spectra: *Jasco-600* spectropolarimeter; thermostatically controlled 1-cm cuvettes. Anal. TLC: glass plates coated with a 0.25-mm layer of silica gel *Sil G-25* with fluorescent indicator UV_{254} (*Merck*, Germany). Flash chromatography (FC): silica gel *60 H* (*Merck*, Germany); at 0.8 bar. Ion-exchange chromatography: *DEAE-Sephadex A25* (HCO_3^- form; *Kabi Pharmacia*, Sweden). Solvent systems: *A* = light petroleum ether/AcOEt 3:2, *B* = CH_2Cl_2/acetone 95:5, *C* = light petroleum ether/AcOEt 7:3, *D* = CH_2Cl_2/MeOH 95:5, *E* = CH_2Cl_2/MeOH 9:1, *F* = CH_2Cl_2/MeOH 8:2, *G* = light petroleum ether/AcOEt 1:4, *H* = i-PrOH/NH_3/H_2O 3:1:1.

*Glycosylation of 7-Methoxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine* (**5**) *with 2,3-Dideoxy-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-*D-glycero-*pentofuranosyl Chloride* (**6**). To a suspension of KOH (0.75 g, 13.4 mmol) in MeCN (50 ml) were added TDA-1 (40 µl, 0.12 mmol) and **5** (0.9 g, 6 mmol) [36]. After stirring for 10 min at r.t., a freshly prepared cold (–80°) THF soln. (30 ml) of **6** (12 mmol; calculated on the basis of 100% yield of **6**) [17] [25] was added in portions of 5 ml within 30 min. Stirring was continued for another 30 min, insoluble material filtered off, and the filtrate poured into 20% aq. $NaHCO_3$ soln. (100 ml). The aq. layer was extracted twice with CH_2Cl_2 and the combined org. phase dried (Na_2SO_4) and evaporated. FC (column 50 × 3 cm, *A*) gave five fractions. *Fr. 2*, which contained **11a** and some non-nucleoside by-products, was rechromatographed (FC, column 15 × 3 cm, *B*) to give **11a**. Rechromatography of *Fr. 3* (FC, column 20 × 3 cm, *B*) led to **7a** and **8a**.

*3-{2,3-Dideoxy-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-β-*D-glycero-*pentofuranosyl}-7-methoxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine* (**7a**). The faster-migrating part of *Fr. 3* yielded a colourless gum (265 mg, 12%). TLC (*B*): R_f 0.65. UV (MeOH): 250 (9900). ^{1}H-NMR ((D_6)DMSO): –0.19, –0.15 (2*s*, Me_2Si); 0.72 (*s*, *t*-Bu); 2.14–2.39 (*m*, CH_2(3')); 2.59, 2.81 (2*m*, CH_2(2')); 3.55 (*dd*, *J* = 11.0, 5.9, CH_2(5')); 4.21 (*s*, MeO); 4.26 (*m*, H–C(4')); 6.67 (*dd*, *J* = 7.1, 1.7, H–C(1')); 8.79 (*s*, H–C(5)). Anal. calc. for $C_{16}H_{27}N_5O_3Si$ (365.51): C 52.58, H 7.45, N 19.16; found: C 52.53, H 7.44, N 18.92.

*2-{2,3-Dideoxy-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-β-*D-glycero-*pentofuranosyl}-7-methoxy-2*H*-1,2,3-triazolo[4,5-*d*]pyrimidine* (**8a**). The slower-migrating part of *Fr. 3* gave a colourless syrup (230 mg, 10.6%). TLC (*B*): R_f 0.55. UV (MeOH): 260 (9800). ^{1}H-NMR ((D_6)DMSO): –0.16, –0.11 (2*s*, Me_2Si); 0.72 (*s*, *t*-Bu); 2.17 (*m*, CH_2(3')); 2.65, 2.56 (2*m*, CH_2(2')); 3.66 (*m*, CH_2(5')); 4.18 (*s*, MeO); 4.31 (*m*, H–C(4')); 6.59 (*d*, *J* = 5.6, H–C(1')); 8.75 (*s*, H–C(5)). Anal. calc. for $C_{16}H_{27}N_5O_3Si$ (365.51): C 52.58, H 7.45, N 19.16; found: C 52.52, H 7.51, N 19.10.

*1-{2,3-Dideoxy-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-β-*D-glycero-*pentofuranosyl}-7-methoxy-1*H*-1,2,3-triazolo[4,5-*d*]pyrimidine* (**9a**). *Fr. 4* yielded a colourless gum (240 mg, 11.0%). TLC (*A*): R_f 0.5. UV (MeOH): 270

(5500), 233 (4100). ^{1}H-NMR ((D_6)DMSO): 0.24, –0.20 (2*s*, Me_2Si); 0.67 (*s*, *t*-Bu); 2.15 (*m*, H–C(3')); 2.87, 2.60 (2*m*, $CH_2(2')$); 3.40, 3.59 (2*m*, $CH_2(5')$); 4.19 (*s*, MeO); 4.28 (*m*, H–C(4')); 6.68 (*d*, *J* = 6.9, H–C(1')); 8.80 (*s*, H–C(5)). Anal. calc. for $C_{16}H_{27}N_5O_3Si$ (365.51): C 52.58, H 7.45, N 19.16; found: C 52.62, H 7.46, N 19.02.

*3-{2,3-Dideoxy-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-β-*D-glycero*-pentofuranosyl}-7-methoxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine* (**10a**). Evaporation of the fast-migrating *Fr. 1* gave **10a** (225 mg, 10.3%). Colourless syrup. TLC (*C*): R_f 0.6. UV (MeOH): 250 (9800). ^{1}H-NMR ((D_6)DMSO): 0.03, 0.05 (2*s*, Me_2Si); 0.86 (*s*, *t*-Bu); 1.97 (*m*, H–C(3')); 2.6 (*m*, $CH_2(2')$); 3.66 (*m*, $CH_2(5')$); 4.21 (*s*, MeO); 4.40 (*m*, H–C(4')); 6.72 (*dd*, *J* = 6.8, 3.3, H–C(1')); 8.76 (*s*, H–C(5)).

*2-{2,3-Dideoxy-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-α-*D-glycero*-pentofuranosyl}-7-methoxy-2*H*-1,2,3-triazolo[4,5-*d*]pyrimidine* (**11a**). From the slower-migrating part of *Fr. 2*, **11a** (180 mg, 8.3%) was obtained. Colourless oil. TLC (*C*): R_f 0.5. UV (MeOH): 260 (9600). ^{1}H-NMR ((D_6)DMSO): –0.06, 0.07 (2*s*, Me_2Si); 0.86 (*s*, *t*-Bu); 1.96 (*m*, H–C(3')); 2.5 (*m*, $CH_2(2')$); 3.68 (*m*, $CH_2(5')$); 4.18 (*s*, MeO); 4.50 (*m*, H–C(4')); 6.67 (*dd*, *J* = 5.9, 2.7, H–C(1')); 8.76 (*s*, H–C(5)).

*1-{2,3-Dideoxy-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-α-*D-glycero*-pentofuranosyl}-7-methoxy-1*H*-1,2,3-triazolo[4,5-*d*]pyrimidine* (**12a**). Evaporation of *Fr. 5* gave **12** (170 mg, 7.8%). Colourless oil. TLC (*A*): R_f 0.35. UV (MeOH): 270 (5500), 234 (4100). ^{1}H-NMR ((D_6)DMSO): 0.05, 0.06 (2*s*, Me_2Si); 0.87 (*s*, *t*-Bu); 1.98 (2*m*, $CH_2(3')$); 2.75, 2.6 (2*m*, $CH_2(2')$); 3.66 (*m*, $CH_2(5')$); 4.20 (*s*, MeO); 4.33 (*m*, H–C(4')); 6.77 (*dd*, *J* = 6.9, 2.9, H–C(1')); 8.80 (*s*, H–C(5)).

*3-(2,3-Dideoxy-β-*D-glycero*-pentofuranosyl)-7-methoxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine* (**7b**). To a soln. of **7a** (510 mg, 1.4 mmol) in THF (20 ml) was added 1.1M Bu_4NF in THF (2 ml). The mixture was stirred for 1 h at r.t. FC (column 20 × 3 cm, *D*) afforded **7b** (295 mg, 84%). Colourless solid. TLC (*E*): R_f 0.70. UV (MeOH): 251 (10300). ^{1}H-NMR ((D_6)DMSO): 2.24 (*m*, H–C(3')); 2.63, 2.74 (2*m*, $CH_2(2')$); 3.42 (*m*, $CH_2(5')$); 4.22 (*m*, H–C(4'), MeO); 4.70 (*t*, *J* = 5.7, OH–C(5')); 6.66 (*dd*, *J* = 7.2, 2.2, H–C(1')); 8.80 (*s*, H–C(5)). Anal. calc. for $C_{10}H_{13}N_5O_3$ (251.24): C 47.81, H 5.22, N 27.88; found: C 48.11, H 5.18, N 27.74.

*2-(2,3-Dideoxy-β-*D-glycero*-pentofuranosyl)-7-methoxy-2*H*-1,2,3-triazolo[4,5-*d*]pyrimidine* (**8b**). As described for **7b**, **8a** (580 mg, 1.59 mmol) was treated with Bu_4NF/THF. After chromatography (column 20 × 3 cm, *E*), **8b** (330 mg, 83%) was obtained. Colourless solid. TLC (*E*): R_f 0.65. UV (MeOH): 260 (10200). ^{1}H-NMR ((D_6)DMSO): 2.17 (*m*, H–C(3')); 2.57 (*m*, $CH_2(2')$); 3.50 (*m*, $CH_2(5')$); 4.16 (*s*, MeO); 4.28 (*m*, H–C(4')); 4.76 (*t*, *J* = 5.6, OH–C(5')); 6.60 (*dd*, *J* = 4.8, 3.2, H–C(1')); 8.75 (*s*, H–C(5)). Anal. calc. for $C_{10}H_{13}N_5O_3$ (251.24): C 47.81, H 5.22, N 27.88; found: C 47.90, H 5.22, N 27.76.

*1-(2,3-Dideoxy-β-*D-glycero*-pentofuranosyl)-7-methoxy-1*H*-1,2,3-triazolo[4,5-*d*]pyrimidine* (**9b**). Deprotection of **9a** (285 mg, 0.78 mmol) was carried out as described for **7b**. FC (column 20 × 3 cm, *E*) afforded **9b** (140 mg, 72%). Colourless solid. TLC (*E*): R_f 0.6. UV (MeOH): 271 (6000). ^{1}H-NMR ((D_6)DMSO): 1.97 (*m*, H–C(3')); 2.71, 2.6 (2*m*, $CH_2(2')$); 3.47 (*m*, $CH_2(5')$); 4.21 (*s*, MeO); 4.29 (*m*, H–C(4')); 4.81 (*t*, *J* = 5.7, OH–C(5')); 6.79 (*dd*, *J* = 7.4, 3.3, H–C(1')); 8.75 (*s*, H–C(5)). Anal. calc. for $C_{10}H_{13}N_5O_3$ (251.24): C 47.81, H 5.22, N 27.88; found: C 47.97, H 5.20, N 27.70.

*3-(2,3-Dideoxy-α-*D-glycero*-pentofuranosyl)-7-methoxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine* (**10b**). As described for **7b**, **10a** (420 mg, 1.15 mmol) was treated with TBAF/THF (2 h). Evaporation and FC (column 20 × 3 cm, *E*) gave **10b** (220 mg, 76%). Colourless solid. TLC (*E*): R_f 0.55. UV (MeOH): 251 (10300). ^{1}H-NMR ((D_6)DMSO): 1.97 (*m*, H–C(3')); 2.63 (*m*, $CH_2(2')$); 3.47 (*m*, $CH_2(5')$); 4.21 (*s*, MeO); 4.36 (*m*, H–C(4')); 4.81 (*t*, *J* = 5.7, OH–C(5')); 6.74 (*dd*, *J* = 7.0, 3.4, H–C(1')); 8.79 (*s*, H–C(5)). Anal. calc. for $C_{10}H_{13}N_5O_3$ (251.24): C 47.81, H 5.22, N 27.88; found: C 48.02, H 5.33, N 27.71.

*2-(2,3-Dideoxy-α-*D-glycero*-pentofuranosyl)-7-methoxy-2*H*-1,2,3-triazolo[4,5-*d*]pyrimidine* (**11b**). As described for **7b**, **11b** was prepared from **11a** (280 mg, 0.77 mmol; 75 min). FC (column 20 × 3 cm, *D*) yielded **11b** (140 mg, 73%). Colourless solid. TLC (*E*): R_f 0.60. UV (MeOH): 260 (10100). ^{1}H-NMR ((D_6)DMSO): 1.94, 2.34 (2*m*, $CH_2(3')$); 2.56 (*m*, $CH_2(2')$); 3.48 (*m*, $CH_2(5')$); 4.18 (*s*, MeO); 4.46 (*m*, H–C(4')); 4.85 (*t*, *J* = 5.8, OH–C(5')); 6.67 (*dd*, *J* = 6.2, 2.5, H–C(1')); 8.76 (*s*, H–C(5)). Anal. calc. for $C_{10}H_{13}N_5O_3$ (251.24): C 47.81, H 5.22, N 27.88; found: C 47.93, H 5.21, N 27.68.

*1-(2,3-Dideoxy-α-*D-glycero*-pentofuranosyl)-7-methoxy-1*H*-1,2,3-triazolo[4,5-*d*]pyrimidine* (**12b**). Deprotection of **12a** (350 mg, 0.96 mmol) was carried out as described for **7b** (30 min). FC (column 20 × 3 cm, *E*) yielded **12b** (185 mg, 77%). Colourless solid. TLC (*E*): R_f 0.55. UV (MeOH): 271 (5800). ^{1}H-NMR ((D_6)DMSO): 2.19 (*m*, $CH_2(3')$); 2.6, 2.79 (2*m*, $CH_2(2')$); 3.33 (*m*, $CH_2(5')$); 4.20 (*s*, MeO); 4.23 (*m*, H–C(4')); 4.64 (*t*, *J* = 5.6, OH–C(5')); 6.69 (*d*, *J* = 5.7, H–C(1')); 8.75 (*s*, H–C(5)). Anal. calc. for $C_{10}H_{13}N_5O_3$ (251.24): C 47.81, H 5.22, N 27.88; found: C 47.75, H 5.33, N 27.73.

*7-Amino-3-(2,3-dideoxy-β-*D-glycero-*pentofuranosyl)-3*H-*1,2,3-triazolo[4,5-*d*]pyrimidine* (**1**). *From* **7b**: For 12 h **7b** (250 mg, 1 mmol) was stirred in MeOH (saturated with NH_3 at 0°; 20 ml). The mixture was evaporated, the residue dissolved in CH_2Cl_2/MeOH 9:1, and the soln. filtered over a 5-cm layer of silica gel. The filtrate was evaporated, and crystallization of the residue from MeOH afforded **1** (210 mg, 89%). Colourless needles. M.p. 182°. TLC (*E*): R_f 0.55. UV (MeOH): 278 (11000). ^{1}H-NMR ((D_6)DMSO): 2.24 (*m*, H–C(3′)); 2.6, 2.70 (2*m*, CH_2(2′)); 3.46 (*m*, CH_2(5′)); 4.21 (*m*, H–C(4′)); 4.81 (*t*, *J* = 5.7, OH–C(5′)); 6.55 (*dd*, *J* = 7.1, 2.7, H–C(1′)); 8.14, 8.47 (2*s*, NH_2); 8.33 (*s*, H–C(5)). Anal. calc. for $C_9H_{12}N_6O_2$ (236.23): C 45.76, H 5.12, N 35.58; found: C 45.89, H 5.30, N 35.64.

From **14**: A soln. of **14** (250 mg, 0.7 mmol) in THF (10 ml) was treated with 1.1M Bu_4NF in THF (2 ml) and stirred for 30 min at r.t. FC (column 10 × 3 cm, *E*) afforded **1** (140 mg, 83%).

*7-Amino-2-(2,3-dideoxy-β-*D-glycero-*pentofuranosyl)-2*H-*1,2,3-triazolo[4,5-*d*]pyrimidine* (**2**). *From* **8b**: As described for **1**, **8b** (340 mg, 1.35 mmol) was treated with NH_3/MeOH (8 h). FC (column 10 × 3 cm, *E*) and crystallization from AcOEt yielded **2** (265 mg, 83%). Colourless crystals. M.p. 122° (dec.). TLC (*F*): R_f 0.6. UV (MeOH): 295 (8700), 264 (sh, 2400), 255 (sh, 1800). ^{1}H-NMR ((D_6)DMSO): 2.17 (*m*, CH_2(3′)); 2.54 (*m*, CH_2(2′)); 3.48 ('*t*', *J* = 5.6, CH_2(5′)); 4.24 (*m*, H–C(4′)); 4.75 (*t*, *J* = 5.6, OH–C(5′)); 6.47 (*d*, *J* = 4.4, H–C(1′)); 8.10 (*s*, NH_2); 8.30 (*s*, H–C(5)). Anal. calc. for $C_9H_{12}N_6O_2$ (236.23): C 45.76, H 5.12, N 35.58; found: C 45.86, H 5.13, N 35.60.

From **15**/**17**: As described for **1**, 350 mg (1 mmol) of **15**/**17** were dissolved in THF and treated with Bu_4NF (1 h). FC afforded **2** (110 mg, 46.6%) from the faster migrating zone.

*7-Amino-1-(2,3-dideoxy-β-*D-glycero-*pentofuranosyl)-1*H-*1,2,3-triazolo[4,5-*d*]pyrimidine* (**3**). As described for **1**, **9b** (200 mg, 0.8 mmol) was treated with NH_3/MeOH (36 h). FC (column 110 × 3 cm, *E*) and crystallization from acetone yielded **3** (125 mg, 66.5%). Colourless needles. M.p. 148° (dec.). TLC (*F*): R_f 0.55. UV (MeOH): 289 (7500). ^{1}H-NMR ((D_6)DMSO): 1.91, 2.13 (2*m*, CH_2(3′)); 2.5, 3.09 (2*m*, CH_2(2′)); 3.51 (*m*, CH_2(5′)); 4.15 (*m*, H–C(4′)); 4.89 (*t*, *J* = 5.7, OH–C(5′)); 6.74 (*dd*, *J* = 6.3, 1.7, H–C(1′)); 7.76 (*s*, NH_2); 8.33 (*s*, H–C(5)). Anal. calc. for $C_9H_{12}N_6O_2$ (236.23): C 45.76, H 5.12, N 35.58; found: C 45.83, H 5.24, N 35.64.

7-Amino-3-(2,3-dideoxy-α- D-glycero-*pentofuranosyl)-3*H-*1,2,3-triazolo[4,5-*d*]pyrimidine* (**18**). *From* **10b**: As described for **1**, **10b** (240 mg, 0.96 mmol) was treated with NH_3/MeOH (24 h). FC (column 10 × 3 cm, *E*) and crystallization from MeOH gave **18** (190 mg, 84%). Colourless needles. Dec. > 170°. TLC (*E*): R_f 0.40. UV (MeOH): 278 (10900). ^{1}H-NMR ((D_6)DMSO): 1.91, 2.36 (2*m*, CH_2(3′)); 2.7–2.5 (*m*, CH_2(2′)); 3.46 (*m*, CH_2(5′)); 4.33 (*m*, H–C(4′)); 4.80 (*t*, *J* = 5.7, OH–C(5′)); 6.61 (*dd*, *J* = 7.0, 3.5, H–C(1′)); 8.12, 8.45 (2*s*, NH_2); 8.32 (*s*, H–C(5)). Anal. calc. for $C_9H_{12}N_6O_2$ (236.23): C 45.76, H 5.12, N 35.58; found: C 46.10, H 5.34, N 35.34.

From **16**: Deprotection of **16** (320 mg, 0.91 mmol) was carried out as described for **1**. Crystallization from MeOH yielded **18** (180 mg, 84%).

7-Amino-2-(2,3-dideoxy-α- D-glycero-*pentofuranosyl)-2*H-*1,2,3-triazolo[4,5-*d*]pyrimidine* (**19**). *From* **11b**: As described for **1**, **11b** (200 mg, 0.8 mmol) was treated with NH_3/MeOH (7 h). FC (column 10 × 3 cm, *E*) and crystallization from AcOEt yielded **19** (150 mg, 80%). Colourless crystals. M.p. 145° (dec.). TLC (*F*): R_f 0.50. UV (MeOH): 295 (8800), 264 (sh, 2400), 255 (sh, 1800). ^{1}H-NMR ((D_6)DMSO): 1.94, 2.35 (2*m*, CH_2(3′)); 2.55 (*m*, CH_2(2′)); 3.49 (*m*, CH_2(5′)); 4.43 (*m*, H–C(4′)); 4.85 (*t*, *J* = 5.3, OH–C(5′)); 6.56 (*dd*, *J* = 7.1, 2.7, H–C(1′)); 8.10 (*s*, NH_2); 8.32 (*s*, H–C(5)). Anal. calc. for $C_9H_{12}N_6O_2$ (236.23): C 45.76, H 5.12, N 35.58; found: C 46.00, H 5.22, N 35.62.

From **15**/**17**: From the slower migrating zone (see **2**), 95 mg (40.3%) of **19** were obtained.

7-Amino-1-(2,3-dideoxy-α- D-glycero-*pentofuranosyl)-1*H-*1,2,3-triazolo[4,5-*d*]pyrimidine* (**20**). As described **1**, **12b** (200 mg, 0.8 mmol) was treated with NH_3/MeOH (36 h). FC (column 10 × 3 cm, *E*) and crystallization from AcOEt gave (135 mg, 72%). Colourless crystals. Dec. > 150°. TLC (*F*): R_f 0.55. UV (MeOH): 289 (7600). ^{1}H-NMR ((D_6)DMSO): 1.93, 2.16 (2*m*, CH_2(3′)); 2.49 (*m*, CH_2(2′)); 3.36 (*m*, CH_2(5′)); 4.34 (*m*, H–C(4′)); 4.76 (*t*, *J* = 5.2, OH–C(5′)); 6.62 (*d*, *J* = 4.5, H–C(1′)); 7.74 (*s*, NH_2); 8.32 (*s*, H–C(5)). Anal. calc. for $C_9H_{12}N_6O_2$ (236.23): C 45.76, H 5.12, N 35.58; found: C 46.06, H 5.21, N 35.80.

*Glycosylation of 7-Amino-3*H-*1,2,3-triazolo[4,5-*d*]pyrimidine* (**13**) [4] *with* **6**. Powdered K_2CO_3 (1.0 g, 7.24 mmol) and TDA-1 (100 µl, 0.31 mmol) were stirred in DMF (100 ml) for 5 min. Then, **13** [4] (1.1 g, 8 mmol) was added and dissolved under warming (60°). The soln. was brought to r.t. and a freshly prepared, cold (−80°) THF soln. (40 ml) of **6** (16 mmol; calculated on the basis of 100% yield of **6**) was added in portions of 5 ml within 30 min. Stirring was continued for another 30 min, insoluble material filtered off, and the filtrate poured into 20% aq. $NaHCO_3$ soln. (150 ml). The aq. layer was twice extracted with CH_2Cl_2 and the combined org. layer dried ($NaSO_4$). After evaporation (40°), the residue was dissolved in *G* and applied to the top of a silica-gel column (40 × 3 cm). FC (*G*) gave 3 fractions.

7-Amino-3-{2,3-dideoxy-5-O-[(1,1-dimethylethyl)dimethylsilyl]-β-D-glycero-pentofuranosyl}-3H-1,2,3-triazolo[4,5-d]pyrimidine (**14**). From *Fr. 2*, **14** (260 mg, 9.3%) was obtained. Colourless solid. TLC (*E*): R_f 0.6. UV (MeOH): 278 (11200), 255 (sh, 6100). ^{1}H-NMR ((D_6)DMSO): –0.17, –0.13, (2*s*, Me_2Si); 0.74 (*s*, *t*-Bu); 2.15–2.36 (*m*, $CH_2(3')$); 2.72, 2.6 (2*m*, $CH_2(2')$); 3.60 (*m*, $CH_2(5')$); 4.22 (*m*, H–C(4')); 6.52 (*dd*, *J* = 7.2, 2.2, H–C(1')); 8.10, 8.44 (2*s*, NH_2); 8.30 (*s*, H–C(5)). Anal. calc. for $C_{15}H_{26}N_6O_2Si$ (350.50): C 51.40, H 7.48, N 23.98; found: C 51.41, H 7.44, N 23.82.

7-Amino-3-{2,3-dideoxy-5-O-[(1,1-dimethylethyl)dimethylsilyl]-α-D-glycero-pentofuranosyl}-3H-1,2,3-triazolo[4,5-d]pyrimidine (**16**). Evaporation of *Fr. 1* yielded **16** (240 mg, 8.5%). Colourless solid. TLC (*E*): R_f 0.6. UV (MeOH): 278 (11100), 255 (sh, 6000). ^{1}H-NMR ((D_6)DMSO): 0.03, 0.48 (2*s*, Me_2Si); 0.86 (*s*, *t*-Bu); 1.93 (*m*, H–C(3')); 2.6 (*m*, $CH_2(2')$); 3.65 (*m*, $CH_2(5')$); 4.37 (*m*, H–C(4')); 6.59 (*dd*, *J* = 6.7, 3.1, H–C(1')); 8.13, 8.46 (2*s*, NH_2); 8.31 (*s*, H–C(5)). Anal. calc. for $C_{15}H_{26}N_6O_2Si$ (350.50): C 51.40, H 7.48, N 23.98; found: C 51.74, H 7.62, N 23.69.

7-Amino-2-{2,3-dideoxy-5-O-[(1,1-dimethylethyl)dimethylsilyl]-β-D-glycero-pentofuranosyl}-2H-1,2,3-triazolo[4,5-d]pyrimidine (**15**) *and 7-Amino-2-{2,3-dideoxy-5-O-[(1,1-dimethylethyl)dimethylsilyl]-α-D-glycero-pentofuranosyl}-2H-1,2,3-triazolo[4,5-d]pyrimidine* (**17**). From *Fr. 3*, **15**/**17** were obtained (390 mg, 13.9%), which could not be separated. For the desilylation and separation of the deprotected compounds, see **2** and **19**.

7-Amino-3-(2,3-dideoxy-β-D-glycero-pentofuranosyl)-3H-1,2,3-triazolo[4,5-d]pyrimidine 5'-[Tetrakis(triethylammonium) Triphosphate] (**21**·4 Et_3N). Compound **1** (47 mg, 0.2 mmol) and *N,N,N',N'*-Tetramethylnaphthalene-1,8-diamine (65 mg, 0.3 mmol) were dissolved in trimethyl phosphate (2 ml) under warming. The soln. was cooled to 0°, freshly distilled $POCl_3$ (50 µl, 0.54 mmol) added, and the mixture allowed to stand at 4° for 2 h and then treated with a soln. of tributylammonium diphosphate (0.5N in DMF, 2 ml) and Bu_3N (200 µl, 0.84 mmol). After stirring for 3 min at 0°, 20 ml of 1M aq. $(Et_3NH)HCO_3$ (TBK) was added. Evaporation resulted in a semi-solid, which was applied to the top of a *DEAE-Sephadex* column (30 × 1.5 cm, HCO_3^- form). The elution was performed by a linear gradient of 0.8M TBK buffer (1 l) and H_2O (1 l). The main zone was eluted at 0.52M TBK and yielded **21** (0.11 mmol, 55%). Colourless solid. TLC (*H*): R_f 0.15. UV (H_2O): 280 (11000). ^{31}P-NMR (0.1M *Tris*-HCl, pH 7.5, 100 nM EDTA/D_2O): –8.32 (*d*, *J* = 19.9, P(γ)); –10.40 (*d*, *J* = 19.4, P(α)); –21.97 (*t*, *J* = 19.4, P(β)).

7-Amino-2-(2,3-dideoxy-β-D-glycero-pentofuranosyl)-2H-1,2,3-triazolo[4,5-d]pyrimidine 5'-[Tetrakis(triethylammonium) Triphosphate] (**22**·4 Et_3N). Compound **2** (23.5 mg, 0.1 mmol) was phosphorylated as described for **21**. After chromatography on *DEAE-Sephadex* (column 30 × 1.5 cm, HCO_3^- form), **22** was eluted at 0.45M TBK. Evaporation yielded a colourless solid (0.058 mmol, 58%). TLC (*H*): R_f 0.2. UV (H_2O): 294 (8500). ^{31}P-NMR (0.1M *Tris*-HCl, pH 7.5, 100 nM EDTA/D_2O): –9.98 (*d*, *J* = 19.2, P(γ)); –10.49 (*d*, *J* = 20.1, P(α)); –22.34 (*t*, *J* = 19.4, P(β)).

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