Regioselective Syntheses of 7-Halogenated 7-Deazapurine Nucleosides Related to 2-Amino-7-deaza-2′-deoxyadenosine and 7-Deaza-2′-deoxyisoguanosine

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Abstract: The syntheses of 7-halogenated derivatives **3b**–**e** of 2-amino-7-deaza-2′-deoxyadenosine as well as 7-bromo and 7-chloro-7-deaza-2′-deoxyisoguanosines **4b**–**c** are described. Nucleobase anion glycosylation was employed for the convergent nucleoside synthesis. The regioselective 7-halogenation was performed either on the nucleoside precursor **7** or on the nucleobase **12**. Two bromo substituents were introduced in the 7- and 8-position when the unprotected 2-amino nucleoside **9** was used. Conformational analysis of the sugar moiety of nucleosides **3a**–**e** and **4a**–**c** was performed on the basis of vicinal ^{1}H,^{1}H NMR coupling constants.

Key words: glycosylations, nucleosides, pyrrolo[2,3-*d*]pyrimidines, halogenation, regioselectivity, sugar conformation

7-Deazapurine (pyrrolo[2,3-*d*]pyrimidine; purine numbering is used throughout the general section) nucleosides have gained extensive attention since some of them, such as tubercidin (**1a**), toyocamycin (**1b**), sangivamycin (**1c**), queuosine (**2a**), or archaeosine (**2b**) exhibit a broad spectrum of biological activity.[1–10] Moreover, 7-iodotubercidin (**1d**) is a potent inhibitor of adenosine kinase.[11,12] Apart from the naturally occurring compounds, a number of 7-deazapurine 2′-deoxyribonucleosides have been synthesized.[13–21] Several have been incorporated into oligonucleotides. Among these, the 7-halogeno substituents have been found to enhance the DNA-duplex stability compared to their unmodified counterparts.[22–25] As oligonucleotides containing 7-deaza-2′-deoxyisoguanosine (**4a**) form supramolecular assemblies, they can be used in nanotechnology and material science. Compound **4a** (Figure 1), when incorporated in DNA, quenches the ethidium bromide fluoroscence strongly.

The first synthesis of 2-amino-7-deaza-2′-deoxyadenosine (**3a**) and 7-deaza-2′-deoxyisoguanosine (**4a**) was reported from our laboratory.[16,17] Compound **4a** has been incorporated into oligonucleotides and found to be an ideal substitute of 2′-deoxyisoguanosine.[21] Recently, it was reported that **3a** can form a stable base pair not only with thymine but also with cytosine without duplex destabilization.[24] Until now, the synthesis of 7-halogenated 7-deaza-2′-deoxyisoguanosines or 7-bromo- or 7-chloro-2-amino-7-deaza-2′-deoxyadenosine has not been reported. Continuing our studies on a series of 7-deazapurine nucleosides, we report herein the synthesis and the conformational properties of the 7-halogenated 7-deazapurine deoxynucleosides **3b**–**e** and **4b**,**c**. They are the key intermediates for later studies on oligonucleotides.

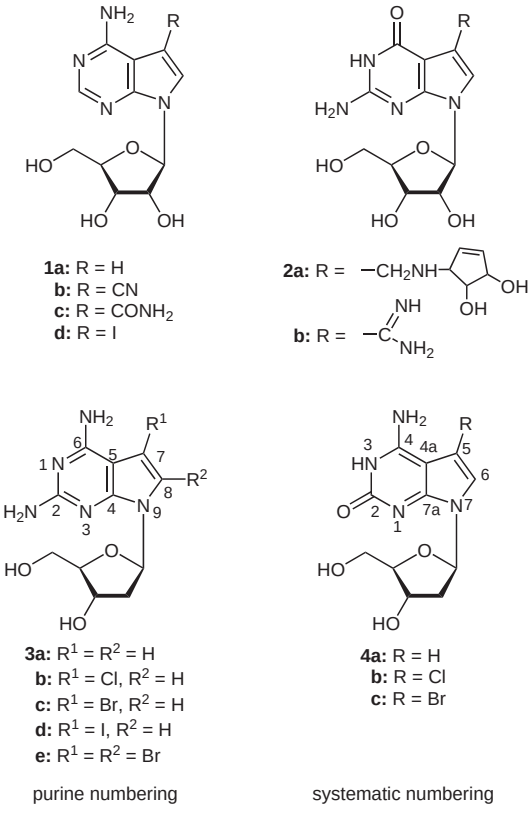

Figure 1

Two routes were employed for the synthesis of 7-halogenated 7-deazapurine nucleosides: (i) conversion of a preformed nucleoside precursor into a 7-halogenated nucleoside; and (ii) the halogenation of the nucleobase followed by glycosylation. In these two routes, the regioselectivity of halogenation is of decisive importance. During recent years, several detailed studies on the halogenations of 7-deazapurines have appeared.[20,26–29] The outcome of these experiments indicated that a direct halogenation of 2-amino-7-deazapurines to the corresponding 7-halo derivatives shows drawbacks as the 2-amino group directs the electrophilic attack into the undesired 8-position - a fact which was first recognized during the Mannich reaction of 7-deazaguanine and 7-deaza-2′-

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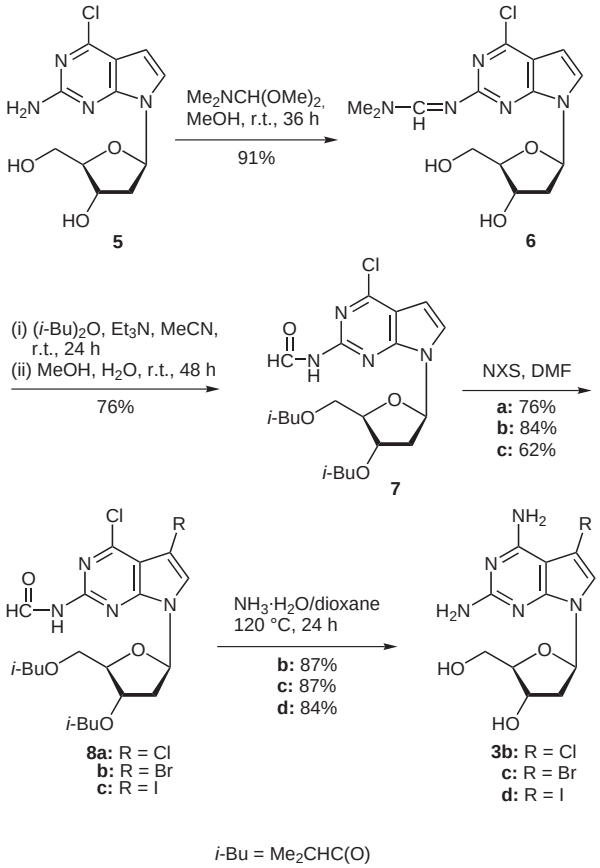
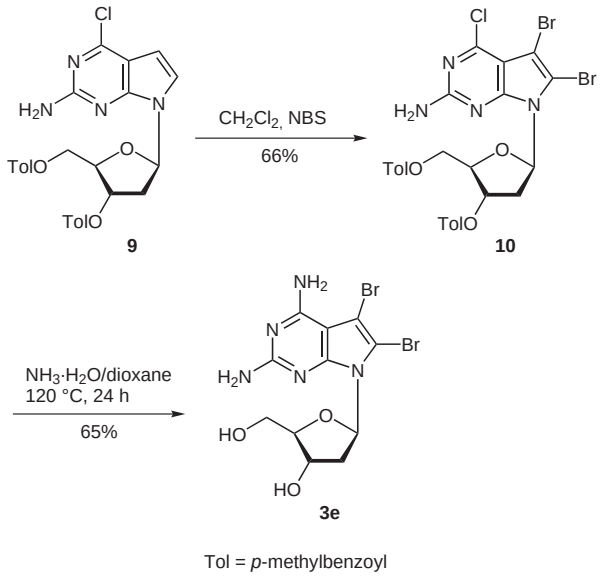
deoxyguanosine.[30,31] However, a regioselective 7-halogenation with *N*-halosuccinimide was accomplished by using the 2-amino-protected derivative 7-[2-deoxy-3,5-di-*O*-(2-methylpropanoyl)-β-D-*erythro*-pentofuranosyl]-2-(formylamino)-4-methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine (systematic numbering) as the precursor.[20] Compared to the 6-methoxy nucleoside, 6-halogeno functionalized derivatives can be more easily displaced by nucleophiles, leading to nucleosides with various substituents at C(6).[32–35] Thus, in our present work, the 6-chloro compounds **5** and **11** have been chosen as starting materials. Compounds **5** and **11** were synthesized as described earlier.[17]

In the first route, the nucleoside **5** was converted into the key intermediate **7** in which both of the hydroxyl groups as well as the base moiety were protected (Scheme 1). Then, compound **7** was treated with *N*-halosuccinimide (NXS, X = Cl, Br, I) in DMF or CH_2Cl_2. A clean reaction was observed, affording the 7-substituted derivatives **8a**–**c** in 60–90% yield. No formation of 7,8-dihalo compound was detected by TLC inspection. For bromination, the reaction was carried out either in DMF or CH_2Cl_2, which gave a complete conversion at room temperature. The chloro and iodo analogues **8a** and **8c** were prepared only in DMF between 50 and 60 °C. Compounds **3b**–**d** were obtained by treatment of **8a**–**c**, respectively, with 25% aqueous ammonia in a sealed stainless steel vessel at 120 °C (Scheme 1).



Scheme 1



Scheme 2

When the 2-amino compound **9**[17] was used as the precursor for bromination with *N*-bromosuccinimide, the 7,8-dibromonucleoside **10** was formed but no 7-halogenated compound was detected (Scheme 2). Nucleoside **10** was treated with 25% aqueous ammonia in a steel bomb to give 2-amino-7-deaza-7,8-dibromo-2′-deoxyadenosine (**3e**).

The most likely explanation for the regioselective formation of 7-halogenated nucleoside is the mesomeric stabilization of the δ-complex formed during electrophilic attack at the 7-position which is stabilized by the structure shown in formula **A** (Figure 2).[20]

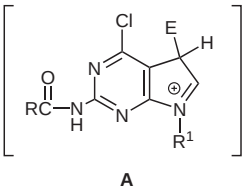


Figure 2 Structure of **A**

Compounds **3b**–**d** were also prepared by nucleobase-anion glycosylation.[15,36] As in the case of nucleosides, direct halogenation of 2-amino-6-chloro-7-deazapurine (**11**) was unsuccessful, but selective 7-halogenation was achieved by using 2-amino-protected derivatives. A pivaloyl group as well as (dimethylamino)methylidene was used as the NH_2 protecting group. It was observed that the yield of halogenation is strongly affected by the protecting group. 6-Chloro-2-[(dimethylamino)methylidene]amino-7-deazapurine resulted in a rather low yield (ca. 40%), whereas a much better yield (ca. 85%) was obtained when the pivaloyl derivative **12** was used (Scheme 3). Both derivatives gave the 7-halogenated products selectively.

Thus, **12** was selected as the precursor for halogenation, and 7-chloro (**13a**), 7-bromo (**13b**), and 7-iodo (**13c**) derivatives of **12** were prepared by the action of *N*-chloro-, *N*-bromo- and *N*-iodosuccinimide, respectively, on **12** in DMF or CH_2Cl_2.

Subsequent nucleobase-anion glycosylation[15,36] of **13a**–**c** with 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**14**) afforded the toluoyl-protected β-D-nucleosides **15a**–**c** in 60–70% yields (Scheme 3). In all cases, the reaction was stereoselective and gave the β-D anomer exclusively. All compounds were isolated in crystalline form. Removal of the toluoyl protecting groups and displacement of the 6-chloro group of **15a**–**c** were effected by treatment with 25% aqueous ammonia in a steel bomb without affecting the 7-halogeno substituents, thereby furnishing compounds **3b**–**d**. The second route is superior to the first one because of its higher total yield (30–35% for route 1 and 40–45% for route 2). Also, route 2 requires fewer reaction steps.

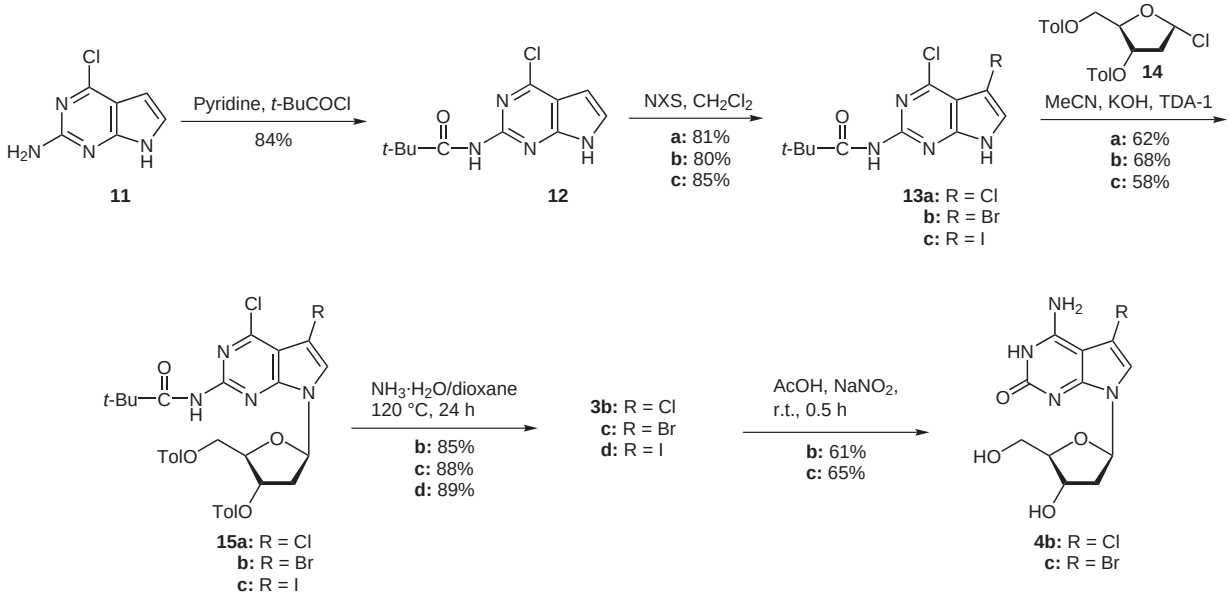
Selective deamination of compounds **3b** and **3c** with sodium nitrite in HOAc–H_2O (1:5) furnished the nucleosides 7-chloro-7-deaza-2′-deoxyisoguanosine (**4b**) and 7-bromo-7-deaza-2′-deoxyisoguanosine (**4c**) in 60–70% yield, respectively. Unfortunately, 7-deaza-7-iodo-2′-deoxyisoguanosine could not be obtained by this method because of the insolubility of precursor **3d** under the reaction conditions.

The compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as by elemental analysis. To confirm the position of halogenation of all halogenated nucleosides and intermediates, ^{1}H-NOE difference spectra of compounds **3c** and **4c** were measured as representative examples. Irradiation of the corresponding H-8 signals resulted in NOE effects at H-1′ (6.0% for **3c** and 6.8% for **4c**). This proves both the halogenation site at C-7 as well as a preferred *syn*-conformation at the *N*-glycosylic bond which is 55% *syn* for **3c** and 59% for **4c**.[37] Characteristic NOEs were also observed for H_β2′ (4.2% for **3c** and 3.2%

Table 1 ^{13}C NMR Chemical Shifts (δ) of 7-Deazapurine 2′-Deoxynucleosides[a]

Product[b,c]	C(2)[d] C(2)	C(4)[d] C(6)	C(4a) C(5)	C(5) C(7)	C(6) C(8)	C(7a)[d] C(4)	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)
3a[17]	159.3	157.5	96.3	99.7	117.5	152.2	82.7	–[e]	71.0	86.8	62.1
3b	160.4	157.2	93.3	103.3	114.5	151.9	82.0	–[e]	71.0	86.9	62.0
3c	160.1	157.2	94.3	87.4	117.0	152.1	81.9	–[e]	70.9	86.9	61.9
3d	159.7	157.5	96.4	52.3	122.4	152.6	82.0	–[e]	70.9	86.9	61.9
3e	159.5	156.5	104.7	91.7	95.4	151.9	85.2	37.3	71.2	87.5	62.3
4a[21]	153.9	156.3	92.6	100.8	118.9	152.6	83.4	–[e]	71.2	87.2	62.0
4b	153.2	156.2	90.2	103.7	116.2	–[f]	82.6	–[e]	70.9	87.2	61.9
4c	153.6	156.0	91.0	87.4	118.8	–[f]	82.5	–[e]	70.8	87.2	61.8
7	152.0	151.3	114.0	100.5	126.9	151.8	83.4	35.6	73.7	81.2	63.4
8a	152.6	150.9	110.3	103.8	124.1	151.0	83.3	35.7	73.9	81.4	63.5
8b	152.3	151.2	111.1	88.2	126.5	151.1	83.2	35.7	73.8	81.3	63.4
8c	151.9	151.8	113.7	54.5	131.7	151.6	83.2	35.7	73.8	81.3	63.4
10	159.1	153.0	107.2	92.4	113.0	150.7	85.7	35.0	75.0	81.4	64.3
13a	151.9	149.7	101.6	109.1	124.8	151.5	–	–	–	–	–
13b	151.9	150.0	110.1	85.8	127.3	151.7	–	–	–	–	–
13c	152.5	150.6	112.3	51.7	132.7	151.4	–	–	–	–	–
15a[g]	152.2	151.8	110.9	106.1	122.7	150.9	84.4	40.3	74.8	82.6	63.9
15b[g]	152.5	151.7	112.0	89.8	125.4	151.3	84.5	40.3	74.8	82.6	63.9
15c	152.5	152.4	113.9	54.9	133.4	152.1	84.8	-[e]	75.9	82.4	64.9

[a] Measured in DMSO-d_6.
[b] Systematic numbering.
[c] Purine numbering.
[d] Tentative.
[e] Superimposed by DMSO.
[f] Not detected.
[g] Measured in $CDCl_3$.



TDA-1 = tris[2-(2-methoxyethoxy)ethyl]amine

Scheme 3

for **4c**), establishing β-D configuration. The position of the halogenation was also confirmed by ^{13}C NMR spectroscopy (Table 1). Compared to the nonhalogenated compound, the C-7 signal is shifted about 15 ppm upfield upon bromination (**3c**, **4c**, **8b**, **13b**, **15b**), about 50 ppm upfield upon iodination (**3d**, **8c**, **13c**, **15c**), and about 3 ppm downfield upon chlorination. For the dibromo nucleosides **10** and **3e**, the bromo substituent shifts the signals for both C-7 and C-8 upfield (about 8 ppm for C-7 and 12 ppm for C-8).

Next, a conformational analysis of the sugar moiety of nucleosides **3a**–**e** and **4a**–**c** was performed with the aid of the PSEUROT program (version 6.3).[38] In this program, a minimization of the differences between the experimental and calculated couplings is accomplished by a nonlinear Newton–Raphson minimization; the quality of the fit is expressed by the root-mean-square (rms) difference. This procedure presupposes the existence of a two state *N*/*S* equilibrium (Figure 3).[39] The input contained the following coupling constants: *J*(H1′,H2′), *J*(H1′,H2″), *J*(H2′,H3′), *J*(H2″,H3′), *J*(H3′,H4′). During the iterations either the puckering parameters (P, ψ_{max}) of the minor conformer (*N*) or the puckering amplitudes of both conformers were constrained. The coupling constants *J*(H1′,H2′), *J*(H1′,H2″), *J*(H2′,H3′), *J*(H2″,H3′), *J*(H3′,H4′) and the pseudorotational parameters are shown in Table 2.

From the data given in Table 2, it is apparent that all nucleosides are in the *N*⇆*S* equilibrium in solution showing a preferred *S* conformer population. The value of the nonhalogenated nucleosides **3a** and **4a** show a population of around 74% *S*; while the conformations of the nucleosides

Table 2 $^3J_{H,H}$ Coupling Constant of the Sugar Moiety and Conformer Population of Nucleosides **3a**–**e** and **4a**–**c**[a]

Product	$^3J_{H,H}$ (Hz)					Pseudorotational Parameters[b]					
	1′,2′	1′,2″	2′,3′	2″,3′	3′,4′	%*N*	% *S*	P_S (deg)	ψ_S (deg)	rms (Hz)	$\lvert\Delta J_m\rvert$
3a	7.64	6.43	6.16	2.89	3.34	26	74	152.7	31.0	0.14	0.19
3b	6.99	6.57	6.54	3.13	3.52	28	72	153.3	27.6	0.20	0.33
3c	6.92	6.46	6.52	3.18	3.54	29	71	153.5	28.1	0.25	0.42
3d	6.99	6.62	6.52	3.18	3.49	28	72	154.7	27.6	0.17	0.30
3e	8.34	6.61	5.84	2.02	2.68	17	83	159.6	30.6	0.22	0.28
4a	6.99	6.21	6.40	2.88	3.38	27	73	154.6	28.9	0.36	0.58
4b	7.20	6.50	6.00	2.98	3.24	28	72	163.2	30.5	0.22	0.27
4c	6.54	5.80	6.16	2.88	3.68	31	69	153.9	30.6	0.61	0.90

[a] Measured in D_2O.
[b] P_N (deg) = 18 and ψ_N (deg) = 38 were fixed during the final minimization.

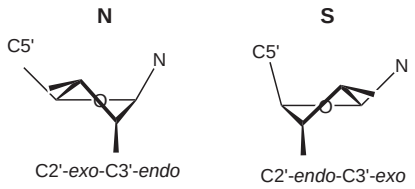


Figure 3 *N* and *S* conformations of nucleosides

3b–d and **4b**,**c** with 7-halogeno substituents are shifted a little towards the *N*-population (around 70% *S*). In the case of the 7,8-dibromo-substituted derivative **3e**, the *S*-conformer population increases to 83%, which is 12% higher than that of the 7-bromo nucleoside **3c** (71% *S*). As bulky 8-substituent can shift the equilibrium around the *N*-glycosylic bond more to the *syn* population which can change the *N*⇆*S* equilibrium of **3e** towards *S*. These findings demonstrate that electron-withdrawing substituents in position-7 of 7-deazapurine shift the sugar conformation towards *N*, while bulky substituents in position 8 drive the *N*⇆*S* equilibrium towards the *S* population.[40,41]

All chemicals were purchased from Sigma-Aldrich. Solvents were of laboratory grade. Petroleum ether used had bp 40–60 °C. TLC: aluminum sheets, silica gel 60 F_{254} (0.2 mm, VWR International). Column flash chromatography (FC): silica gel 60 (VWR International) at 0.4 bar. Solvent systems of FC and TLC: CH_2Cl_2–MeOH, 99:1 (A), CH_2Cl_2–MeOH, 98:2 (B), CH_2Cl_2–MeOH, 9:1 (C), CH_2Cl_2–MeOH, 4:1 (D), NH_3 (25%)–*i*-PrOH–H_2O (1:7:2) (E). UV Spectra: U-3200 UV-Vis spectrometer (Hitachi, Japan). NMR spectra: Avance-250 or AMX-500 spectrometers (Bruker); δ values in ppm relative to Me_4Si as internal standard, *J* values are in Hz. Melting points were determined by a Linström apparatus and are not corrected. Elemental analyses were performed by the Mikroanalytisches Laboratorium Beller, Göttingen, Germany.

4-Chloro-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-*N*^{2}-[(dimethylamino)methylidene]-7*H*-pyrrolo[2,3-*d*]pyrimidine (6)

A solution of 2-amino-4-chloro-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine[17] (**5**; 1.70 g, 5.97 mmol) in MeOH (50 mL) was stirred with dimethylformamide dimethyl acetal (5.0 mL, 37.3 mmol) for 36 h at r.t. After evaporation, the residue was subjected to FC (silica gel, column 5 × 15 cm, B → C), yielding a colorless foam (1.85 g, 91%); TLC (silica gel, C): R_f = 0.50.

^{1}H NMR (DMSO-d_6): δ = 2.20–2.24 (m, 1 H, H-2′), 2.44–2.50 (m, 1 H, H-2′), 3.03 (s, 3 H, CH_3), 3.15 (s, 3 H, CH_3), 3.47–3.55 (m, 2 H, H-5′), 3.80–3.83 (m, 1 H, H-4′), 4.34–4.36 (m, 1 H, H-3′), 4.99 (t, 1 H, *J* = 5.6 Hz, 5′-OH), 5.32 (d, 1 H, *J* = 4.1 Hz, 3′-OH), 6.49 (d, 1 H, *J* = 3.8 Hz, H-5), 6.55 (t, 1 H, *J* = 6.0 Hz, H-1′), 7.59 (d, 1 H, *J* = 3.8 Hz, H-6), 8.61 (s, 1 H, CH=N).

UV (MeOH): λ_{max} (ε) = 264 (19000), 299 nm (16800).

Anal. Calcd for $C_{14}H_{18}ClN_5O_3$ (339.8): C, 49.49; H, 5.34; N, 20.61. Found: C, 48.48; H, 5.39; N, 20.39.

4-Chloro-7-[2-deoxy-3,5-bis-*O*-(2-methylpropanoyl)-β-D-*erythro*-pentofuranosyl]-2-(formylamino)-7*H*-pyrrolo[2,3-*d*]pyrimidine (7)

A suspension of compound **6** (1.80 g, 5.30 mmol) in MeCN (30 mL) was treated with isobutyric anhydride (9.0 mL, 54.3 mmol) in the presence of Et_3N (4.0 mL) at r.t. for 24 h. Then, a clear solution was obtained. To this solution, MeOH (10.0 mL) and H_2O (5.0 mL) were added, and the mixture was stirred at r.t. for 48 h. The solvent was evaporated, and the residue was subjected to FC (silica gel, column 5 × 15 cm, A → B). After evaporation, the main zone gave a colorless semisolid material. Crystallization from CH_2Cl_2–petroleum ether (2:1) yielded colorless needles (1.83 g, 76%); mp 130 °C; TLC (silica gel, B): R_f = 0.38.

^{1}H NMR (DMSO-d_6): δ = 1.05 (d, 6 H, *J* = 6.7 Hz, 2 CH_3), 1.13 (d, 6 H, *J* = 6.8 Hz, 2 CH_3), 2.49–2.52 (m, 3 H, 2 CH, H- 2′); 2.96–2.98 (m, 1 H, H-2′), 4.20–4.23 (m, 3 H, H-4, 2 H-5′), 5.37–5.39 (m, 1 H, H-3′), 6.50–6.52 (m, 1 H, H-1′), 6.68 (d, 1 H, *J* = 3.7 Hz, H-5), 7.72 (d, 1 H, *J* = 3.7 Hz, H-6), 9.38 (d, 1 H, *J* = 9.0 Hz, NH), 11.10 (d, 1 H, *J* = 9.0 Hz, HCO).

UV (MeOH): λ_{max} (ε) = 244 (33400), 279 nm (8900).

Anal. Calcd for $C_{20}H_{25}ClN_4O_6$ (452.9): C, 53.04; H, 5.56; N,12.37. Found: C, 53.15; H, 5.38; N, 12.26.

4,5-Dichloro-7-[2-deoxy-3,5-bis-*O*-(2-methylpropanoyl)-β-D-*erythro*-pentofuranosyl]-2-(formylamino)-7*H*-pyrrolo[2,3-*d*]pyrimidine (8a); Typical Procedure

To a solution of compound **7** (1.1 g, 2.43 mmol) in DMF (30 mL) was added *N*-chlorosuccinimide (390 mg, 2.92 mmol). After stirring for 24 h at 50 °C, the reaction mixture was evaporated to dryness, redissolved in CH_2Cl_2 and chromatographed (silica gel, column 4 × 12 cm, A → B). From the main zone, a colorless foam was obtained. Crystallization from CH_2Cl_2–petroleum ether (2:1) gave colorless crystals (900 mg, 76%); mp 127 °C; TLC (silica gel, B): R_f = 0.42.

^{1}H NMR (DMSO-d_6): δ = 1.06 (d, 6 H, *J* = 6.9 Hz, 2 CH_3), 1.13 (d, 6 H, *J* = 6.9 Hz, 2 CH_3), 2.50–2.64 (m, 3 H, 2 CH, H-2′), 2.86–2.94 (m, 1 H, H-2′), 4.18–4.28 (m, 3 H, H-4′, 2 H-5′), 5.35–5.37 (m, H-3′), 6.52 (t, 1 H, *J* = 6.8, 6.8 Hz, H-1′), 7.93 (s, 1 H, H-6), 9.37 (d, 1 H, *J* = 9.5 Hz, NH), 11.21 (d, 1 H, *J* = 9.5 Hz, HCO).

UV (MeOH): λ_{max} (ε) = 248 nm (38100).

Anal. Calcd for $C_{20}H_{24}Cl_2N_4O_6$ (487.3): C, 49.29; H, 4.96; N, 11.50. Found: C, 49.29; H, 4.90; N, 11.33.

5-Bromo-4-chloro-7-[2-deoxy-3,5-bis-*O*-(2-methylpropanoyl)-β-D-*erythro*-pentofuranosyl]-2-(formylamino)-7*H*-pyrrolo[2,3-*d*]pyrimidine (8b)

As described for **8a**, the reaction was carried out with **7** (1.1 g, 2.43 mmol) and *N*-bromosuccinimide (516 mg, 2.90 mmol, 5 h) in DMF or CH_2Cl_2 (30 mL). FC resulted in a colorless foam of **8b**. Crystallization from CH_2Cl_2–petroleum ether (2:1) yielded colorless crystals (1.08 g, 84%); mp 121 °C; TLC (silica gel, B): R_f = 0.42.

^{1}H NMR (DMSO-d_6): δ = 1.06 (d, 6 H, *J* = 6.9 Hz, 2 CH_3), 1.13 (d, 6 H, *J* = 6.9 Hz, 2 CH_3), 2.53–2.67 (m, 3 H, 2 CH, H-2′), 2.87–2.99 (m, 1 H, H-2′), 4.19–4.27 (m, 3 H, H-4′, 2 H-5′), 5.34–5.37 (m, 1 H, H-3′), 6.53 (t, 1 H, *J* = 6.8 Hz, H-1′), 7.98 (s, 1 H, H-6), 9.38 (d, 1 H, *J* = 9.5 Hz, NH), 11.21 (d, 1 H, *J* = 9.5 Hz, HCO).

UV (MeOH): λ_{max} (ε) = 250 nm (39400).

Anal. Calcd for $C_{20}H_{24}BrClN_4O_6$ (531.8): C, 45.17; H, 4.55; N, 10.54. Found: C, 45.57; H, 4.62; N, 10.33.

4-Chloro-7-[2-deoxy-3,5-bis-*O*-(2-methylpropanoyl)-β-D-*erythro*-pentofuranosyl]-2-(formylamino)-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (8c)

As described for **8a**, the reaction was carried out with **7** (1.10 g, 2.43 mmol) and *N*-iodosuccinimide (655 mg, 2.91 mmol, 25 h) in DMF (30 mL). Compound **8c** (867 mg, 62%) was obtained as colorless crystals from CH_2Cl_2–petroleum ether (2:1); mp 126 °C; TLC (silica gel, B): R_f = 0.42.

^{1}H NMR (DMSO-d_6): δ = 1.02 (d, 6 H, J = 6.9 Hz, 2 CH_3), 1.12 (d, 6 H, J = 6.9 Hz, 2 CH_3), 2.53–2.66 (m, 3 H, 2 CH, H-2′), 2.85–2.97 (m, 1 H, H-2′), 4.19–4.29 (m, 3 H, H-4′, 2 H-5′), 5.34–5.36 (m, 1 H, H-3′), 6.50 (t, 1 H, J = 6.6 Hz, H-1′), 7.95 (s, 1 H, H-6), 9.36 (d, 1 H, J = 9.2 Hz, NH), 11.21 (d, 1 H, J = 9.2 Hz, HCO).

UV (MeOH): λ_{max} (ε) = 252 nm (38500).

Anal. Calcd for $C_{20}H_{24}ClIN_4O_6$ (578.8): C, 41.50; H, 4.18; N, 9.68. Found: C, 41.49; H, 4.20; N, 9.70.

5-Chloro-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (3b); Typical Procedure

A suspension of compound **8a** (1.12 g, 2.30 mmol) in dioxane (20 mL) and 25% NH_3/H_2O (60 mL) was introduced into an autoclave and stirred at 120 °C for 24 h. The clear solution was evaporated, and the residue was submitted to flash chromatography (silica gel, column 4 × 16 cm, B → C). After evaporation, the main zone gave crude **3b**. Crystallization from MeOH yielded colorless crystals (596 mg, 87%); mp 210 °C (dec.); TLC (silica gel, C): R_f = 0.33.

^{1}H NMR (DMSO-d_6): δ = 2.00–2.07 (m, 1 H, H-2′), 2.28–2.38 (m, 1 H, H-2′), 3.48–3.50 (m, 2 H, 2 H-5′), 3.74–3.76 (m, 1 H, H-4′), 4.26–4.28 (m, 1 H, H-3′), 5.00 (t, 1 H, J = 5.3 Hz, 5′-OH), 5.21 (d, J = 3.5 Hz, 3′-OH), 5.86 (br s, 2 H, NH_2), 6.32–6.38 (m, 3 H, H-1′, NH_2), 7.09 (s, 1 H, H-6).

UV (MeOH): λ_{max} (ε) = 228 (26800), 268 (9900), 287 nm (shoulder, 7700).

Anal. Calcd for $C_{11}H_{14}ClN_5O_3$ (299.7): C, 44.08; H, 4.71; N, 23.37. Found: C, 44.15; H, 4.81; N, 23.36.

5-Bromo-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (3c)

As described for **3b**, the reaction was carried out with **8b** (1.17 g, 2.20 mmol) and 25% NH_3/H_2O (60 mL) in dioxane (20 mL). FC resulted in crude **3c** as a colorless solid. Crystallization from MeOH afforded colorless crystals (660 mg, 87%); mp 208 °C (dec.); TLC (silica gel, C): R_f = 0.33.

^{1}H NMR (DMSO-d_6): δ = 2.00–2.06 (m, 1 H, H-2′), 2.29–2.40 (m, 1 H, H-2′), 3.48–3.52 (m, 2 H, 2 H-5′), 3.74–3.78 (m, 1 H, H-4′), 4.25–4.29 (m, 1 H, H-3′), 4.99 (t, 1 H, J = 5.4 Hz, 5′-OH), 5.21 (d, 1 H, J = 3.6 Hz, 3′-OH), 5.86 (br s, 2 H, NH_2), 6.28 (br s, 2 H, NH_2), 6.34 (dd, 1 H, J = 6.5, 6.9 Hz, H-1′), 7.15 (s, 1 H, H-6).

UV (MeOH): λ_{max} (ε) = 228 (27800), 268 (9300), 288 nm (shoulder, 7500).

Anal. Calcd $C_{11}H_{14}BrN_5O_3$ (344.2): C, 38.39; H, 4.10; N 20.35. Found: C, 38.22; H, 4.08; N, 20.25.

7-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (3d)

As described for **3b**, the reaction was carried out with **8c** (1.24 g, 2.14 mmol) and 25% NH_3/H_2O (60 mL) in dioxane (20 mL). FC resulted in crude **3d** as white solid, which was crystallized from MeOH to give colorless crystals (700 mg, 84%); mp 204 °C (dec.); TLC (silica gel, C): R_f = 0.33.

^{1}H NMR (DMSO-d_6): δ = 2.00–2.08 (m, 1 H, H-2′), 2.29–2.37 (m, 1 H, H-2′), 3.46–3.52 (m, 2 H, 2 H-5′), 3.73–3.76 (m, 1 H, H-4′), 4.26–4.28 (m, 1 H, H-3′), 4.99 (t, 1 H, J = 5.5 Hz, 5′-OH), 5.20 (d, 1 H, J = 3.7 Hz, 3′-OH), 5.82 (br s, 2 H, NH_2), 6.18 (br s, 2 H, NH_2), 6.33 (dd, J = 6.6, 7.0 Hz, H-1′), 7.19 (s, 1 H, H-6).

UV (MeOH): λ_{max} (ε) = 230 (28100), 269 (9500), 289 nm (shoulder, 8000).

Anal. Calcd for $C_{11}H_{14}IN_5O_3$ (391.2): C, 33.78; H, 3.61; N, 17.90. Found: C, 33.70; H, 3.68; N, 17.81.

2-Amino-5,6-dibromo-4-chloro-7-[2-deoxy-3,5-di-*O*-(4-toluoyl)-β-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (10)

A solution of compound **9** (600 mg, 1.15 mmol) and *N*-bromosuccinimide (499 mg, 2.80 mmol) in CH_2Cl_2 (20 mL) was stirred for 1.5 h at r.t. After evaporation, the residue was redissolved in CH_2Cl_2 (5 mL) and submitted to FC (silica gel, column 4 × 10 cm, A → B). The main zone was collected and evaporated to give a colorless foam. Crystallization from CH_2Cl_2–petroleum ether (2:1) yielded **10** as colorless crystals (518 mg, 66%); mp 180 °C; TLC (silica gel, A): R_f = 0.50.

^{1}H NMR (DMSO-d_6): δ = 2.35 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 2.62–2.69 (m, 1 H, H-2′), 3.54–3.64 (m, 1 H, H-2′), 4.48–4.54 (m, 2 H, 2 H-5′), 4.66–4.75 (m, 1 H, H-4′), 5.88–5.92 (m, 1 H, H-3′), 6.48 (t, 1 H, J = 6.8 Hz, H-1′), 7.09 (br s, 2 H, NH_2), 7.27, 7.35, 7.79, 7.92 (4 d, 8 H, J = 8.1 Hz, 2 C_6H_4).

UV (MeOH): λ_{max} (ε) = 243 (55700), 328 (6200), 341 nm (5300).

Anal. Calcd for $C_{27}H_{23}Br_2ClN_4O_5$ (678.8): C, 47.78; H, 3.42; N, 8.25. Found: C, 47.82; H, 3.31; N, 8.20.

5,6-Dibromo-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (3e)

As described for **3b**, the reaction was carried out with **10** (400 mg, 0.59 mmol) and 25% NH_3/H_2O (50 mL) in dioxane (15 mL). FC (solvent CH_2Cl_2–MeOH 95:5) gave crude **3e** as colorless solid which was crystallized from MeOH to yield colorless crystals (161 mg, 65%); mp 137 °C; TLC (silica gel, C): R_f = 0.54.

UV (MeOH): λ_{max} (ε) = 227 (27200), 267 (10900), 289 nm (shoulder, 8000).

^{1}H NMR (DMSO-d_6): δ = 1.97–2.04 (m, 1 H, H-2′), 3.02–3.13 (m, 1 H, H-2′), 3.46–3.56 (m, 1 H, H-5′), 3.60–3.69 (m, 1 H, H-5′), 3.78–3.81 (m, 1 H, H-4′), 4.36–4.38 (m, 1 H, H-3′), 5.24 (d, J = 4.0 Hz, 3′-OH), 5.35 (dd, J = 4.5 Hz, 5′-OH), 5.84 (br s, 2 H, NH_2), 6.33 (dd, 1 H, J = 6.6, 8.3 Hz, H-1′), 6.47 (br, s, 2 H, NH_2).

Anal. Clacd for $C_{11}H_{13}Br_2N_5O_3$ (423.1): C, 31.23; H, 3.10; N, 16.55. Found: C, 31.41; H, 3.16; N, 16.39.

4-Chloro-2-pivaloylamino-7*H*-pyrrolo[2,3-*d*]pyrimidine (12)

To a solution of 2-amino-4-chloropyrrolo[2,3-*d*]pyrimidine[17] (**11**; 8.70 g, 51.6 mmol) in pyridine (40 mL), was added dropwise pivaloyl chloride (8.04 mL, 65.3 mmol) over 15 min, and the mixture was stirred for 5 h at r.t. The solution was evaporated to an amber solid, which was coevaporated with H_2O (2 × 10 mL). The resulting solid was filtered, washed with cold H_2O and then dried in vacuo over KOH to yield **12** as a reddish solid (10.9 g, 84%); mp 226 °C.

^{1}H NMR (DMSO-d_6): δ = 1.24 (s, 9 H, 3 CH_3), 6.53 (m, 1 H, H-5), 7.63 (m, 1 H, H-6), 10.06 (s, 1 H, CONH), 12.34 (s, 1 H, NH). These data are identical to those published earlier.[23]

4,5-Dichloro-2-pivaloylamino-7*H*-pyrrolo[2,3-*d*]pyrimidine (13a); Typical Procedure

A solution of compound **12** (5.7 g, 22.6 mmol) and *N*-chlorosuccinimide (3.62 g, 27.1 mmol) in CH_2Cl_2 (100 mL) was stirred at 40 °C for 5 h. The yellow solution was evaporated to an amber residue which was crystallized from MeOH to give yellowish crystals (5.26 g, 81%); mp 238 °C.

^{1}H NMR (DMSO-d_6): δ = 1.23 (s, 9 H, 3 CH_3), 7.74 (s, 1 H, H-6), 10.18 (s, 1 H, CONH), 12.65 (s, 1 H, NH).

Anal. Calcd for $C_{11}H_{12}Cl_2N_4O$ (287.2): C, 46.01; H, 4.21; N, 19.51. Found: C, 46.22, H, 4.30; N, 19.35.

5-Bromo-4-chloro-2-pivaloylamino-7*H*-pyrrolo[2,3-*d*]pyrimidine (13b)

As described for **13a**, the reaction was carried out with **12** (5.70 g, 22.6 mmol) and *N*-bromosuccinimide (4.82 g, 27.1 mmol) in CH_2Cl_2 (100 mL). The yellow solution was evaporated to an amber residue which was crystallized from MeOH to give pink crystals (6.0 g, 80%); mp 204 °C (dec.).

^{1}H NMR (DMSO-d_6): δ = 1.23 (s, 9 H, 3 CH_3), 7.78 (s, 1 H, H-6), 10.16 (s, 1 H, CONH), 12.72 (s, 1 H, NH).

Anal. Calcd for $C_{11}H_{12}BrClN_4O$ (331.6): C, 39.84; H, 3.65; N, 16.90. Found: C, 39.87; H, 3.63; N, 16.90.

4-Chloro-5-iodo-2-pivaloylamino-7*H*-pyrrolo[2,3-*d*]pyrimidine (13c)

As described for **13a**, the reaction was carried out with **12** (5.7 g, 22.6 mmol) and *N*-iodosuccinimide (6.12 g, 27.2 mmol) in CH_2Cl_2 (100 mL). The yellow solution was evaporated to an amber residue which was crystallized from MeOH to furnish colorless crystals (7.3 g, 85%); mp 240 °C.

^{1}H NMR (DMSO-d_6): δ = 1.22 (s, 9 H, 3 CH_3), 7.77 (s, 1 H, H-6), 10.13 (s, 1 H, CONH), 12.71 (s, 1 H, NH). These data are identical to those published.[23]

Anal. Calcd for $C_{11}H_{12}ClIN_4O$ (378.6): C, 34.60; H, 3.19; N, 14.80. Found: C, 34.90; H, 3.20; N, 14.95.

4,5-Dichloro-7-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]-2-pivaloylamino-7*H*-pyrrolo[2,3-*d*]pyrimidine (15a); Typical Procedure

To a suspension of powdered KOH (1.15 g, 85%, 17.4 mmol) and TDA-1 (0.2 mL, 0.63 mmol) in MeCN (60 mL), was added compound **13a** (1.44 g, 5.00 mmol). After stirring the mixture for 5 min, 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride[42] (**14**; 2.53 g, 6.51 mmol) was added over 15 min, and the stirring was continued for 1 h. Insoluble material was filtered off, the precipitate was washed with MeCN, and the filtrate was evaporated to dryness. The residue was subjected to FC (silica gel, column 6 × 12 cm), eluting with CH_2Cl_2. The combined fractions containing product were evaporated to give a foam. Crystallization from CH_2Cl_2–petroleum ether (2:1) yielded colorless needles (1.98 g, 62%); mp 234 °C; TLC (silica gel, A): R_f = 0.53.

^{1}H NMR ($CDCl_3$): δ = 1.35–1.37 (m, 9 H, 3 CH_3), 2.42 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 2.78–2.82 (m, 1 H, H-2′), 2.91–2.97 (m, 1 H, H-2′), 4.55–4.58, 4.63–4.66, 4.73–4.76 (3 m, 3 H, H-4′, 2 H-5′), 5.77–4.78 (m, 1 H, H-3′), 6.74 (t, 1 H, *J* = 6.8 Hz, H-1′), 7.25, 7.28, 7.90, 7.98 (4 d, 8 H, *J* = 8.1 Hz, 2 C_6H_4), 8.16 (s, 1 H, H-6), 10.29 (s, 1 H, NH).

UV (MeOH): λ_{max} (ε) = 246 nm (54400).

Anal. Calcd for $C_{32}H_{32}Cl_2N_4O_6$ (639.5): C, 60.10; H, 5.04; N, 8.76. Found: C, 59.99; H, 4.91; N, 8.80.

5-Bromo-4-chloro-7-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]-2-pivaloylamino-7*H*-pyrrolo[2,3-*d*]pyrimidine (15b)

As described for **15a**, the reaction was carried out with **13b** (1.66 g, 5.0 mmol) and **14** (2.53 g, 6.51 mmol) in the presence of KOH (1.15 g, 85%, 17.4 mmol) and TDA-1 (0.2 mL, 0.63 mmol) in MeCN (60 mL). FC (silica gel, column 6 × 12 cm, CH_2Cl_2) resulted in crude **15b** as colorless foam. Crystallization from CH_2Cl_2–petroleum ether (2:1) gave colorless needles (2.32 g, 68%); mp 229–230 °C; TLC (silica gel, A): R_f = 0.53.

^{1}H NMR ($CDCl_3$): δ = 1.38–1.47 (m, 9 H, 3 CH_3), 2.55 (s, 3 H, CH_3), 2.57 (s, 3 H, CH_3), 2.91–2.93 (m, 1 H, H-2′), 3.04–3.08 (m, 1 H, H-2′), 4.69–4.70, 4.76–4.78, 4.85–4.87 (3 m, 3 H, H-4′, 2H-5′), 5.88–5.91 (m, 1 H, H-3′), 6.84 (t, 1 H, *J* = 6.7 Hz, H-1′), 7.37, 7.43, 8.03, 8.10 (4 d, 8 H, *J* = 8.1 Hz, 2 C_6H_4), 8.28 (s, 1 H, H-6), 10.29 (s, 1 H, NH).

UV (MeOH): λ_{max} (ε) = 245 nm (55300).

Anal. Calcd for $C_{32}H_{32}BrClN_4O_6$ (684.0): C, 56.19; H, 4.72; N, 8.19. Found: C, 56.12; H, 4.79; N, 8.33.

4-Chloro-7-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]-5-iodo-2-pivaloylamino-7*H*-pyrrolo[2,3-*d*]pyrimidine (15c)

As described for **15a**, the reaction was carried out with **13c** (1.9 g, 5.0 mmol) and **14** (2.53 g, 6.51 mmol) in the presence KOH (1.15 g, 85%, 17.4 mmol) and TDA-1 (0.2 mL, 0.63 mmol) MeCN (60 mL). FC (silica gel, column 6 × 12 cm, CH_2Cl_2) resulted in **15c** as a foam. Crystallization from CH_2Cl_2–petroleum ether (2:1) yielded colorless needles (2.12 g, 58%); mp 220 °C; TLC (silica gel, A): R_f = 0.53.

^{1}H NMR (DMSO-d_6): δ = 1.21 (s, 9 H, 3 CH_3), 2.37, 2.39 (2 s, 6 H, 2 CH_3), 2.69–2.75 (m, 1 H, H-2′), 3.19–3.25 (m, 1 H, H-2′), 4.47–4.53 (m, 2 H, 2 H-5′), 4.61–4.67 (m, 1 H, H-4′), 5.77–5.79 (m, 1 H, H-3′), 6.63 (t, 1 H, *J* = 6.8 Hz, H-1′), 7.31, 7.37, 7.84, 7.94 (4 d, 8 H, *J* = 8.1 Hz, 2 C_6H_4), 7.99 (s, 1 H, H-6), 10.29 (s, 1 H, NH).

UV (MeOH): λ_{max} (ε) = 247 nm (54500).

Anal. Calcd for $C_{32}H_{32}ClIN_4O_6$ (731.0): C, 52.58; H, 4.41; N, 7.66. Found: C, 52.81; H, 4.43; N, 7.63.

5-Chloro-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-7*H*-pyrrolo-[2,3-*d*]pyrimidine-2,4-diamine (3b); Typical Procedure

A suspension of compound **15a** (1.5 g, 2.35 mmol) in dioxane (30 mL) and 25% NH_3/H_2O (80 mL) was introduced into an autoclave and stirred at 120 °C for 24 h. The clear solution was evaporated and the residue was subjected to flash chromatography (silica gel, column 4 × 16 cm, B → C). The main zone was collected and condensed to a colorless solid, which was crystallized from MeOH to yield colorless crystals of **3b** (596 mg, 85%). NMR data were identical to those obtained for the compound by synthetic route 1.

5-Bromo-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-7*H*-pyrrolo-[2,3-*d*]pyrimidine-2,4-diamine (3c)

As described for **3b**, the reaction was carried out with **15b** (1.5 g, 2.19 mmol) and 25% NH_3/H_2O (80 mL) in dioxane (30 mL). FC resulted in a colorless solid, which was crystallized from MeOH to give colorless crystals of **3c** (667 mg, 88%). NMR data were identical to those obtained for the compound by synthetic route 1.

7-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5-iodo-7*H*-pyrrolo-[2,3-*d*]pyrimidine-2,4-diamine (3d)

As described for **3b**, the reaction was carried out with **15c** (1.5 g, 2.05 mmol) and 25% NH_3/H_2O (80 mL) in dioxane (30 mL). FC resulted in a colorless solid, which was crystallized from MeOH to yield colorless crystals of **3d** (717 mg, 89%). NMR data are identical to those obtained for the compound by synthetic route 1.

4-Amino-5-chloro-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2-one (4b); Typical Procedure

To a stirred solution of compound **3b** (500 mg, 1.67 mL) in AcOH–H_2O (1:5; 40.0 mL), was added dropwise a solution of $NaNO_2$ (250 mg, 3.62 mmol) in H_2O (8.0 mL) at r.t. The stirring was continued for 30 min, and the pH of the dark solution was adjusted to 6.0 with 25% aq NH_3. The solution was applied to a Serdolit AD-4 column (4 × 20 cm, resin 0.1–0.2 mm; Serva, Germany), the column was washed with H_2O (200 mL), and the product was eluted with H_2O–*i*-PrOH (95:5, 500 mL). Compound **4b** was crystallized from the solvent as yellowish needles (306 mg, 61%); mp 223 °C (dec.); TLC (silica gel, E): R_f = 0.9.

^{1}H NMR (DMSO-d_6): δ = 2.03–2.10 (m, 1 H, H-2′), 2.25–2.36 (m, 1 H, H-2′), 3.44–3.51 (m, 2 H, 2 H-5′), 3.75–3.77 (m, 1 H, H-4′), 4.26–4.28 (m, 1 H, H-3′), 5.06–5.09 (m, 1 H, 5′-OH), 5.23 (d, 1 H, *J* = 3.9 Hz, 3′-OH), 6.25 (dd, 1 H, *J* = 6.5, 7.2 Hz, H-1′), 7.15 (br s, 3 H, H-6, NH_2), 10.77 (br s, 1 H, NH).

UV (MeOH): λ_{max} (ε) = 231 (27100), 263 (6500), 310 nm (6600).

Anal. Calcd for $C_{11}H_{13}ClN_4O_4$ (300.7): C, 43.94; H, 4.36; N, 18.63. Found: C, 43.75; H, 4.23; N, 18.39.

4-Amino-5-bromo-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2-one (4c)

As described for **4b**, the reaction was carried out in a mixture of **3c** (500 mg, 1.45 mmol) in AcOH–H_2O (1:5, 40.0 mL) and $NaNO_2$ (250 mg, 3.62 mmol) in H_2O (8.0 mL). The solution was applied to a Serdolit AD-4 column (4 × 20 cm, resin 0.1–0.2 mm; Serva, Germany). The column was washed with H_2O (150 mL), and the product was eluted with H_2O–*i*-PrOH (95:5, 500 mL). Compound **4c** was crystallized from the solvent as yellowish needles (325 mg, 65%); mp 220 °C (dec.); TLC (silica gel, E): R_f = 0.9.

^{1}H NMR (DMSO-d_6): δ = 2.00–2.08 (m, 1 H, H-2′), 2.25–2.33 (m, 1 H, H-2′), 3.50–3.51 (m, 2 H, 2 H-5′), 3.74–3.77 (m, 1 H, H-4′), 4.25–4.28 (m, 1 H, H-3′), 5.04–5.06 (m, 1 H, 5′-OH), 5.23 (d, 1 H, *J* = 3.9 Hz, 3′-OH), 6.25 (dd, 1 H, *J* = 5.8, 6.5 Hz, H-1′), 6.85 (br s, 2 H, NH_2), 7.21 (s, 1 H, H-6), 10.77 (br s, 1 H, NH).

UV (MeOH): λ_{max} (ε) = 232 (26800), 262 (5900), 310 nm (5800).

Anal. Calcd for $C_{11}H_{13}BrN_4O_4$ (345.2): C, 38.28; H, 3.80; N, 16.23. Found: C, 38.54; H, 3.72; N, 16.45.

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