172. Synthesis of 8-Aza-2′-deoxyadenosine and Related 7-Amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine 2′-Deoxyribofuranosides: Stereoselective Glycosylation *via* the Nucleobase Anion

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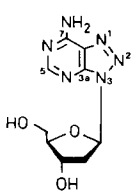
The synthesis of 8-aza-2′-deoxyadenosine (= 7-amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine N^3-(2′-deoxy-β-D-ribofuranoside); **1**) as well as the N^2- and N^1-(2′-deoxy-β-D-ribofuranosides) **2** and **3** is described. Glycosylation of the anion of 7-amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**6**) in DMF yielded three regioisomeric protected 2′-deoxy-β-D-ribofuranosides, *i.e.* the N^3-, N^2-, and N^4-glycosylated isomers **7** (14%), **9** (11%), and **11** (3%), respectively, together with nearly equal amounts of their α-D-anomers **8** (13%), **10** (12%), and **12** (4%; *Scheme 1*). The reaction became stereoselective for the β-D-nucleosides if the anion of 7-methoxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**13**) was glycosylated in MeCN: only the N^3-, N^2-, and N^1- (2′-deoxy-β-D-nucleosides) **14** (29%), **15** (32%), and **16** (23%), respectively, were formed *(Scheme 2)*. NH_3 Treatment of the methoxynucleosides **14**–**16** afforded the aminonucleosides **1**–**3**. The anomeric configuration as well as the position of glycosylation were determined by combination of ^{13}C-NMR, ^{1}H-NMR, and 1D-NOE difference spectroscopy. Compound **1** proved to be a substrate for adenosine deaminase, whereas the regioisomers **2** and **3** were not deaminated.

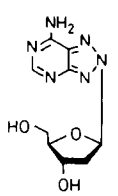
Introduction. – The 3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (= 8-azapurine; for reviews, see [1–6]) nucleosides exhibit extraordinary biochemical and pharmacological activities [7]. In many biological systems, they act as nucleoside antimetabolites. As they are isosteric to purine nucleosides, their incorporation into DNA or RNA fragments is of interest.

During the last decade, a number of 8-azaadenine D-ribofuranosyl [8–11], D-arabinofuranosyl [10–12], and other glycosyl derivatives [13][14] have been prepared. However, their synthesis was encompassed with difficulties as the additional N-atom at position 8 caused problems of regioselectivity enlarging the number of glycosylation products. The problem became even more severe as anomeric mixtures were formed within the series of 2′-deoxyribonucleosides not carrying a participating group at C(2′) [15].

In 1983, our laboratory has developed a stereoselective synthesis of 2′-deoxyribonucleosides employing the nucleobase anion [16]. This was achieved in the series of



1 systematic numbering



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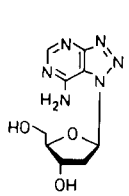

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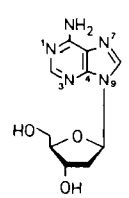


4 purine numbering

pyrrolo[2,3-*d*]pyrimidines [16] [17] and pyrazolo[3,4-*d*]pyrimidines [18] and was later applied to other heterocyclic systems [19–21]. In the following, we use nucleobase-anion glycosylation employing either the solid-liquid phase-transfer technique or the NaH-mediated reaction for the synthesis of 8-azaadenine 2′-deoxyribofuranosides such as **1**–**3** and assign the structure of glycosylation products by combination of ^{1}H-NMR, ^{13}C-NMR, and ^{1}H-NMR NOE-difference spectroscopy (for purine numbering, see 2′-deoxyadenosine (**4**)).

Results and Discussion. – Up to now, only two reports appeared in the literature on the synthesis of 8-aza-2′-deoxyadenosine (**1**). In 1965, *Tong et al.* reported on the glycosylation of 7-(nonanoylamino)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine with the halogenose **5** in the presence of $HgCl_2$ [22]. *Montgomery* and *Thomas* [23] used the same aglycon but a differently protected sugar and carried out glycosylation in the presence of Et_3N/molecular sieve. Apart from other regioisomers, compound **1** together with its α-D-anomer was obtained. Both chemical syntheses were neither regioselective nor diastereoselective, and the yields were extremely low. A selective glycosylation, however, was observed employing nucleoside deoxyribofuranosyltransferase [24].

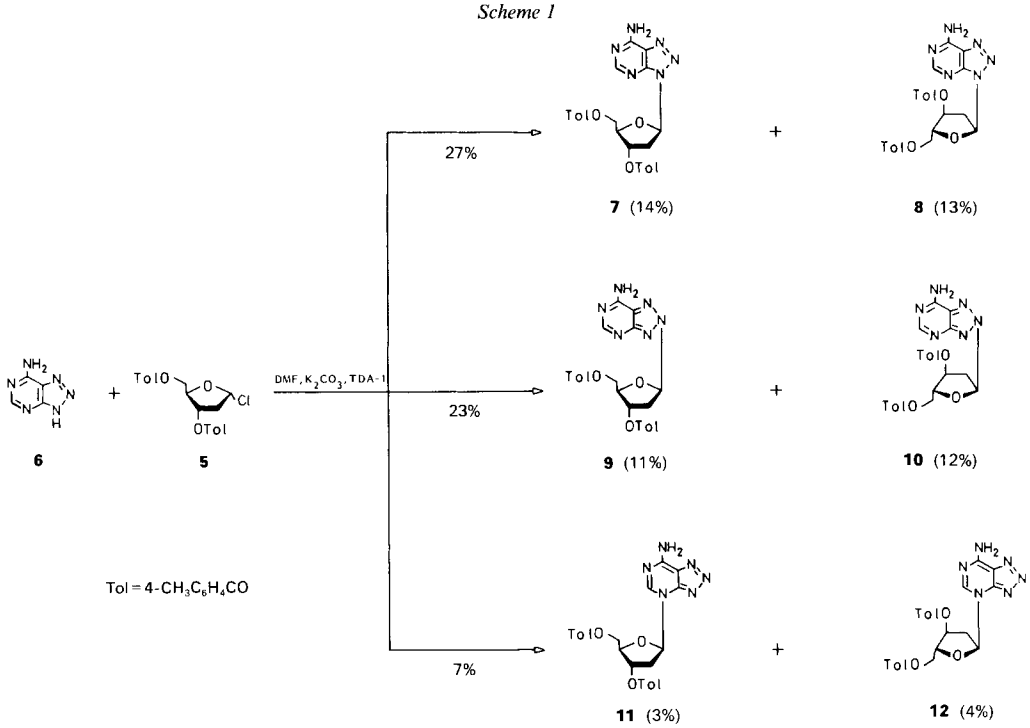
As we have shown [16–18] and has been also demonstrated later by others [19], N anions of many heterocycles react readily at ambient temperature with the anomerically pure halogenose **5** to yield exclusively 2′-deoxy-β-D-ribofuranosides. Therefore, we considered glycosylation of **6** with the halogenose **5** [25] *(Scheme 1)*. Commonly, the reaction is carried out in MeCN with either an excess of powdered KOH or K_2CO_3 and in the presence of the cryptand tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) [26] or in the same solvent with NaH [19]. Unfortunately, 8-azaadenine (**6**) [27] is only badly soluble in MeCN. On the other hand, it forms easily salts with alkali cations being soluble in polar solvents. As a consequence, DMF was used as reaction medium. According to earlier observations, the halogenose anomerizes readily in this solvent [28] [29], thus a stereoselective glycosylation was not expected. Nevertheless, a preferred formation of the N(3) isomer **1** over other regioisomers would improve older synthetic routes.

Glycosylation of 8-azaadenine (**6**) in DMF with a three-fold excess of powdered K_2CO_3 and in the presence of TDA-1 yielded three regioisomeric products. Repeated flash chromatography of the corresponding three zones showed that each regioisomer was an anomeric mixture. All six glycosylation products **7**–**12** were purified by silica-gel column chromatography *(Scheme 1)*.

According to the chemical-shift differences of H–C(4′) and H–C(5′) [30], the glycosylation products **7**–**12** were three pairs of anomers. Thus, the reaction was not stereoselective under those conditions. Only the four glycosylation products **7**–**10** (2 pairs of anomers) could be deprotected in NH_3/MeOH yielding four 2′-deoxynucleosides, whereas the two ones formed in only trace amounts (3 and 4% of **11** and **12**, resp.) decomposed under these conditions. Structural assignment of all glycosylation products will be discussed below. In order to achieve stereoselective glycosylation, another target heterocycle had to be used being soluble in MeCN, thus avoiding anomerization of the halogenose before glycosylation.

As suitable target molecule for further glycosylation studies, 7-methoxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**13**) [31] was selected. Indeed, it has been shown earlier in the series of pyrazolo[3,4-*d*]pyrimidines that methoxynucleosides can be converted success-

Scheme 1



fully into aminonucleosides [32], thus avoiding the use of a Cl-substituted base component which might be too labile as it is the case of 7-chloro-3*H*-1,2,3-triazolo[4,5-*d*] pyrimidine [33].

The synthesis of **13** was performed according to *Ballweg* [31], however, without isolation of 7-chloro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine [33]. Instead of this the reaction mixture was treated *in situ* with excess of NaOMe in MeOH. Upon neutralization, compound **13** was recrystallized from aq. MeOH (yield 56%; m.p. 180°; [31]: 178–180°). This material was then employed in the glycosylation. Two methods have been proved useful for anion formation: *i*) NaH in MeCN and *ii*) powdered KOH/TDA-1 also in MeCN. At first, both were carried out on an analytical scale and afforded the N^3-, N^2-, and N^1-glycosylation products **14**–**16**. Their ratio was determined by TLC scanning at 260 nm and found to be comparable (3:4:3). According to the UV spectra, **14**–**16** are regioisomers. Next, preparative-scale experiments allowed the isolation of **14**–**16** and the recording of their NMR spectra *(Table 1)*. They were then treated with MeOH saturated with NH_3 for 60 h. The products were crystallized and compared with the compounds obtained from the glycosylation products of **6** after treatment with NH_3/MeOH. TLC indicated that two of them (**1** and **2**) were identical, and one (**3**) was different. In order to establish their structures, ^{1}H-NMR and ^{1}H-NMR NOE (see *Exper. Part*), ^{13}C-NMR *(Table 1)*, and ^{1}H,^{13}C-NMR correlation spectra were measured and ^{1}H,^{13}C coupling constants determined *(Table 2)*.

Earlier, we have shown that the anomeric configuration can be established by ^{1}H-NMR NOE difference spectroscopy [34]. For this purpose, the H–C(1′) signal of the

Scheme 2

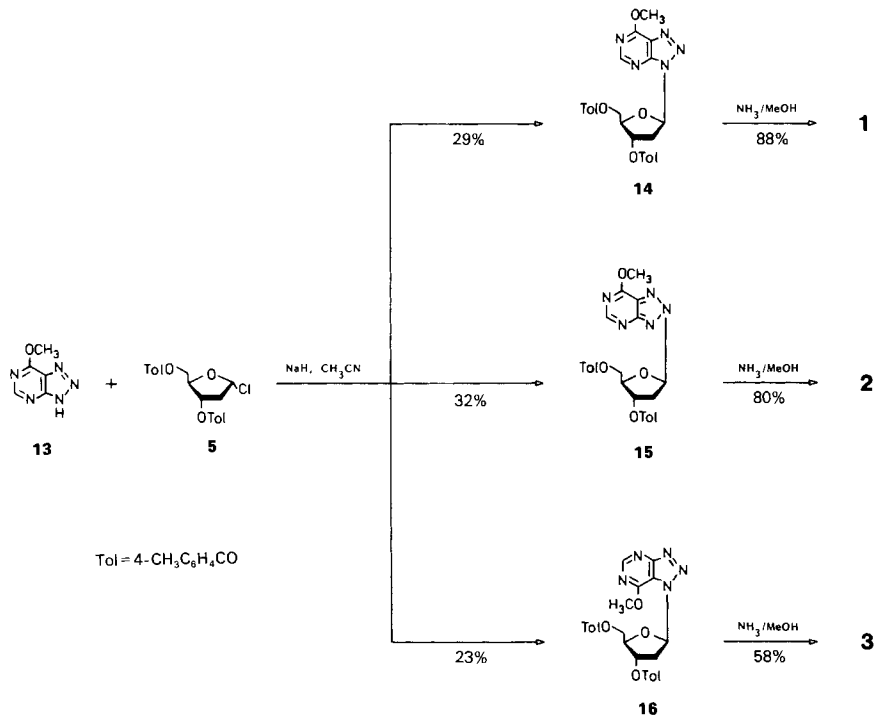


Table 1. *^{13}C-NMR Chemical Shifts of 8-Azaadenine Derivatives*[a][b])

	C(3a)[c] [C(4)][d])	C(5)[c] [C(2)][d])	C(7)[c] [C(6)][d])	C(7a)[c] [C(5)][d])	CH_3	CH_3O
1 (N^3,β)	148.7	157.0	156.3	124.3		
2 (N^2,β)	157.4[f])	157.6	157.1[f])	125.8		
3 (N^1,β)[e])	151.9	154.7	161.5	113.6		
4 (dA)	149.3	152.2	156.3	119.6		
6	150.7[f])	156.4	156.1[f])	123.1		
7 (N^3,β)	149.0	157.2	156.3	124.3	21.3	
8 (N^2,α)	149.0	157.1	156.3	124.2	21.3	
9 (N^2,β)	157.4[f])	157.8	157.1[f])	126.2	21.3	
10 (N^2,α)	157.3[f])	157.8	157.0[f])	125.7	21.3	
11 (N^4,β)	143.8	147.4	156.8	123.5	21.3	
12 (N^4,α)	143.6	147.0	157.0	123.8	21.3	
13	153.5	155.6	160.7	123.4		54.8
14 (N^3,β)	150.4	156.2	161.4	125.5	21.2	55.0
15 (N^2,β)	159.0	156.0	162.2	126.8	21.2	55.0
16 (N^1,β)	154.0	157.2	161.9	114.8	21.3	55.3
17 (N^3,α)	148.5	156.9	156.4	124.4		
18 (N^2,α)	157.6[f])	157.8	157.0[f])	125.7		

Table 1 (cont.)

	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)
1 (N^3,β)	85.5	38.1	70.9	88.5	62.1
2 (N^2,β)	93.8	DMSO	70.7	89.0	62.2
3 (N^1,β)	88.4	39.2	70.0	88.8	61.1
4 (dA)	85.8	40.2	70.8	87.8	61.7
7 (N^3,β)	82.2	35.3	74.6	85.2	63.8
8 (N^3,α)	82.3	36.2	74.3	85.9	64.1
9 (N^2,β)	93.6	36.9	74.1	82.7	63.8
10 (N^2,α)	94.2	DMSO	74.1	84.0	64.0
11 (N^4,β)	90.6	37.8	74.6	84.6	64.0
12 (N^4,α)	90.8	35.6	74.9	82.6	64.1
14 (N^3,β)	82.3	35.3	74.2	85.7	63.5
15 (N^2,β)	94.1	36.9	73.7	82.9	63.4
16 (N^1,β)	88.4	38.3	74.3	82.5	63.6
17 (N^3,α)	85.1	38.2	70.1	86.7	61.1
18 (N^2,α)	93.5	DMSO	70.0	87.5	60.9

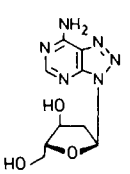
[a]) In (D_6)DMSO. [b]) δ Values in ppm relative to Me_4Si as internal standard. [c]) 1,2,3-Triazolo[4,5-*d*]pyrimidine numbering. [d]) Purine numbering. [e]) According to $^1H,^{13}C$ correlation spectrum. [f]) Tentative.

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

	1	**3**	**17**	**18**	**7**
J(C(3a), *H*–C(5))	14.5	12.3	12.7	12.8	12.9
J(C(3a), *H*–C(1′))	1.6	–	2.0	–	–
J(C(5), *H*–C(5))	200.8	200.4	200.4	199.0	199.7
J(C(7), *H*–C(5))	11.3	11.6	11.4	11.3	11.4
J(C(7a), *H*–C(1′))	*m*	4.7	*m*	*m*	*m*
J(C(4′), *H*–C(4′))	148.9	149.0	146.2	147.0	
J(C(1′), *H*–C(1′))	168.2	171.4	168.9	173.2	
J(C(1′), *H*–C(2′))	4.4		4.9		
J(C(3′), *H*–C(3′))	147.4	145.8	147.3	148.4	
J(C(5′), *H*–C(5′))	141.0	140.1	140.5	139.4	

[a]) Systematic numbering.

deprotected compounds **1**–**3**, **17** (from **8**), and **18** (from **10**) as well as of the protected **11** was irradiated. The resulting NOE effects on H–C(4′) and H_α–C(2′) immediately indicated β-D-configuration for **1**–**3** and **11**, and the NOE effects on H_β–C(2′) and H–C(3′) confirmed α-D-configuration for **17** and **18** (for data, see *Exper. Part*). Simultaneously, the anomeric configuration of the corresponding precursors was established.



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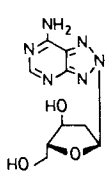

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Apart from the anomeric configuration, the position of glycosylation had to be assigned. Compound **1** and its α-D-anomer **17** have already been described [22] [23]. Their assignment based on UV spectra *(Table 3)* indicating N^3-(2′-deoxyribofuranosides). The ^{13}C-NMR chemical shifts of **1** and **17** *(Table 1)* together with the coupling constants of *Table 2* confirmed these assignments. The ^{13}C-NMR spectra of the other glycosylation products were different from the N^3-substituted compounds and allowed, together with other spectral data, their structure determination.

A downfield shift of C(3a) (9 ppm) of regioisomer **2** as compared to that of **1** immediately indicated that N^3 did not carry a substituent. As C(7a) was unchanged, the position of glycosylation was N^2 which was also underlined by the similarity of the UV spectra with the corresponding ribofuranosides [9] *(Table 3)*. As **1** and **17** as well as **2** and **18** showed almost identical ^{13}C-NMR chemical shifts for the aglycone *(Table 1)* and UV spectra (see *Exper. Part*), they were assigned to be anomers. The product **3**, obtained from the glycosylation product of **13** after treatment with NH_3/MeOH, upon irradiation of H–C(1′), exhibited NOE's on the NH_2 group and also on H_α–C(2′) and H–C(4′) *(Exper. Part)*. This, together with a strong upfield shift of C(7a) in the ^{13}C-NMR as compared to **1**, allowed the assignment of structure **3**.

Table 3. *UV Data and pK_a-Values of 8-Azaadenine β-D-Ribofuranosides and 2′-Deoxy-β-D-ribofuranosides*[a])

	λ_{max} [nm] (ε)		pK_a
	pH 1.0	pH 7.0	
1	263 (10900)	278 (11800)	2.40
8-Azaadenosine [9]	262 (12400)	278 (11600)	
2	285 (11200)	254 (4200)	3.35
		297 (10200)	
8-Azaadenine N^8-β-D-ribofuranoside [9]	286 (11500)	297 (10000)	
		254 (4300)	
3	262 (11700)	287 (8400)	2.5[b])

[a]) In *Teorell-Stenhagen* buffer [35].
[b]) Approximated.

As already mentioned, two of the glycosylation products of **6** could not be deprotected under alkaline conditions without partial decomposition. Having assigned the N^1-, N^2-, and N^3-glycosylated deprotected regioisomers **1**–**3** and an NH_2 group being present in the remaining two (protected) isomers **11** and **12**, their glycosylation site could only be at N^4 or N^6. The ^{13}C-NMR spectra of **11** and **12** were almost identical *(Table 1)* indicating a pair of anomers. NOE experiments on **11** (*Exper. Part;* irradiation of H–C(1′)) showed that either N^4 or N^6 carries a β-D-configurated sugar residue. The chemical shifts of C(3a) and C(5) of **11** and **12** were upfield shifted as compared to the corresponding signals of the N^3-glycosylated (deprotected) isomers **1** or **17**. Therefore, N^4-glycosylation was established confirming the structures of **11** and **12**.

The ^{1}H-NMR spectra ((D$_6$)DMSO) of the N^3-glycosylated anomers **1** and **17**, of the N^2-glycosylated **2**, and of the protected N^4-glycosylated **11** showed two signals for the NH_2 group which differs from the behavior of the parent 2′-deoxyadenosine (dA; **4**). At elevated temperature, coalescence occurred, but the signals were separated again upon cooling, indicating restricted rotation of the NH_2 group. The coalescence temperature was 313 K for **1** and **17**, 305 K for **2**, and 352 K for **11**. Contrary, the N^1-glycosylated **3** showed only one signal for the NH_2 group. It is also interesting that the pK_a of **1** and its N^1-regioisomer **3** is lower than that of **4** (3.6), whereas **2** shows a similar value *(Table 3)*.

It has been already reported that compound **1** is a substrate of adenosine deaminase [24]. We have treated regioisomers **1–3** with this enzyme (0.02M *Sörensen* phosphate buffer, pH 7.0) and followed the reaction by UV. Only the N^3-regioisomer **1** (= 8-aza-2′-deoxyadenosine) was deaminated to form the corresponding hypoxanthine derivative, whereas the N^2- and N^1-regioisomers **2** or **3** were no substrates for the enzyme.

In conclusion, a stereoselective synthesis of 8-aza-2′-deoxyadenosine (**1**) and regioisomeric 2′-deoxynucleosides has been achieved by nucleobase-anion glycosylation of **13** with the halogenose **5** in MeCN. Stereoselectivity was lost, if DMF was used as solvent, necessary to solubilize the corresponding aglycon **6**. The glycosylation position and, therefore, the formation of regioisomers was controlled by the 6-substituent of 8-azapurines. Conversion of **1–3** into building blocks for automated DNA synthesis is in progress.

We thank Dr. *H. Rosemeyer* for the discussion of the NMR spectra and Ms. *M. Beste* for technical assistance. Financial support by the *Stiftung Volkswagenwerk* and the *Bundesminister für Forschung und Technologie* is gratefully acknowledged.

Experimental Part

General. MeCN was distilled from CaH_2. Adenosine deaminase from calf intestine mucosa (EC 3.5.4.4; 5 mg/ml glycerol; 1 mg = 200 units) was purchased from *Boehringer*, Mannheim, FRG. Anal. TLC: glass plates coated with a 0.25-mm layer of silica gel *Sil G-25* with fluorescent indicator UV_{254} (*Merck*, FRG). TLC scanning: *CS-930* TLC scanner (*Shimadzu*, Japan). Column flash chromatography: at 0.8 bar; silica gel *60 H* (*Merck*, FRG); *Uvicord S* detector and *UltroRac II* fractions collector (*LKB Instruments*, Sweden). M.p.: *Büchi-SMP-20* apparatus (*Büchi*, Switzerland); uncorrected. The pK_a value of **1** was determined spectrophotometrically in *Teorell-Stenhagen* buffer [35]. UV spectra: *150–20* spectrometer (*Hitachi*, Japan). NMR spectra: *AC-250-Bruker* spectrometer; operational frequencies 250.134 (^{1}H) and 62.898 (^{13}C) MHz; δ values rel. to Me_4Si as internal standard; NOE's (23°): irradiated proton→observed NOE in %. Microanalyses were performed by *Mikroanalytisches Laboratorium Beller*, Göttingen, FRG.

*Glycosylation of 7-Amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine* (**6**) *with 2-Deoxy-3,5-di-*O*-(*p*-toluoyl)-*α*-*D*-erythro-pentofuranosyl Chloride* (**5**) *under Solid-Liquid Phase-Transfer Conditions.* Powdered K_2CO_3 (1.0 g, 7.24 mmol) and TDA-1 (100 µl, 0.31 mmol) were stirred in DMF (75 ml) for 5 min at r.t. Then, **6** [27] (500 mg, 3.67 mmol) was added and dissolved by heating (60°). The soln. was brought to r.t. and **5** [25] (1.43 g, 3.68 mmol) was added portionwise under stirring within 30 min. Stirring was continued at r.t. for 60 min and the insoluble residue filtered off and washed with DMF. DMF was removed by coevaporation with H_2O. The resultant was dissolved in $CHCl_3$/MeOH 9:1 and applied on the top of a silica gel column (silica gel *60*, 20 × 4 cm). Three zones (*I*, *II*, *III*) were separated by elution with $CHCl_3$/MeOH 95:5, each containing an anomeric mixture.

*7-Amino-3-[2′-deoxy-3′,5′-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine* (**7**). The fast migrating zone *I* was separated by flash chromatography (silica gel *60 H*, column 50 × 5 cm, AcOEt) into two zones. From the faster migrating zone, **7** (260 mg, 14%) was obtained from MeOH as colourless crystals. M.p. 163°. TLC (silica gel, AcOEt): R_f 0.62. UV (MeOH): 241 (30800), 277 (12000). ^{1}H-NMR ((D$_6$)DMSO): 2.37, 2.40 (2*s*, 2 arom. CH_3); 2.92 (*m*, H_β–C(2′)); 3.55 (*m*, H_α–C(2′)); 4.54 (*m*, H–C(4′), 2 H–C(5′)); 5.95 (*m*, H–C(3′)); 6.83 (*t*, *J* = 6.3, H–C(1′)); 7.32, 7.88 (*m*, arom. H); 8.22 (*s*, NH); 8.31 (*s*, H–C(5)); 8.57 (*s*, NH). Anal. calc. for $C_{25}H_{24}N_6O_5$: C 61.46, H 4.95, N 17.21; found: C 61.65, H 5.02, N 17.26.

*7-Amino-3-[2′-deoxy-3′,5′-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine* (**8**). The slower migrating zone of zone *I* yielded a colourless foam upon evaporation from which colourless crystals (240 mg, 13%) were obtained from MeOH. M.p. 187°. TLC (silica gel, AcOEt): R_f 0.58. UV (MeOH): 241 (29700), 276 (11000). ^{1}H-NMR ((D$_6$)DMSO): 2.37, 2.38 (2*s*, 2 arom. CH_3); 3.21 (*m*, H_β–C(2′), H_α–C(2′)); 4.55 (*m*, 2 H–C(5′)); 4.84 (*m*, H–C(4′)); 5.64 (*m*, H–C(3′)); 6.83 (*m*, H–C(1′)); 7.31, 7.86 (2*m*, arom. H); 8.17 (*s*, NH); 8.28 (*s*, H–C(5)); 8.54 (*s*, NH). Anal. calc. for $C_{25}H_{24}N_6O_5$: C 61.46, H 4.95, N 17.21; found: C 61.41, H 4.94, N 17.22.

7-Amino-2-[2'-deoxy-3',5'-di-O-(p-toluoyl)-α-D-erythro-pentofuranosyl]-2H-1,2,3-triazolo[4,5-d]pyrimidine (**10**). Zone *II* was separated on silica gel *60 H* (column 50 × 5 cm, $CHCl_3$/MeOH 98:2) yielding the faster migrating **10** as a foam which yielded colourless crystals (220 mg, 12%) from MeOH. M.p. 166°. TLC (silica gel, $CHCl_3$/MeOH 95:5): R_f 0.60. UV (MeOH): 241 (33000), 295 (10200). ^{1}H-NMR ((D_6)DMSO): 2.33, 2.39 (2*s*, 2 arom. CH_3); 3.04 (*m*, H_β–C(2')); 3.19 (*m*, H_α–C(2')); 4.57 (*m*, 2 H–C(5')); 4.93 (*m*, H–C(4')); 5.63 (*m*, H–C(3')); 6.86 (*dd*, *J* = 2.5, 7.2, H–C(1')); 7.25, 7.77 (2*m*, arom. H); 8.12 (*s*, NH); 8.32 (*m*, H–C(5), NH). Anal. calc. for $C_{25}H_{24}N_6O_5$: C 61.46, H 4.95, N 17.21; found: C 61.26, H 4.96, N 17.04.

7-Amino-2-[2'-deoxy-3',5'-di-O-(p-toluoyl)-β-D-erythro-pentofuranosyl]-2H-1,2,3-triazolo[4,5-d]pyrimidine (**9**). The slower migrating zone of *II* yielded a colourless foam upon evaporation. Crystallization from MeOH gave colourless crystals (190 mg, 11%). M.p. 187°. TLC (silica gel, $CHCl_3$/MeOH 95:5): R_f 0.50. UV (MeOH): 241 (34200), 298 (9900). ^{1}H-NMR ((D_6)DMSO): 2.35, 2.40 (2*s*, 2 arom. CH_3); 2.96 (*m*, H_β–C(2')); 3.40 (*m*, H_α–C(2')); 4.45, 4.57 (2*m*, 2 H–C(5')); 4.70 (*m*, H–C(4')); 5.96 (*m*, H–C(3')); 6.77 (*dd*, *J* = 3.7, 6.9, H–C(1')); 7.30, 7.86 (2*m*, arom. H); 8.20 (*s*, NH); 8.32 (*s*, H–C(5)); 8.34 (*s*, NH). Anal. calc. for $C_{25}H_{24}N_6O_5$: C 61.46, H 4.95, N 17.21; found: C 61.61, H 5.09, N 17.10.

7-Amino-4-[2'-deoxy-3',5'-di-O-(p-toluoyl)-α-D-erythro-pentofuranosyl]-4H-1,2,3-triazolo[4,5-d]pyrimidine (**12**). Zone *III*, separated by flash chromatography (column 50 × 5 cm, silica gel *60 H*, $CHCl_3$/MeOH 95:5) yielded a colourless foam after evaporation of the faster migrating zone (80 mg, 4%). TLC (silica gel, $CHCl_3$/MeOH 9:1): R_f 0.59. UV (MeOH): 241 (36700), 282 (15200). ^{1}H-NMR ((D_6)DMSO): 2.35, 2.41 (2*s*, 2 arom. CH_3); 3.06 (*m*, H_β–C(2'), H_α–C(2')); 4.56 (*m*, 2 H–C(5')); 5.31 (*m*, H–C(4')); 5.64 (*m*, H–C(3')); 6.68 (*m*, H–C(1')); 7.30 7.71, (2*m*, arom. H); 8.70 (*s*, H–C(5)); 9.02 (*s*, NH); 9.31 (*s*, NH). Anal. calc. for $C_{25}H_{24}N_6O_5$: C 61.46, H 4.95, N 17.21; found: C 61.52, H 4.95, N 17.33.

7-Amino-4-[2'-deoxy-3',5'-di-O-(p-toluoyl)-β-D-erythro-pentofuranosyl]-4H-1,2,3-triazolo[4,5-d]pyrimidine (**11**). The slower migrating zone of *III* was evaporated to give a colourless foam (50 mg, 3%). TLC (silica gel, $CHCl_3$/MeOH 9:1): R_f 0.56. UV (MeOH): 239 (37800), 282 (14600). ^{1}H-NMR ((D_6)DMSO): 2.36, 2.41 (2*s*, 2 arom. CH_3); 2.84 (*m*, H_β–C(2')); 3.36 (*m*, H_α–C(2')); 4.71 (*m*, H–C(4'), 2 H–C(5')); 5.95 (*m*, H–C(3')); 6.59 (*t*, *J* = 6.0, H–C(1')); 7.33, 7.90 (2*m*, arom. H); 8.66 (*s*, H–C(5)); 9.11 (*s*, NH); 9.47 (*s*, NH); NOE: H–C(1')→H_α–C(2') (5.5), H–C(5) (3.8).

7-Amino-3-(2'-deoxy-α-D-erythro-pentofuranosyl)-3H-1,2,3-triazolo[4,5-d]pyrimidine (**17**). Compound **8** (130 mg, 0.27 mmol) in MeOH (50 ml, saturated with NH_3 at 0°) was stirred for 12 h at r.t. The soln. was evaporated, the residue adsorbed on silica gel *60* (3.0 g) and applied onto the top of a silica-gel column (15 × 2 cm). Chromatography with $CHCl_3$/MeOH 4:1 yielded a colourless foam (60 mg, 89%) which crystallized from H_2O. M.p. 191° ([23]: 193.5°). TLC (silica gel, $CHCl_3$/MeOH 4:1): R_f 0.60. UV (H_2O): 278 (11600). ^{1}H-NMR ((D_6)DMSO): 2.58 (*m*, H_α–C(2'), H_β–C(2')); 3.45, 3.62 (2*m*, 2 H–C(5')); 4.05 (*m*, H–C(4')); 4.23 (*m*, H–C(3')); 4.81 (*t*, *J* = 5.6, OH–C(5')); 5.72 (*d*, *J* = 6.4, OH–C(3')); 6.58 (*t*, *J* = 5.6, H–C(1')); 8.20 (*s*, NH); 8.34 (*s*, H–C(5)); 8.54 (*s*, NH); NOE: H–C(1')→H–C(3') (1.3), H_β–C(2') (5.8).

7-Amino-2-(2'-deoxy-α-D-erythro-pentofuranosyl)-2H-1,2,3-triazolo[4,5-d]pyrimidine (**18**). Deprotection of **10** (400 mg, 0.82 mmol) was carried out as described for **17**. After usual workup (column 15 × 2 cm, $CHCl_3$/MeOH 9:1), **18** was obtained in colourless crystals (150 mg, 73%). M.p. 226° (H_2O). TLC (silica gel, $CHCl_3$/MeOH 4:1): R_f 0.30. UV (H_2O): 253 (4100), 261 (3800), 295 (9700). ^{1}H-NMR ((D_6)DMSO): 2.68 (*m*, H_β–C(2')); 2.88 (*m*, H_α–C(2')); 3.49, 3.63 (2*m*, 2 H–C(5')); 4.11 (*m*, H–C(4')); 4.23 (*m*, H–C(3')); 4.84 (*t*, *J* = 5.7, OH–C(5')); 5.29 (*d*, *J* = 5.5, OH–C(3')); 6.48 (*dd*, *J* = 4.5, 7.0, H–C(1')); 8.12 (*s*, NH); 8.31 (*m*, H–C(5), NH); NOE: H–C(1')→H–C(3') (0.9), H_β–C(2') (5.5). Anal. calc. for $C_9H_{12}N_6O_3$: C 42.86, H 4.79, N 33.32; found: C 42.52, H 4.87, N 33.47.

Glycosylation of 7-Methoxy-3H-1,2,3-triazolo[4,5-d]pyrimidine (**13**) *with* **5**. The suspension of **13** [31] (1.66 g, 11 mmol) in 70 ml of MeCN was treated with 340 mg (11.3 mmol) of 80% NaH (in oil) and the mixture stirred 15 min at r.t. Then, **5** (4.27 g, 11 mmol) was added portionwise within 30 min and stirring continued for 30 min. The mixture was filtered through *Celite*. The filtrate was evaporated, the residue applied on a silica-gel *60H* column (35 × 5 cm), and chromatographed with petroleum ether/AcOEt 7:3. Three main zones were separated.

7-Methoxy-3-[2'-deoxy-3',5'-di-O-(p-toluoyl)-β-D-erythro-pentofuranosyl]-3H-1,2,3-triazolo[4,5-d]pyrimidine (**14**). From the fast migrating zone *I*, a solid foam (1.62 g, 29%) was obtained. TLC (petroleum ether/AcOEt 7:3): R_f 0.46. ^{1}H-NMR ((D_6)DMSO): 2.37, 2.41 (2*s*, 2 CH_3); 2.99 (*m*, H_β–C(2')); 3.59 (*m*, H_α–C(2')); 4.22 (*s*, CH_3O); 4.59 (*m*, H–C(4'), 2 H–C(5')); 5.98 (*m*, H–C(3')); 6.96 (*t*, *J* = 6.4, H–C(1')); 7.32, 7.88 (2*m*, arom. H); 8.77 (*s*, H–C(5)). Anal. calc. for $C_{26}H_{25}N_5O_6$: C 62.02, H 5.00, N 13.91; found: C 62.17, H 5.07, N 13.87.

7-Methoxy-2-[2'-deoxy-3',5'-di-O-(p-toluoyl)-β-D-erythro-pentofuranosyl]-2H-1,2,3-triazolo[4,5-d]pyrimidine (**15**). The second zone yielded a solid foam: 1.76 g (32%). R_f (petroleum ether/AcOEt 7:3) 0.33. ^{1}H-NMR ((D_6)DMSO): 2.36, 2.41 (2*s*, 2 arom. CH_3); 3.01 (*m*, H_β–C(2')); 3.44 (*m*, H_α–C(2')); 4.18 (*s*, CH_3O); 4.46 (*m*, 2

H–C(5′)); 4.75 (*m*, H–C(4′)); 5.96 (*m*, H–C(3′)); 6.89 (*dd*, *J* = 3.8, 6.8, H–C(1′)); 7.30, 7.85 (2*m*, arom. H); 8.77 (*s*, H–C(5)). Anal. calc. for $C_{26}H_{25}N_5O_6$: C 62.02, H 5.00, N 13.91; found: C 62.16, H 5.09, N 13.73.

*7-Methoxy-1-[2′-deoxy-3′,5′-di-*O*-(p-toluoyl)-β-*D*-erythro-pentofuranosyl]-1*H*-1,2,3-triazolo[4,5-d]pyrimidine* (**16**). The slowest migrating product gave crystals from MeOH: 1.26 g (23%). M.p. 115–117°. R_f (petroleum ether/AcOEt 7:3) 0.18. ^{1}H-NMR ((D$_6$DMSO): 2.35, 2.39 (2*s*, 2 arom. CH_3); 2.98 (*m*, H_β–C(2′)); 3.56 (*m*, H_α–C(2′)); 4.19 (*s*, CH_3O); 4.43 (*m*, 2 H–C(5′)); 4.72 (*m*, H–C(4′)); 5.88 (*m*, H–C(3′)); 6.95 (*t*, *J* = 6.1, H–C(1′)); 7.30, 7.82 (2*m*, arom. H); 8.76 (*s*, H–C(5)). Anal. calc. for $C_{26}H_{25}N_5O_6$: C 62.02, H 5.00, N 13.91; found: C 62.16, H 5.09, N 13.73.

*7-Amino-3-[2′-deoxy-β-*D*-erythro-pentofuranosyl]-3*H*-1,2,3-triazolo[4,5-d]pyrimidine* (**1**). *From* **7**: Compound **7** (230 mg, 0.47 mmol) in MeOH (50 ml, saturated with NH_3 at 0°) was stirred for 12 h at r.t. The soln. was evaporated and the residue adsorbed on silica gel *60* (3.0 g) and applied to the top of the silica-gel *60* column (20 × 2 cm). Chromatography with $CHCl_3$/MeOH 4:1 yielded **1** (90 mg, 76%). M.p. 195° (H_2O; [22]: 193.5°).

From **14**: The suspension of **14** (1.3 g, 2.6 mmol) in MeOH (45 ml, saturated with NH_3 at 0°) was stirred for 4 days at r.t. The soln. was evaporated followed by coevaporation with H_2O (100 ml). The residue was dissolved in H_2O and applied on a *Dowex 1X2* column (100–200 mesh, OH^-, 2 × 18 cm). Elution with H_2O (100 ml) removed inorganic material. The nucleoside-containing fractions were obtained by elution with H_2O/MeOH 7:3. Upon evaporation, the product crystallized from aq. EtOH: 570 mg (88%) of colourless crystals. M.p. 193–195°. Mixed m.p. 193–195°. TLC (silica gel, $CHCl_3$/MeOH 4:1): R_f 0.60. UV (H_2O): 278 (11800; [22]: 278 (11700)). ^{1}H-NMR ((D$_6$)DMSO): 2.42 (*m*, H_β–(2′)); 3.04 (*m*, H_α–C(2′)); 3.42, 3.58 (2*m*, 2 H–C(5′)); 3.91 (*m*, H–C(4′)); 4.56 (*m*, H–C(3′)); 4.90 (*t*, *J* = 5.9, OH–C(5′)); 5.39 (*d*, *J* = 4.6, OH–C(3′)); 6.62 (*t*, *J* = 6.4, H–C(1′)); 8.17 (*s*, NH); 8.32 (*s*, H–C(5)); 8.50 (*s*, NH); NOE: H–C(1′)→H_α–C(2′) (5.8), H–C(4′) (1.6).

*7-Amino-2-[2′-deoxy-β-*erythro*-pentofuranosyl]-2*H*-1,2,3-triazolo[4,5-d]pyrimidine* (**2**). *From* **9**: Compound **2** was prepared as described for **1**, but using **9** (220 mg, 0.45 mmol) and MeOH (50 ml, saturated with NH_3 at 0°). After chromatography (column 15 × 2 cm, $CHCl_3$/MeOH 9:1), colourless needles (90 mg, 79%) were obtained from H_2O. Decomp. > 200° without significant melting.

From **15**: The suspension of **15** (1.4 g, 2.78 mmol) in MeOH (45 ml, saturated with NH_3 at 0°) was stirred 2 days at r.t., then 1 day at 50°. The soln. was evaporated and coevaporated with H_2O (100 ml, 3 times). An aq. soln. of the residue was applied on a *Dowex 1X2* (100–200 mesh, OH^-, 2 × 18 cm) column. The column was washed with 100 ml of H_2O, then with 40% aq. MeOH. The nucleoside-containing fractions were evaporated yielding colourless crystals from aq. EtOH (560 mg, 80%). Decomp. > 200° without melting. TLC (silica gel, $CHCl_3$/MeOH 4:1): R_f 0.30. UV (H_2O): 254 (4300), 262 (4100), 294 (9900). ^{1}H-NMR ((D$_6$)DMSO): 2.45 (*m*, H_β–C(2′)); 2.89 (*m*, H_α–C(2′)); 3.43, 3.58 (2*m*, 2 H–C(5′)); 3.93 (*m*, H–C(4′)); 4.56 (*m*, H–C(3′)); 4.77 (*t*, *J* = 5.6, OH–C(5′)); 5.42 (*d*, *J* = 4.7, OH–C(3′)); 6.52 (*dd*, *J* = 4.2, 6.9, H–C(1′)); 8.14 (*s*, NH); 8.31 (*s*, H–C(5)); 8.34 (*s*, NH); NOE: H–C(1′)→H_α–C(2′) (4), H–C(4′) (1.5). Anal. calc. for $C_9H_{12}N_6O_3$: C 42.86, H 4.79, N 33.32; found: C 43.13, H 4.80, N 32.94.

*7-Amino-1-(2′-deoxy-β-*erythro*-pentofuranosyl)-1*H*-1,2,3-triazolo[4,5-d]pyrimidine* (**3**). A suspension of **16** (1.1 g, 2.18 mmol) in MeOH (35 ml, saturated with NH_3 at 0°) was stirred for 1 day at r. t. and then for 2 days at 50°. The mixture was evaporated and the residue crystallized from EtOH to give colourless crystals (320 mg, 58%). Decomp. > 200° without sharp m. p. UV (pH 7): 287 (8400). ^{1}H-NMR ((D$_6$)DMSO): 2.44 (*m*, H_β–C(2′)); 3.14 (*m*, H_α–C(2′)); 3.28, 3.45 (2 *m*, 2H–C(5′)); 4.00 (*m*, H–C(4′)); 4.45 (*m*, H–C(3′)); 4.84 (*t*, *J* = 5.2, OH–C(5′)); 5.44 (*d*, *J* = 4.8, OH–C(3′)); 6.71 (*t*, *J* = 5.0, 1.2, H–C(1′)); 7.73 (br.*s*, NH_2); 8.33 (*s*, H–C(5)); NOE: H–C(1′) → H_α–C(2′) (7.3), H–C(4′) (1.8), NH_2 (1.5), H–C(5) (0); H–C(5) → no NOE. Anal. calc. for $C_9H_{12}N_6O_3$: C 42.86, H 4.79, N 33.32; found: C 42.83, H 4.87, N 33.30.

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