7-Halogenated 7-Deazapurine 2′-Deoxyribonucleosides Related to 2′-Deoxyadenosine, 2′-Deoxyxanthosine, and 2′-Deoxyisoguanosine: Syntheses and Properties

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A series of 7-fluorinated 7-deazapurine 2′-deoxyribonucleosides related to 2′-deoxyadenosine, 2′-deoxyxanthosine, and 2′-deoxyisoguanosine as well as intermediates **4b**–**7b**, **8**, **9b**, **10b**, and **17b** were synthesized. The 7-fluoro substituent was introduced in 2,6-dichloro-7-deaza-9*H*-purine (**11a**) with *Selectfluor* (*Scheme 1*). Apart from 2,6-dichloro-7-fluoro-7-deaza-9*H*-purine (**11b**), the 7-chloro compound **11c** was formed as by-product. The mixture **11b**/**11c** was used for the glycosylation reaction; the separation of the 7-fluoro from the 7-chloro compound was performed on the level of the unprotected nucleosides. Other halogen substituents were introduced with *N*-halogenosuccinimides (**11a** → **11c**–**11e**). Nucleobase-anion glycosylation afforded the nucleoside intermediates **13a**–**13e** (*Scheme 2*). The 7-fluoro- and the 7-chloro-7-deaza-2′-deoxyxanthosines, **5b** and **5c**, respectively, were obtained from the corresponding MeO compounds **17b** and **17c**, or **18** (*Scheme 6*). The 2′-deoxyisoguanosine derivative **4b** was prepared from 2-chloro-7-fluoro-7-deaza-2′-deoxyadenosine **6b** *via* a photochemically induced nucleophilic displacement reaction (*Scheme 5*). The pK_a values of the halogenated nucleosides were determined (*Table 3*). ^{13}C-NMR Chemical-shift dependencies of C(7), C(5), and C(8) were related to the electronegativity of the 7-halogen substituents (*Fig. 3*). In aqueous solution, 7-halogenated 2′-deoxyribonucleosides show an approximately 70% *S* population (*Fig. 2* and *Table 1*).

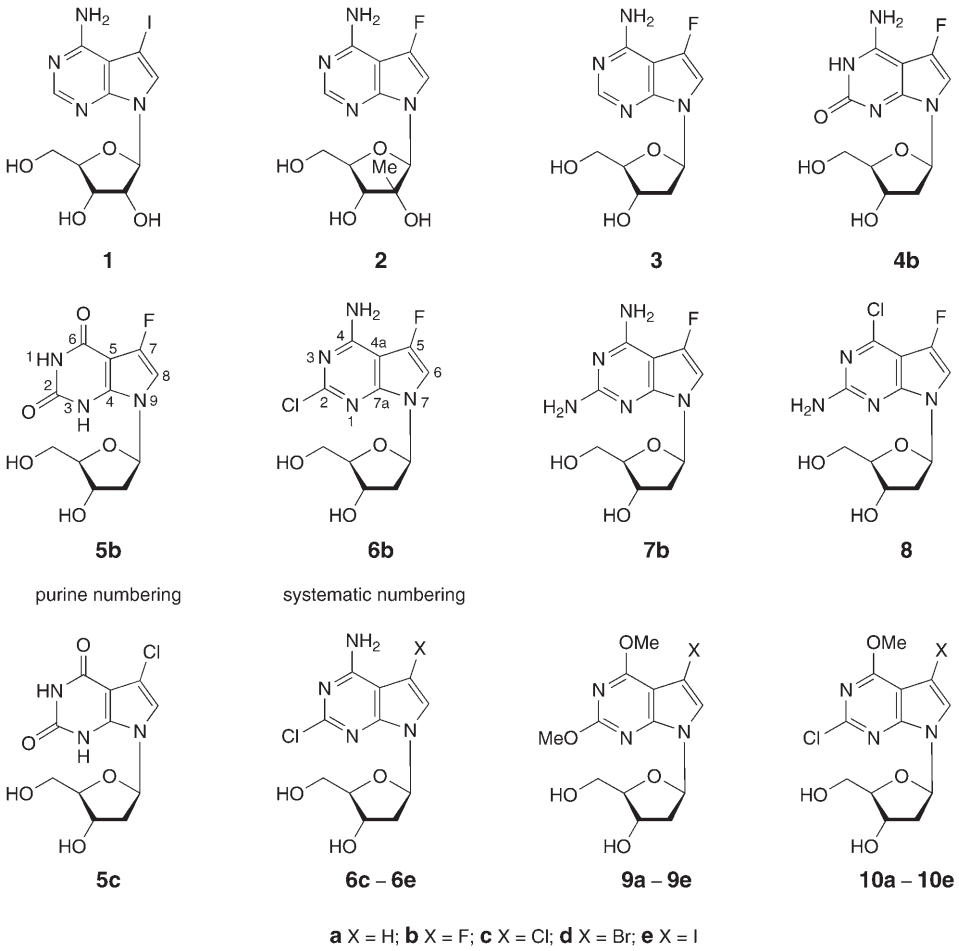
Introduction. – The 7-halogenated 7-deazapurine (pyrrolo[2,3-*d*]pyrimidine) nucleosides have gained attention since some of them exhibit a broad spectrum of biological activity [1–10]. The 7-iodotubercidin (**1**) (purine numbering is used throughout the general section) is a potent inhibitor of adenosine kinase [11][12]. The 2′-*C*-methyl derivative **2** of 7-fluorotubercidin is one of the most potent and selective inhibitors of HCV polymerase [13]. The 7-fluorinated 2′-deoxytubercidin **3** and its 2′-fluoroarabinofuranosyl derivative [14] were synthesized, and X-ray analyses were performed showing the influence of the fluoro substituent on the nucleoside conformation [15][16]. Several halogenated pyrrolo[2,3-*d*]pyrimidine nucleosides have been incorporated into oligonucleotides enhancing DNA-duplex stability compared to their unmodified counterparts [17–19]. The synthesis and properties of 7-deazapurine ribonucleosides and 7-deazapurine 2′-deoxyribonucleosides have been reviewed recently [20].

Although a series of 7-halogenated 7-deazapurine 2′-deoxyribonucleosides have been already synthesized [21–28], the number of 7-fluorinated compounds is limited

[14][29]. As the F-atom is the substituent with the highest electronegativity (3.98 *vs.* 3.44 of the O-atom) [30] but with the smallest size [31] of the halogen substituents, various positive effects on the biological activity of nucleosides are observed [13][32]. Thus, we became interested in 7-fluorinated 7-deazapurine nucleosides related to 2′-deoxyisoguanosine, 2′-deoxyxanthosine, 2-amino-2′-deoxyadenosine, and 2-chloro-2′-deoxyadenosine which are all unknown.

Earlier, we have shown that 2-substituents introduced into purine and 7-deazapurine nucleosides change the base-paring properties due to the presence of a bulky 2-substituent or the absence of the N(7)-atom [33][34], a phenomenon which has been also recognized by others [35][36]. So, 2-halogenated 7-deazapurines neither form *Watson–Crick* nor *Hoogsteen* base pairs [33]. Here, we report the 7-fluorination of the 2,6-dichloro-7-deazapurine and its stereoselective glycosylation giving access to the 7-fluorinated nucleosides **4b**–**6b**, **9b**, and **10b** related to 2′-deoxyisoguanosine, 2′-deoxyxanthosine, and 2-chloro-2′-deoxyadenosine, while the 7-fluorinated 2-amino-2′-deoxyadenosine related **7b** and the intermediate **8** were prepared from an already known precursor [14]. The 7-halogenated 7-deazapurine 2′-deoxynucleosides **5c**, **6c**–**6e**, **9c**–**9e**, and **10c**–**10e** containing chloro, bromo, or iodo substituents were also synthesized as well as the corresponding 7-nonfunctionalized compounds **6a** [25], **9a** [37], and **10a**. The spectroscopic and physicochemical properties, which include pK_a data and the influence of the electronegativity of the 7-halogen substituents on the ^{13}C-NMR chemical shifts of the 7-deazapurine moieties, are reported. The sugar conformation of the halogenated nucleosides is determined in aqueous solution by using the ^3J(H,H) coupling constants and applying the program PSEUROT [38].

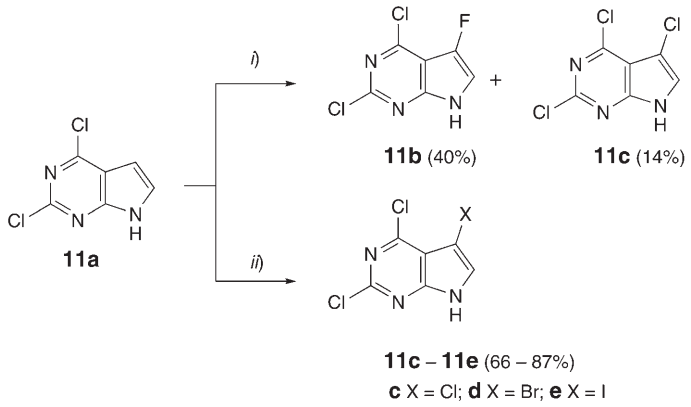
Results and Discussion. – 1. *Synthesis of 7-Halogenated 7-Deazapurine 2′-Deoxyribonucleosides.* The 7-halogenated 7-deazapurine nucleosides can be prepared either by the regioselective halogenation of an appropriately protected nucleoside [20][39] or from a halogenated 7-deazapurine which is glycosylated afterwards [14][40]. Here, the halogenation was performed on the nucleobase level. The 2,6-dichloro-7-deazapurine (**11a**) [41] (*Scheme 1*) was chosen as the starting material, since the selective displacement of the chloro substituents makes various NH_2- and OH-substituted derivatives accessible. Moreover, it was expected that a 7-fluoro substituent, as in **11b**, can be introduced by an electrophilic fluorination of compound **11a** with the hazard-free source *Selectfluor* [42a] in a similar manner as it was already reported for the 6-chloro-7-deazapurine (=4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine) [32]. However, the reaction conditions employed for 6-chloro-7-deazapurine (20% AcOH/MeCN (1:5), 70°, 14 h) [32] led to the decomposition of **11a**. Thus, the fluorination reaction was investigated in more detail leading to the observation that much milder conditions (50–60°, 5 h, and 10% AcOH/MeCN (1:10)) had to be employed. However, in all cases the formation of compound **11b** was inevitably accompanied by the chloro compound **11c**. Therefore, a mixture of **11b**/**11c** was obtained in yields of around 54% with an **11b**/**11c** ratio of 3:1 (*Scheme 1*). This ratio was determined by ^{1}H- and ^{13}C-NMR spectra as well as HPLC analysis (*Fig. 1*). At first, we thought that the starting material **11a** contains already the trichloro compound **11c** as both compounds show similar retention factors on TLC. However, according to the ^{1}H-NMR spectrum, only traces of **11c** could be detected in the reaction mixture purified by flash



chromatography. Thus, the main amount of the corresponding protected trichloro nucleoside **11c** must be formed during the fluorination reaction. It is likely that the introduction of the 7-chloro substituent results from a partial decomposition of the starting material **11a** which together with the fluorination reagent (*Selectfluor*) can form electrophilic Cl^+, a route which has been described for other cases [42a]. As compounds **11b** and **11c** can hardly be separated on a preparative scale employing flash column chromatography or recrystallization, the nucleobase mixture **11b**/**11c** was used for the glycosylation procedure without further purification. An analytical amount of pure **11b** was obtained after HPLC purification (*Exper. Part*). Other halogen substituents (Cl, Br, and I) were introduced selectively into the 7-position of **11a** employing *N*-halogenosuccinimides to yield the halogenated bases **11c** – **11e** in 66 – 87% yields (*Scheme 1*).

Next, the nucleobase-anion glycosylation [23][42b] of **11a** – **11e** was performed. The reactions were carried out under standard conditions with 2-deoxy-3,5-di-*O*-(4-

Scheme 1



i) Selectfluor, MeCN, AcOH, 60°. *ii*) NCS, DMF (→**11c**), NBS, CH_2Cl_2 (→**11d**), or NIS, CH_2Cl_2 (→**11e**).

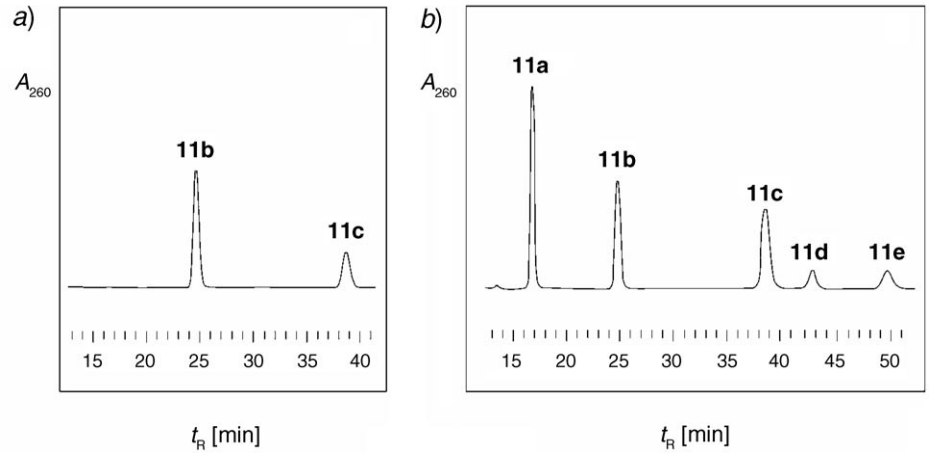
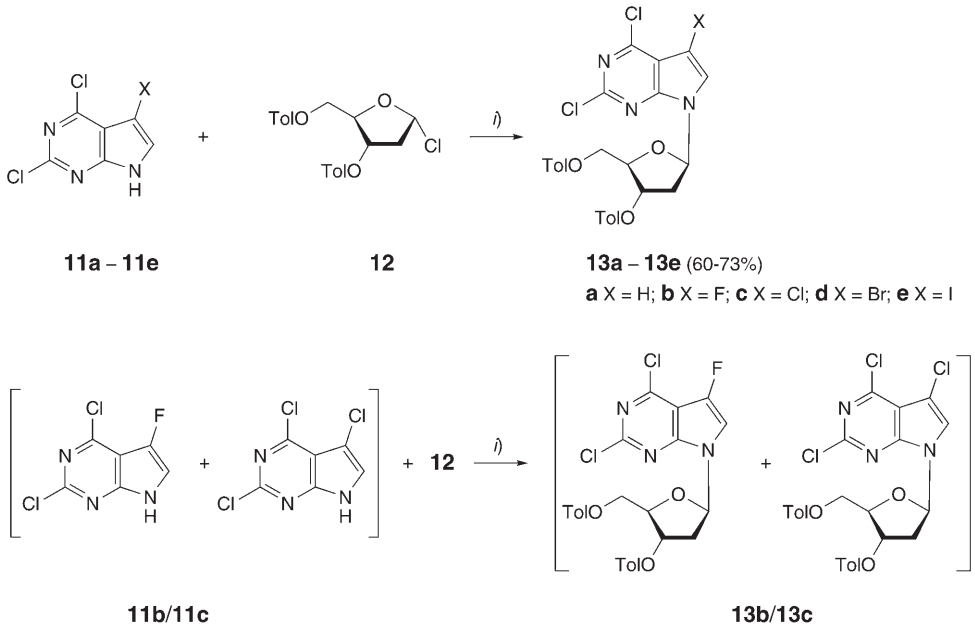


Fig. 1. *Reversed-phase HPLC* (*RP-18*) *profiles of* a) *products obtained from the fluorination reaction;* b) *an artificial mixture of compounds* **11a**–**11e**. The mixtures were analyzed by reversed-phase HPLC at 260 nm on a *RP-18* column (250 × 4 mm). Gradient: 30% MeCN, 70% buffer (buffer: 0.1M $Et_3NH \cdot OAc$ (pH 7.0)/MeCN 95 : 5). Flow rate 0.7 ml/min.

toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**12**) [43] as sugar component, MeCN as solvent, and powdered KOH/TDA-1 (TDA-1 = tris[2-(2-methoxyethoxy)ethyl]amine) to generate the nucleobase anion. The protected nucleosides **13a**–**13e** were isolated in 60–73% yield (*Scheme 2*). For the preparation of sufficient amounts of **13b**, a mixture **11b**/**11c** was glycosylated as described above to yield **13b**/**13c** which was used for the deprotection procedures without further purification (*Scheme 2*; *Exper. Part*).

From the intermediates **13b**/**13c**, the 7-fluorinated 2′-deoxyisoguanosine and 2′-deoxyxanthosine derivatives were prepared. For that, the NH_2 and MeO groups had to

Scheme 2

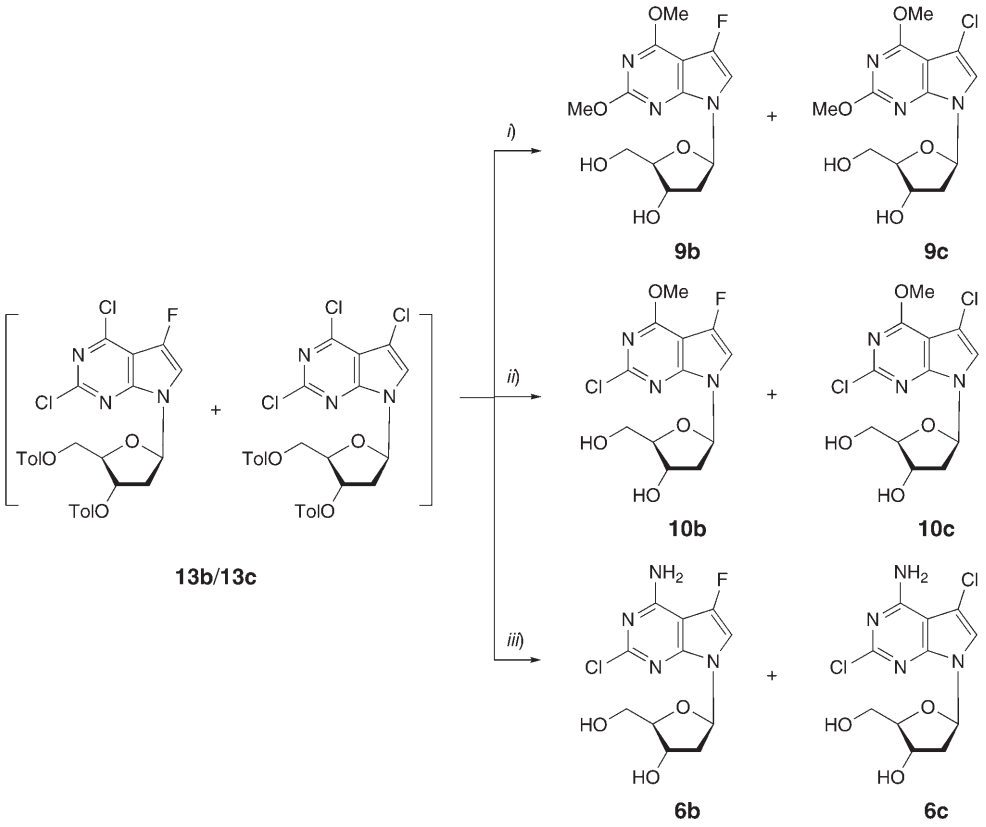


be introduced. Thus, the nucleosides **13b**/**13c** were deprotected in MeONa/MeOH or NH_3/MeOH (*Scheme 3*). Treatment of **13b**/**13c** in 0.5M MeONa at 60° (autoclave) afforded the dimethoxy nucleosides **9b** and **9c**, which were separated from each other by flash chromatography. When **13b**/**13c** was treated with NH_3/MeOH (sat. at 0°) at room temperature overnight, the monomethoxy compounds **10b** and **10c** were obtained. Treatment with NH_3/MeOH (100°, autoclave) converted **13b**/**13c** to the 2-chloro-2′-deoxyadenosine derivatives **6b** and **6c**. The fluoro compounds (**b** series) and chloro derivatives (**c** series) were isolated in a ratio of *ca.* 3:1. The exact individual yields of the free nucleosides were determined on the basis of the F/Cl contents of the starting material, the overall yield was in the range of 80–90%, slightly changing according to the 3:1 ratio of the staring material **13b**/**13c** (*Scheme 3*).

In the same way as described for the fluoro and chloro compounds, the other halogenated and the nonfunctionalized intermediates **13a** and **13c**–**13e** were converted to the corresponding free nucleosides **6**, **9**, and **10** as shown in *Scheme 4*. In the case of the conversion **13a** → **10a**, compound **10a** (48%) was formed together with **14** (30%). Therefore, the 6-chloro substituent can partially be retained under these conditions when no halogen atom is present at the 7-position. On the contrary, the 7-halogenated nucleosides **13b**–**13e** were always displaced at the 6-position (*Schemes 3* and *4*).

To access the 'isoguanosine' derivatives, 2,6-diamino nucleosides are normally used as starting materials which undergo NH_2 → OH displacement by selective diazotization at the 2-position [40]. However, attempts to prepare the 2,6-diamino compound **7b**

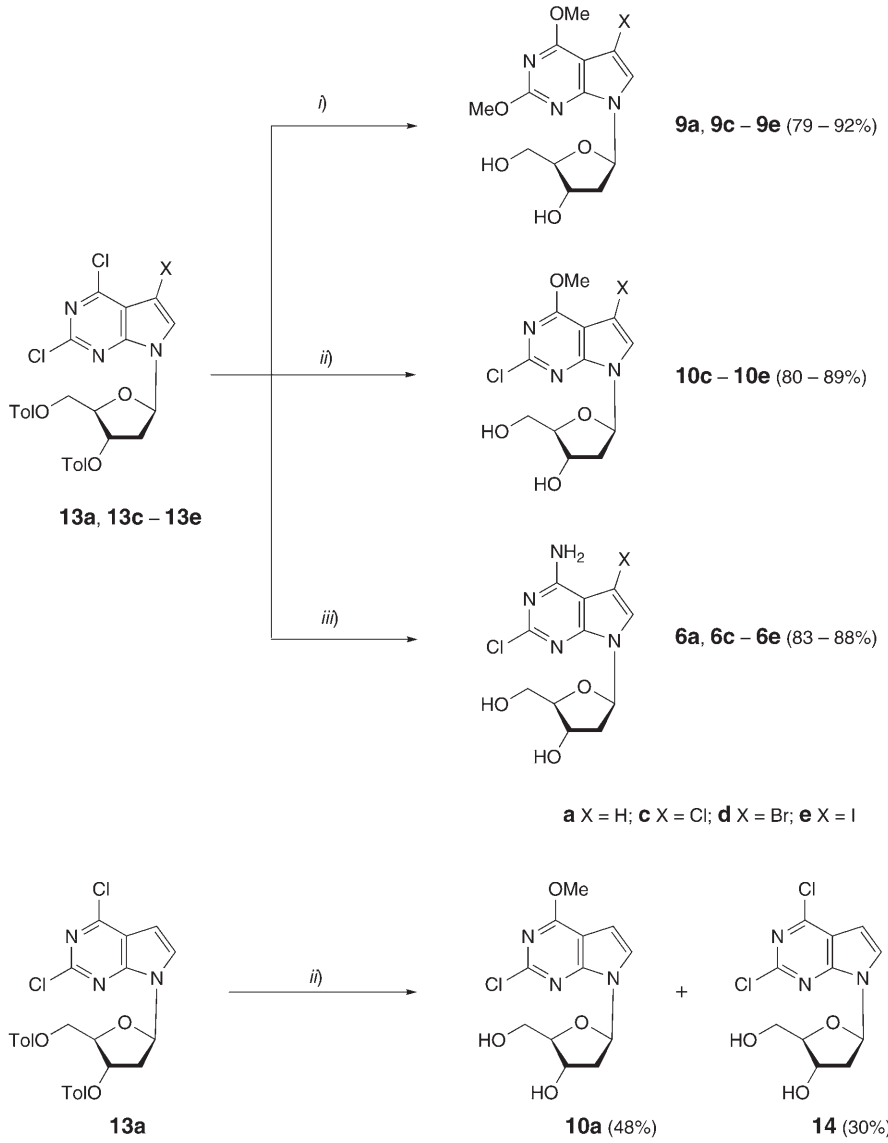
Scheme 3



i) 0.5M MeONa, 60°, overnight. *ii*) NH_3/MeOH, r.t., overnight. *iii*) NH_3/MeOH, 100°, 12 h.

from compound **13b** encountered difficulties. As described above, treatment of **13a**–**13e** with NH_3/MeOH (sat. at 0°) can only displace the 6-Cl substituent by a MeO or NH_2 group, leaving the 2-chloro substituent untouched (→**10** and **6**). Efforts to complete the reaction by increasing the temperature, prolonging the reaction time, or employing aqueous NH_3 solution resulted in no further conversion. Thus, we chose another starting material, namely compound **15** [14] (*Scheme 5*). For the displacement of the 6-chloro substituent by an NH_2 group, harsh conditions are required. Treatment with NH_3/MeOH or NH_3/H_2O in a steel vessel at elevated temperature removes the pivaloyl protecting group accompanied by the displacement of the 6-choro substituent. These reaction conditions worked well with other halogenated derivatives [40][44] but failed to access compound **7b** due to decomposition. Thus, conditions were elaborated (70°, 5 d) to perform the reaction without significant decomposition of the molecule. Under those moderate conditions, compound **7b** was formed together with **8** and **16** as by-products (*Scheme 5*). Unfortunately, the selective $NH_2 \rightarrow OH$ exchange on compound **7b** failed as the acidic diazotization conditions led to the decomposition

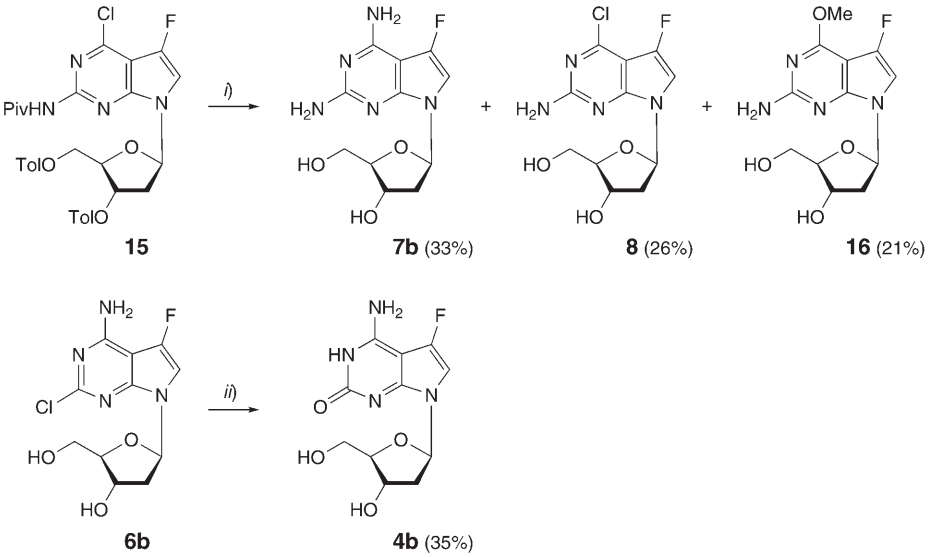
Scheme 4



i) 0.5M MeONa, 60°, overnight. *ii*) NH_3/MeOH, r.t., overnight. *iii*) NH_3/MeOH, 100°, overnight.

of the nucleosides. Therefore, another approach was chosen. As reported earlier, isoguanine nucleosides are accessible from 2-halogenated adenosine derivatives by a photochemically catalyzed nucleophilic displacement reaction [45]. Consequently, the 7-fluorinated nucleoside **6b** was irradiated in aqueous solution in a quartz reactor for

Scheme 5

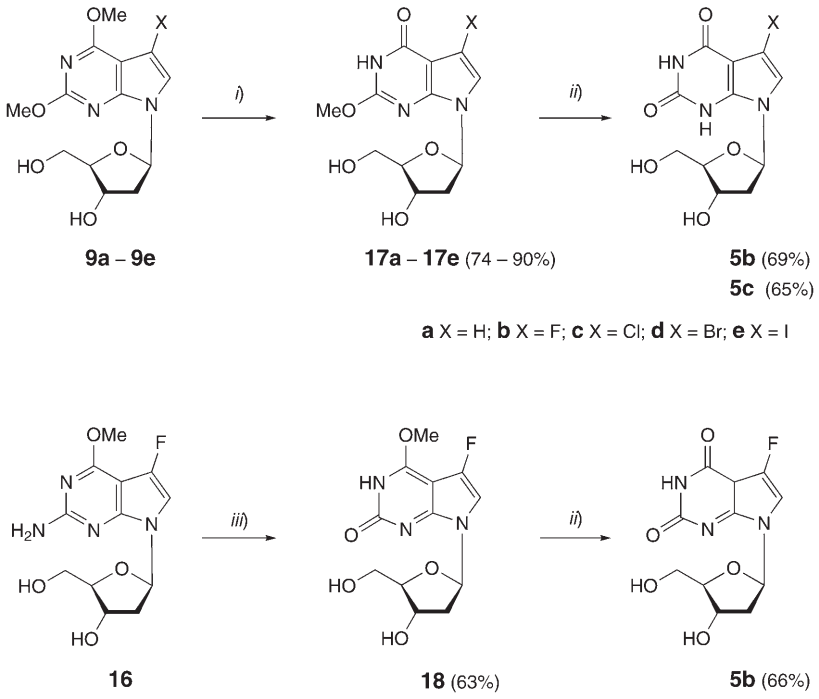


i) NH_3/MeOH, 70°, 5 d. *ii*) 0.1% NH_3/H_2O, *hv*.

1 h. Purification by means of a *Serdolit-AD-4* column afforded nucleoside **4b** in 35% yield (*Scheme 5*).

Next, the conversion of **9b** and **9c** into the xanthosine derivatives **5b** and **5c** was studied. Different protocols have been described for the conversion of the MeO to C=O groups in nucleosides: *a*) acidic cleavage, HBr/AcOH in absolute THF [37]; *b*) Me_3SiCl/NaI in MeCN [46]; *c*) 2N NaOH, reflux [46]. Efforts to use protocols *a*) and *b*) for the cleavage of **9b** failed due to the decomposition of the compounds. Therefore, **9b** was treated according to protocol *c*) with 2N NaOH under reflux to yield a new product, **17b**. NMR Spectra (see *Exper. Part* and *Table 4* (below)) showed that this compound still carries one MeO group but is different from the 6-methoxy compound **18** (*Scheme 6*). Thus, the structure of a 2-methoxy nucleoside was assigned to **17b**. Extension of the reaction time did not improve the situation. In the same way, the dimethoxy compounds **9a** and **9c**–**9e** were converted into the corresponding monomethoxy derivatives **17a** and **17c**–**17e** (*Scheme 6*). With only one MeO group, compound **17b** is more likely to be converted to **5b** by using protocol *b*) compared to **9b** which has two MeO substituents. Protocol *b*) was successfully employed for compounds **17b** and **17c**. Milder conditions (lower concentration of the reactant, see *Exper. Part*) must be used to avoid the decomposition and halogen exchange as reported [46]. Compounds **5b** and **5c** were obtained in 69 and 65% yields, respectively (*Scheme 6*). This reaction carried out under the same conditions was also performed with compound **18** as starting material which was obtained from **16** [14] by diazotization (63%). The monomethoxy nucleoside **18** was converted to **5b** in 66% yield (*Scheme 6*).

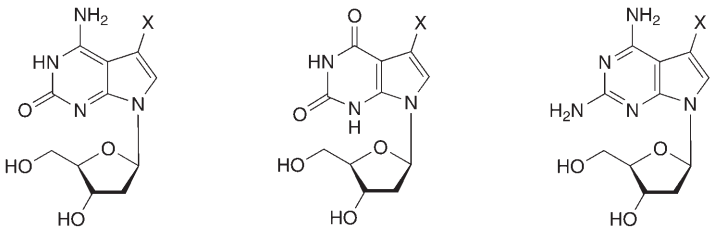
Scheme 6



i) 2N NaOH, reflux. *ii*) Me_3SiCl, NaI, MeCN. *iii*) $NaNO_2$, AcOH.

2. *Conformational Analysis.* The conformation of oligonucleotides is believed to depend strongly upon the conformation of the nucleotide monomers that constitute them. Thus, a conformational analysis of the sugar moiety of nucleosides **5a**–**5e** and **7a**–**7e** 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 coupling constants 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 in aqueous solution (*Fig. 2*) [47]. The input contained the following coupling constants: *J*(1′,2′), *J*(1′,2″), *J*(2′,3′), *J*(2″,3′), and *J*(3′,4′) (2″ = short form of H′–C(2′)). 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 and the pseudorotational parameters are shown in *Table 1*. From the data given in *Table 1*, it is apparent that all nucleosides are in the $N \rightleftharpoons S$ equilibrium in aqueous solution showing a preferred *S* (71–74% *S*) conformer population. Halogenation bias the equilibrium slightly towards *N*. However, little difference was observed for the various halogen-substituted nucleosides.

3. *UV/VIS Spectra and p*K_a *Values.* All compounds are characterized by UV/VIS spectra (*Table 2* and *Exper. Part*). The UV/VIS spectra of compounds **9a**–**9e**, **10a**–**10e**, **11a**–**11e**, and **17a**–**17e** were measured in MeOH and indicate that 7-halogen



a X = H; **b** X = F; **c** X = Cl; **d** X = Br; **e** X = I

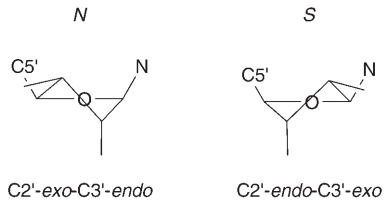


Fig. 2. N *and* S *Conformation of the Nucleosides*

Table 1. *^3J(H,H) Coupling Constants of the Sugar Moiety and Conformer Population of Nucleosides*[a])

	^3J(H,H) [Hz]					Pseudorotational parameters[b])				
	1′,2′	1′,2″[c])	2′,3′	2″,3′[c])	3′,4′	% *N*	% *S*	P_S [°]	Ψ_S [°]	rms [Hz]
5a	6.90	6.31	6.22	2.89	2.90	26	74	168.0	29.1	0.35
5b	6.92	6.53	6.18	3.22	3.20	29	71	165.8	29.6	0.22
5c	7.17	6.47	6.07	3.16	3.09	28	72	165.4	30.8	0.19
5d	7.05	6.60	6.40	3.20	3.10	28	72	162.9	28.4	0.18
5e	6.89	5.90	5.81	2.75	3.00	27	73	168.3	31.8	0.53
6a	7.64	6.43	6.16	2.89	3.34	26	74	152.7	31.0	0.14
6b	7.00	6.51	6.51	3.04	3.25	27	73	158.0	27.6	0.24
7a	7.64	6.43	6.16	2.89	3.34	26	74	152.7	31.0	0.14
7b	7.75	6.31	6.27	3.13	3.43	27	73	148.9	32.4	0.09
7c	6.99	6.57	6.54	3.13	3.52	28	72	153.3	27.6	0.20
7d	6.92	6.46	6.52	3.18	3.54	29	71	153.5	28.1	0.25
7e	6.99	6.62	6.52	3.18	3.49	28	72	154.7	27.6	0.17
8	6.99	6.81	6.60	3.26	3.52	28	72	154.3	26.8	0.10

[a]) Measured in D_2O at 25°. [b]) $P_N = 18°$ and $\Psi_N = 38°$ were fixed during the final minimization. [c]) 2″ = short form of H′–C(2′).

substituents induce a bathochromic shift of *ca.* 1–13 nm (*Table 2*) as in 7-deazaadenosines and 7-deazainosines [48]. The spectra of compounds **9a** and **9c**–**9e** show two peaks in the range of 260–280 nm which are poorly resolved. In the case of the fluoro compound **9b**, there is only one broad peak with an absorbance maximum at 269 nm.

Moreover, it is also interesting to notice that the Cl-, Br-, and I-substituents reduce the extinction coefficient of the nucleosides as observed in other cases [48], while the F-substituent enhances the absorbance, especially in nucleosides **9b** and **10b** (*Table 2*).

Table 2. *UV Absorption Maxima and Extinction Coefficients of Nucleosides and Bases*[a])

	λ_{max} (ε)		λ_{max} (ε)
9a	257 (7500), 272 (7800)	**11a**	289 (4100)
9b	269 (20100)	**11b**	302 (3900)
9c	264 (5900), 273 (6100)	**11c**	305 (3100)
9d	264 (6100), 274 (6300)	**11d**	307 (2900)
9e	264 (7300), 275 (7700)	**11e**	312 (2600)
10a	271 (8500)	**17a**	255 (9500)
10b	273 (26100)	**17b**	255 (10000)
10c	282 (6500)	**17c**	258 (8800)
10d	281 (6900)	**17d**	259 (9500)
10e	284 (5800)	**17e**	261 (8400)

[a]) Measured in MeOH at 25°.

Protonation and deprotonation influence base-pairing selectivity and mismatch formation of DNA and RNA duplexes. The addition of a phosphate to form nucleotides raises the nucleoside pK_a values by 0.2–0.6 pH units. In oligonucleotides, a further increase is observed. The negatively charged phosphate group attracts the ionizable proton and thus raises the pK_a. Therefore, pK_a values of the nucleosides **4**–**8** and **14** were determined by spectrophotometric titration [49] (pH 1.0–13.5) at 220–400 nm. As shown in *Table 3*, xanthosine derivatives are already deprotonated under slightly acidic conditions (pK_a 6.2 for **5b** and 6.1 for **5c**), the 2-chloroadenosine derivatives have very low pK_a values for protonation (2.0 for **6a** and 1.6 for **6b**–**6e**). The pK_a value of the dichloro nucleoside **14** is even lower and cannot be detected in aqueous solution. In contrast, the pK_a value of the diamino compound **7b** (5.0) is in the range of that of 2′-deoxytubercidin (5.08 [14]), while that of the 2-amino-6-chloro derivative **8** is significantly lower (4.2). Thus, as expected, electron-donating substituents such as the 2-amino group increase the basicity of the 7-deazapurine moiety, while a 2-chloro group

Table 3. *p*K$_a$ *Values of the Nucleosides*[a])[b])

	Wavelength [nm]	pK_a[c])[d])		Wavelength [nm]	pK_a[c])
4a	305	4.6, 10.5	**6a**	232	2.0
4b	279	3.6, 10.1	**6b**	234	1.6
5a	255	6.7	**6c**	239	1.6
5b	257	6.2	**6d**	240	1.6
5c	259	6.1	**6e**	312	1.6
7a	230	5.7	**8**	310	4.2
7b	234	5.0	**14**	248	< 1

[a]) Measured in phosphate buffer (0.1M NaH_2PO_4) from pH 1 to pH 13. [b]) Wavelength with the most significant absorbance change. [c]) Protonation. [d]) Deprotonation.

reduces the basic character. In the case of the related antimalignant 2-chloro-2′-deoxyadenosine (pK_a 1.4), a similar trend was observed [50]. However, this molecule became extremely labile under acidic condition as the protonation site changed from N(7) to N(1). This is not observed for compound **6a** which is extraordinarily stable, due to the pyrrolo[2,3-*d*]pyrimidine system. The X-ray structure of compound **4a** shows that the molecule adopts the H–N(1), C(2)=O form as indicated in the formula [51]. The 7-halogen substituents decrease the pK_a values of the functionalized compounds compared to those of nonfunctionalized nucleosides (**5a**–**5c** and **6a**–**6e**).

4. *NMR Spectra and Influence of the 7-Substituent Electronegativity on ^{13}C-NMR Chemical Shifts.* The nucleosides and the intermediates were characterized by ^{1}H-, ^{13}C-, and ^{19}F-NMR spectra as well as by elemental analysis or mass spectra. The ^{13}C-NMR chemical shifts of all new compounds, were measured in (D_6)DMSO apart from **13a**–**13c** and **13e** which were measured in $CDCl_3$ due to their poor solubility in (D_6)DMSO (*Table 4*). The δ(C) of the 7-unsubstituted compounds **6a**, **9a**, **11a**, and **13a** were assigned according to references [25][37][41] which report the corresponding chemical shifts. The C-atoms of the 7-halogenated heterocycles were assigned according to the influence of the halogen substituents as well as on the basis of ^{1}H/^{13}C-NMR gated-decoupled spectra. The chemical shifts of the sugar moieties of the deprotected nucleosides were assigned according to [20][46] and on the basis of ^{1}H/^{13}C-NMR gated-decoupled spectra of compounds **10b** and **10d** (*Table 5*).

Table 4 shows that the 7-halogen substituents shifts the C(5), C(7), and C(8) signals significantly, while other C-atoms are not affected. Compared to the non-functionalized base or nucleosides (**a** series), the C(7) signals of the 7-fluoro derivatives (**b** series) are shifted strongly downfield (by *ca.* 40 ppm), while the 7-chloro compounds (**c** series) show only minor downfield shifts of 3–5 ppm. The other halogen substituents induce upfield shifts of 12–13 ppm for the bromo compounds (**d** series) and of 47–49 ppm for iodo derivatives (**e** series). This trend is also observed for other ring systems such as for 5-halogenated uracil derivatives [52] and 7-halogenated inosine derivatives [48]. The atoms C(5) and C(8) also experience chemical shift changes due to the halogen substituents. The F-substituent biases the C(5) signals upfield by *ca.* 10 ppm and C(8) by 17.5 ppm. Other halogen atoms induce chemical-shift changes of C(5) and C(8), *e.g.*, a value of *ca.* 2–4 ppm is observed for Cl (upfield) and I (downfield).

A dependence of the chemical shifts on the electronegativity of the halogen substituents is observed. This is demonstrated for C(5), C(7), and C(8) in *Fig. 3.* The graphs correlate the chemical shifts *vs.* the electronegativity of the 7-halogen substituents for two series, compounds **6b**–**6e** (*Fig. 3*,*a*) and **10b**–**10e** (*Fig. 3*,*b*); a similar correlation is found for the other halogenated compounds (*Table 4*). The chemical shift of C(7) is increasing almost linearly with increasing electronegativity of the substituents. For C(8) and C(5), the effect is lower relative to that of C(7). Additionally, the chemical shifts of C(8) and C(5) decrease linearly with increasing electronegativity of the C(7) substituents.

To confirm the position of halogenation (C(7) *vs.* C(8)), the ^{13}C,^{19}F coupling constants J(C,F) of the fluorinated compounds were calculated (*Table 5*). Moreover, gated-decoupled ^{1}H/^{13}C-NMR spectra of the 7-fluoro nucleoside **10b** and 7-bromo compound **10d** which were selected as representative examples were measured. The

Table 4. *^{13}C-NMR Chemical Shifts* (δ [ppm]) *of Nucleosides and Precursors*[a])[b])

	C(2)[c]) C(2)	C(6)[c]) C(4)	C(5) C(4a)	C(7) C(5)	C(8) C(6)	C(4)[c]) C(7a)	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)
11a [41]	150.9	150.1	115.8	99.4	129.5	152.8	–	–	–	–	–
11b	150.9	147.6	104.9	140.0	112.1	149.3	–	–	–	–	–
11c	151.6	150.6	112.0	102.3	127.1	150.9	–	–	–	–	–
11d	152.0	150.7	113.1	86.6	129.6	150.9	–	–	–	–	–
11e	152.7	150.2	115.1	52.6	134.7	151.4	–	–	–	–	–
13a[d])	152.0	152.2	117.0	101.5	126.6	152.8	84.2[c])	38.5	75.0	82.7[c])	64.2
13b[d])	153.1	147.5	106.6	141.9	109.1	151.5	84.3[c])	38.5	74.8	82.8[c])	64.0
13c[d])	150.7	150.7	113.3	106.4	123.6	152.8	84.3[c])	38.7	74.9	83.0[c])	63.9
13d	151.2	151.6	114.0	88.5	126.5	151.6	83.8	36.3	74.6	81.8	64.0
13e[d])	152.3	151.5	116.3	53.4	131.8	153.6	84.5[c])	38.8	75.0	83.1[c])	64.0
9a [37]	161.0	163.4	100.2	98.8	122.3	152.9	82.9	39.4	70.9	87.1	61.9
9b	161.6	162.8	90.6	142.1	104.5	148.6	82.5	[e])	70.9	87.3	61.9
9c	161.5	163.6	98.1	103.2	119.5	151.8	82.9	[e])	71.0	87.5	61.9
9d	161.3	163.6	99.4	87.1	121.9	152.3	82.9	[e])	70.9	87.5	61.8
9e	161.0	163.6	101.9	51.8	127.1	152.9	82.8	[e])	70.9	87.4	61.8
10a	152.1	162.9	104.0	99.4	125.1	151.0	83.1	[e])	70.9	87.5	61.8
10b	152.0	162.1	93.9	141.5	107.6	147.3	82.7	[e])	70.7	87.6	61.7
10c	150.6	162.8	101.6	103.3	122.1	151.9	83.1	[e])	70.7	87.7	61.6
10d	151.6	162.9	103.0	87.1	124.6	151.2	83.2	[e])	70.7	87.7	61.6
10e	151.3	162.9	105.6	52.1	129.6	152.0	83.1	[e])	70.7	87.6	61.6
17a	155.2	159.3	102.7	103.0	119.2	147.7	82.8	[e])	71.2	87.3	62.1
17b	155.5	157.2	92.7	145.4	101.5	143.7	82.4	[e])	71.0	87.4	61.9
17c	155.7	157.9	99.9	106.6	116.2	146.8	82.7	[e])	71.0	87.5	61.9
17d	155.7	158.3	101.5	90.9	118.9	147.5	82.9	[e])	71.2	87.6	62.0
17e	155.2	158.3	102.8	54.7	123.9	147.7	82.7	[e])	71.0	87.5	61.9
4a [24]	153.9	156.0	92.6	100.8	118.9	152.6	83.4	[e])	71.1	87.2	62.0
4b	153.5	156.2	[f])	144.2	100.6	[f])	82.5	[e])	71.1	87.2	62.1
5a [37]	150.7	159.5	99.4	103.1	117.6	138.0	85.5	40.0	70.8	87.3	61.4
5b	150.5	157.7	89.5	145.7	99.9	134.8	85.1	[e])	70.6	87.4	61.4
5c	150.6	158.4	96.3	107.3	114.7	137.9	85.5	[e])	70.7	87.6	61.4
6a [17]	150.3	158.2	101.3	99.9	121.6	152.6	82.7	38.5	70.8	87.1	61.8
6b	153.8	156.7	91.0	142.7	104.4	146.3	82.2	[e])	70.8	87.3	61.8
6c	149.4	157.6	98.5	103.6	119.2	153.6	82.7	[e])	70.8	87.5	61.7
6d	149.9	157.8	99.6	87.3	121.8	153.4	82.8	[e])	71.9	87.5	61.7
6e	150.6	158.2	101.8	52.6	127.1	152.9	82.7	[e])	70.8	87.5	61.7
7b	160.5	156.2	86.2	144.0	99.2	149.1	81.7	[e])	71.0	86.8	62.1
8	159.5	150.0	98.9	141.8	105.3	149.6	82.2	[e])	71.1	87.3	62.0
14	151.2	150.5	116.6	100.3	129.4	151.7	82.0	[e])	70.8	87.8	61.6
18	160.1	163.1	[f])	142.6	102.7	[f])	82.8	[e])	70.8	87.2	61.8

[a]) Measured in (D_6)DMSO at 25°. [b]) First heading row = purine numbering, second heading row = systematic numbering. [c]) Tentative. [d]) Measured in $CDCl_3$ at 25°. [e]) Superimposed by DMSO signal. [f]) Not detected.

^{19}F,^{13}C couplings indicate a ^1J(C(7),F–C(7)) value of *ca.* 250 Hz for all fluorinated compounds, and ^2J(C(8),F–C(7)) and ^2J(C(5),F–C(7)) amount to *ca.* 25 and 15 Hz, respectively. Moreover, for some compounds, *i.e.*, **6b**, **8**, **9b**–**10b**, **13b**, and **17b**, long-range couplings ^3J(C(4),F–C(7)) and ^3J(C(6),F–C(7)) are observed (*Table 5*). The

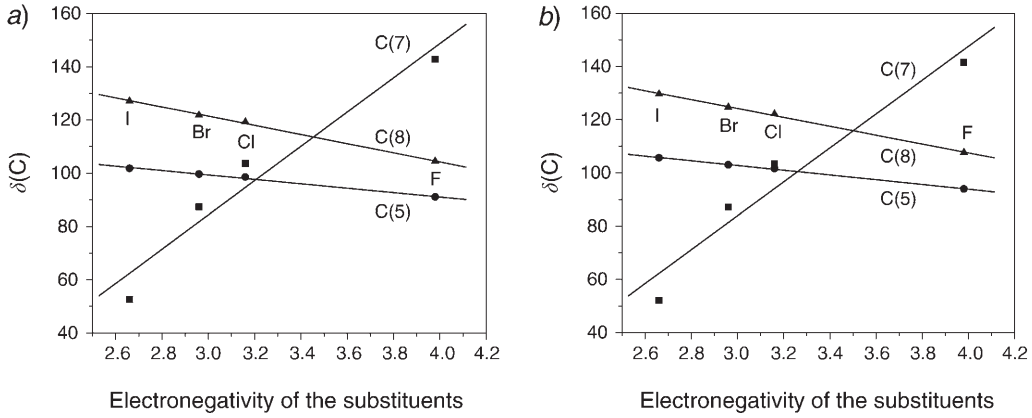


Fig. 3. *^{13}C-NMR Chemical shift of C(5), C(7), and C(8)* vs. *halogen-substituent electronegativity for* a) *compounds* **6b**–**6e**, *and* b) *compounds* **10b**–**10e**. Chemical-shift data from *Table 4* and electronegativity data from [30].

Table 5. *J(C,F) and J(C,H) Coupling Constants of 7-Halogenated Nucleosides*[a])[b])

	^1J(C(7),F–C(7))	^2J(C(8),F–C(7))	^2J(C(5),F–C(7))	^3J(C(4),F–C(7))	^3J(C(6),F–C(7))
4b	245.9	25.8	16.4	[d])	[d])
5b	245.6	26.9	16.7	[d])	[d])
6b	246.2	26.8	16.5	3.1	2.8
7b	243.5	26.9	16.9	[d])	1.7
8	247.5	27.4	15.9	3.7	1.7
9b	246.1	27.2	16.4	3.1	3.0
10b	247.6	26.8	15.8	2.8	3.2
11b	247.1	25.7	14.3	[d])	[d])
13b[c])	255.7	21.7	14.9	4.2	1.4
17b	245.4	26.8	14.0	3.4	2.8
18	245.5	24.7	16.0	[d])	[d])
	^1J(C(8),H–C(8))	^2J(C(7),H–C(8))	^3J(C(4),H–C(8))	^3J(C(4),H–C(1′))	^3J(C(8),H–C(1′))
10b	194.0	[d])	8.6	2.6	5.0
10d	196.1	3.5	8.2	2.5	4.8
	^3J(C(5),H–C(8))	^4J(C(6),H–C(8))	^1J(C(1′),H–C(1′))	^1J(C(4′),H–C(4′))	^1J(C(3′),H–C(3′))
10b	6.2	3.9	167.4	147.7	148.6
10d	6.9	4.1	167.2	147.3	149.1

[a]) Data taken from measurements in (D_6)DMSO at 25°. [b]) Data are given in Hz. [c]) Data taken from measurements in $CDCl_3$ at 25°. [d]) Not detected.

gated-decoupled spectra of **10b** and **10d** showed a three-bond coupling of the heterocyclic C(8) with the anomeric H–C(1′) with ^3J (C(8),H–C(1′)) of 5.0 (**10b**) and 4.8 (**10d**) Hz. Furthermore, the angular C-atom C(4) is coupled with H–C(8) by ^3J(C(4),H–C(8) values of 8.6 (**10b**) and 8.2 (**10d**) Hz. Therefore, position C(7) is confirmed as halogenation site. ^1J(C,H) coupling constants of sugar C-atoms are also

given in *Table 5*. The coupling constant for C(1′) is *ca.* 20 Hz larger than that of C(4′) and C(3′), due to the electron-withdrawing effect of the base moiety, a phenomenon observed in ribonucleosides by *Seela* and *Bussmann* [53]. For further coupling constants, see *Table 5*.

Conclusions. – A 7-fluoro substituent was introduced to 2,6-dichloro-7-deazapurine by *Selectfluor* affording a mixture **11b**/**11c** of the fluorinated and chlorinated nucleobases. It was not possible to perform the fluorination reaction without formation of the 7-chloro compound **11c** as by-product. As this mixture was difficult to separate, nucleobase-anion glycosylation reaction was performed with **11b**/**11c** yielding a mixture of the nucleosides **13b**/**13c**. The 2-chloro and 6-chloro substituents were displaced under simultaneous deprotection of the sugar moiety yielding a series of 7-deazapurine nucleosides related to 2-amino-2′-deoxyadenosine, 2′-deoxyxanthosine, and 2′-deoxyisoguanosine. The 7-fluorination induces instability of the nucleosides. Therefore, much milder conditions have to be used in these cases to avoid the decomposition of the molecules. Other halogen substituents were introduced to the same base, and various new 7-chloro, 7-bromo, and 7-iodo derivatives were synthesized. The 7-halogen substituents decrease the basicity of the 7-deazapurine nucleosides and bias the sugar conformation towards *N*, while UV/VIS data show an auxochromic effect of the halogen substituents. NMR Studies confirmed the halogenation position and showed that the chemical shifts of C(5), C(7), and C(8) have an almost linear dependency on the electronegativity of the halogen substituents.

Experimental Part

General. All chemicals were purchased from *Acros*, *Fluka*, or *Sigma-Aldrich*. Solvents were distilled from technical-grade solvents. The used petroleum ether had b.p. 40–60°. Quartz reactor: 30-W germicidal lamp (*Philips*, Netherlands). In the irradiation reaction, the light was passed through a 2-mm layer of 20% AcOH to avoid transmission below 230 nm. TLC: aluminium sheets, silica gel (SiO_2) *60* F_{254} (0.2 mm; *VWR International*, Darmstadt, Germany). Flash chromatography (FC): 0.4 bar, SiO_2 *60* (*VWR International*). M.p.: *Electrothermal 9200*; not corrected. UV Spectra: *U-3200* UV/VIS spectrometer (*Hitachi*, Japan); λ_{max} (ε) in nm. NMR Spectra: *Avance-PX-50* or *-DPX-300* spectrometers (*Bruker*, Germany); δ values in ppm rel. to Me_4Si as internal standard, *J* values in Hz. Elemental analyses: *Mikroanalytisches Laboratorium Beller*, Göttingen, Germany. ESI-TOF-MS: *MicrOTOF Bruker Daltonics* spectrometer; electropositive mode; in *m*/*z*.

*2,4-Dichloro-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**11b**). To a suspension of **11a** [41] (1.13 g, 6 mmol) and *Selectfluor* (3.18 g, 9 mmol) in anh. MeCN (60 ml) was added glacial AcOH (6 ml). The mixture was kept stirring at 60° and became clear gradually. After 5 h, the mixture was cooled to r.t. and diluted with CH_2Cl_2 (150 ml). The org. layer was washed with 5% aq. $NaHCO_3$ soln., dried (Na_2SO_4), and concentrated and the residue subjected to FC (SiO_2, 15 × 2.5 cm column, CH_2Cl_2/AcOEt 15:1): **11b**/**11c** (0.67 g, *ca.* 54%) as colorless solid which was used for the next step without further purification. An anal. sample (100 mg) of **11b**/**11c** was purified by HPLC (*RP-18* column (250 × 4 mm), MeCN/buffer 3:7 (buffer: 0.1M $Et_3NH \cdot OAc$ (pH 7.0)/MeCN 95:5), flow rate 0.7 ml/min). The fractions containing **11b** were concentrated, and the residue was subjected to FC (SiO_2, 8 × 2.5 cm column, CH_2Cl_2/AcOEt 15:1): **11b** (60 mg) as colorless solid which was recrystallized from CH_2Cl_2. Colorless needles. M.p. 234°. TLC (SiO_2, CH_2Cl_2/AcOEt 15:1): R_f 0.46. UV (MeOH): 230 (35400), 273 (3800), 302 (3900). ^{1}H-NMR ((D$_6$)DMSO): 7.76 (*s*, H–C(6)); 12.71 (*s*, H–N(7)). ^{19}F-NMR ((D$_6$)DMSO): –170.58. Anal. calc. for $C_6H_2Cl_2FN_3$ (206.00): C 34.98, H 0.98, N 20.40; found: C 35.42, H 1.03, N 19.95.

*2,4,5-Trichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**11c**). To a soln. of **11a** [41] (261 mg, 1.39 mmol) in anh. DMF (4 ml) was added *N*-chlorosuccinimide (NCS; 278 mg, 2.09 mmol). The mixture was stirred at r.t. for 2 d. The soln. was concentrated and the residue subjected to FC (SiO_2, 8 × 2.5 cm column), CH_2Cl_2/AcOEt 15:1): **11c** (203 mg, 6%) as colorless solid which was recrystallized from CH_2Cl_2. Colorless needles. M.p. 225°. TLC (SiO_2, CH_2Cl_2/AcOEt 15:1): R_f 0.46. UV (MeOH): 234 (27900), 274 (3300), 305 (3100). ^{1}H-NMR ((D$_6$)DMSO): 7.95 (*s*, H–C(6)); 12.94 (*s*, H–N(7)). Anal. calc. for $C_6H_2Cl_3N_3$ (222.46): C 32.39, H 0.91, N 18.89; found: C 32.60, H 1.03, N 18.90.

*5-Bromo-2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**11d**). To a suspension of **11a** [41] (564 mg, 3 mmol) in CH_2Cl_2 (20 ml) was added *N*-bromosuccinimide (NBS; 640 mg, 3.6 mmol). The suspension was stirred at r.t. overnight (TLC: complete conversion to **11d**). The solid was filtered and washed with CH_2Cl_2 (3 ml) to afford **11d** as pale yellow solid (320 mg). The filtrate was evaporated and the residue subjected to FC (SiO_2, column 8 × 2.5 cm, CH_2Cl_2/AcOEt 15:1) to afford another 230 mg of **11d** as colorless solid. The combined solid gave 550 mg (69%) of **11d** which was recrystallized from CH_2Cl_2. Colorless needles. M.p. 226°. TLC (SiO_2, CH_2Cl_2/AcOEt 15:1): R_f 0.48. UV (MeOH): 234 (29400), 273 (3200), 307 (2900). ^{1}H-NMR ((D$_6$)DMSO): 7.98 (*s*, H–C(6)); 13.18 (*s*, H–N(7)). Anal. calc. for $C_6H_2BrCl_2N_3$ (266.91): C 27.00, H 0.76, N 15.74; found: C 27.12, H 0.80, N 15.75.

*2,4-Dichloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**11e**). As described for **11d**, with **11a** [41] (200 mg, 1.06 mmol), CH_2Cl_2 (10 ml), and *N*-iodosuccinimide (NIS; 287 mg 1.28 mmol): **11e** (288 mg, 87%) as colorless solid which was recrystallized from CH_2Cl_2. Colorless needles. M.p. 224°. TLC (SiO_2, CH_2Cl_2/AcOEt 15:1): R_f 0.49. UV (MeOH): 238 (27600), 272 (3500), 312 (2600). ^{1}H-NMR ((D$_6$)DMSO): 7.96 (*s*, H–C(6)); 13.14 (*s*, H–N(7)). Anal. calc. for $C_6H_2Cl_2IN_3$ (313.91): C 22.96, H 0.64, N 13.39; found: C 23.05, H 0.70, N 13.50.

*2,4-Dichloro-7-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-*D*-*erythro*-pentofuranosyl]-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**13b**). To a stirred suspension of powdered KOH (35 mg, 80%, 0.5 mmol) and TDA-1 (0.01 ml, 0.03 mol) in MeCN (3 ml), **11b** (50 mg, 0.24 mmol) was added. After 5 min stirring, 2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-α-D-*erythro*-pentofuranosyl chloride (**12**) [43] (116 mg, 0.3 mmol) was added within 15 min (→ thick suspension). Stirring was continued for another 10 min, the mixture filtered, and the solid washed with MeCN (2 ml). The filter cake and the funnel were washed with CH_2Cl_2 (20 ml). The CH_2Cl_2 soln. was concentrated affording **13b** as colorless solid. Recrystallization from AcOEt/petroleum ether gave **13b** (80 mg, 60%). Colorless needles M.p. 205°. TLC (SiO_2, petroleum ether/AcOEt 6:1): R_f 0.24. UV (MeOH): 235 (52500), 274 (4900), 309 (3500). ^{1}H-NMR ($CDCl_3$): 2.43 (*s*, Me); 2.45 (*s*, Me); 2.62–2.83 (*m*, 2 H–C(2′)); 4.60–4.75 (*m*, H–C(4′), 2 H–C(5′)); 5.70–5.72 (*m*, H–C(3′)); 6.80 (*t*, *J* = 6.8, H–C(1′)); 7.14 (*s*, H–C(6)); 7.19–7.98 (*m*, 8 arom. H). ^{19}F-NMR ($CDCl_3$): 165.93. Anal. calc. for $C_{27}H_{22}Cl_2FN_3O_5$ (558.38): C 58.08, H 3.97, N 7.53; found: C 58.01, H 4.00, N 7.52.

*2,4,5-Trichloro-7-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-*D*-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**13c**). As described for **13b**, with **11c** (900 mg, 4.05 mmol), **12** [43] (2.04 g, 5.25 mmol), KOH (840 mg, 80%, 12 mmol), and TDA-1 (0.15 ml, 0.47 mmol): **13c** as colorless needles (1.7 g, 73%) after recrystallization from AcOEt/petroleum ether. M.p. 167°. TLC (SiO_2, petroleum ether/AcOEt 6:1): R_f 0.25. UV (MeOH): 237 (61500), 304 (3900). ^{1}H-NMR ($CDCl_3$): 2.43 (*s*, Me); 2.45 (*s*, Me); 2.63–2.82 (*m*, 2 H–C(2′)); 4.60–4.78 (*m*, 2 H–C(4′), 2 H–C(5′)); 5.70–5.71 (*m*, H–C(3′)); 6.75 (*t*, *J* = 6.5, H–C(1′)); 7.37 (*s*, H–C(6)); 7.27–7.98 (*m*, 8 arom. H). Anal. calc. for $C_{27}H_{22}Cl_3N_3O_5$ (574.84): C 56.41, H 3.86, N 7.31; found: C 56.33, H 3.80, N 7.22.

*5-Bromo-2,4-dichloro-7-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-*D*-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**13d**). As described for **13b**, with **11d** (295 mg, 1.1 mmol), **12** [43] (556 mg, 1.43 mmol), KOH (154 mg, 80%, 2.2 mmol), and TDA-1 (0.02 ml, 0.06 mmol): **13d** as colorless needles (500 mg, 73%) after recrystallization from AcOEt/petroleum ether. M.p. 178°. TLC (SiO_2, petroleum ether/AcOEt 6:1): R_f 0.26. UV (MeOH): 238 (55400), 273 (4800), 305 (3900). ^{1}H-NMR ((D$_6$)DMSO): 2.36 (*s*, Me); 2.39 (*s*, Me); 2.74–2.80 (*m*, H$_\alpha$–C(2′)); 3.02–3.10 (*m*, H$_\beta$–C(2′)); 4.57–4.64 (*m*, H–C(4′), 2 H–C(5′)); 5.72–5.73 (*m*, H–C(3′)); 6.67 (*t*, *J* = 6.6, H–C(1′)); 7.28–7.94 (*m*, 8 arom. H); 8.23 (*s*, H–C(6)). Anal. calc. for $C_{27}H_{22}BrCl_2N_3O_5$ (619.29): C 52.36, H 3.58, N 6.79; found: C 52.48, H 3.68, N 6.65.

*2,4-Dichloro-7-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-*D*-*erythro*-pentofuranosyl]-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**13e**). As described for **13b**, with **11e** (460 mg, 1.47 mmol), **12** [43] (683 mg,

1.76 mmol), KOH (210 mg, 80%, 3 mmol), and TDA-1 (0.02 ml, 0.06 mmol): **13e** as colorless needles (700 mg, 71%) from AcOEt/petroleum ether. M.p. 185°. TLC (SiO_2, petroleum ether/AcOEt 6:1): R_f 0.27. UV (MeOH): 240 (52500), 310 (3000). ^{1}H-NMR ($CDCl_3$): 2.43 (*s*, Me); 2.45 (*s*, Me); 2.63–3.01 (*m*, 2 H–C(2′)); 4.61–4.79 (*m*, 2 H–C(4′), 2 H–C(5′)); 5.72–5.73 (*m*, H–C(3′)); 6.76 (*t*, *J* = 6.5, H–C(1′)); 7.55 (*s*, H–C(6)); 7.27–7.98 (*m*, 8 arom. H). Anal. calc. for $C_{27}H_{22}BrCl_2N_3O_5$ (666.29): C 48.67, H 3.33, N 6.31; found: C 48.54, H 3.33, N 6.18.

Glycosylation of **11b**/**11c** *to* **13b**/**13c**. As described for **13b**, with **11b**/**11c** (800 mg), **12** [43] (2.48 g, 6.39 mmol), KOH (560 mg, 80%, 8 mmol), and TDA-1 (0.1 ml, 0.3 mmol): **13b**/**13c** (1.62 g). Colorless solid which was used for the next steps (see below) without further purification.

*2-Chloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-7*H-*pyrrolo[2,3-*d*]pyrimidin-4-amine* (**6a**). A suspension of **13a** [25] (540 mg, 1 mmol) in NH_3/MeOH (100 ml; sat. at 0°) was introduced into an autoclave and stirred at 100° overnight. The clear soln. was concentrated to give a solid residue which was subjected to FC (SiO_2, 10 × 2.5 cm column, CH_2Cl_2/MeOH (20:1 → 10:1). The obtained colorless solid, was recrystallized from MeOH/CH_2Cl_2: **6a** (250 mg, 88%). Colorless crystals. Anal. data: identical to those published earlier [25].

*2,5-Dichloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-7*H-*pyrrolo[2,3-*d*]pyrimidin-4-amine* (**6c**). As described for **6a**, with **13c** (480 mg, 0.84 mmol) and NH_3/MeOH (80 ml). FC and recrystallization of the obtained colorless solid from MeOH/CH_2Cl_2 afforded **6c** (225 mg, 84%). Colorless crystals. M.p. 195° (dec.). TLC (SiO_2, CH_2Cl_2/MeOH 10:1): R_f 0.33. UV (MeOH): 280 (10500). ^{1}H-NMR ((D$_6$)DMSO): 2.13–2.22 (*m*, H_α–C(2′)); 2.36–2.47 (*m*, H_β–C(2′)); 3.45–3.57 (*m*, 2 H–C(5′)); 3.79–3.80 (*m*, H–C(4′)); 4.30–4.31 (*m*, H–C(3′)); 4.94 (*t*, *J* = 5.4, OH–C(5′)); 5.29 (*d*, *J* = 4.2, OH–C(3′)); 6.40 (*t*, *J* = 6.80, H–C(1′)); 7.34 (br. *s*, NH_2); 7.59 (*s*, H–C(6)). Anal. calc. for $C_{11}H_{12}Cl_2N_4O_3$ (319.14): C 41.40, H 3.79, N 17.56; found: C 40.97, H 3.72, N 17.78.

*2-Chloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-5-fluoro-7*H-*pyrrolo[2,3-*d*]pyrimidin-4-amine* (**6b**) *and 2,5-Dichloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-7*H-*pyrrolo[2,3-*d*]pyrimidin-4-amine* (**6c**). As described for **6a**, with **13b**/**13c** (730 mg) and NH_3/MeOH (120 ml; sat. at 0°). FC (SiO_2, 12 × 2.5 cm column, CH_2Cl_2/MeOH 20:1 → 10:1) resulted in two compounds. The slower-migrating zone yielded **6b** as colorless solid (240 mg) which was recrystallized from MeOH/CH_2Cl_2. Colorless crystals. M.p. 212°. TLC (SiO_2, CH_2Cl_2/MeOH 10:1): R_f 0.28. UV (MeOH): 279 (9800). ^{1}H-NMR ((D$_6$)DMSO): 2.14–2.17 (*m*, H_α–C(2′)); 2.32–2.37 (*m*, H_β–C(2′)); 3.50 (*m*, 2 H–C(5′)); 3.78–3.79 (*m*, H–C(4′)); 4.28–4.29 (*m*, H–C(3′)); 4.91 (*t*, *J* = 5.3, OH–C(5′)); 5.28 (*d*, *J* = 3.6, OH–C(3′)); 6.42 (*t*, *J* = 6.9, H–C(1′)); 7.27 (*s*, H–C(6)); 7.52 (br. *s*, NH_2). ^{19}F-NMR ((D$_6$)DMSO): −167.03. Anal. calc. for $C_{11}H_{12}ClFN_4O_3$ (302.69): C 43.65, H 4.00, N 18.51; found: C 43.65, H 4.01, N 18.30.

The faster-migrating zone yielded **6c** (100 mg). Anal. data: identical to those shown above.

*5-Bromo-2-chloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-7*H-*pyrrolo[2,3-*d*]pyrimidin-4-amine* (**6d**). As described for **10a**, with **13d** (300 mg, 0.48 mmol) and NH_3/MeOH (80 ml). FC resulted in a colorless solid which was recrystallized from MeOH/CH_2Cl_2: **6d** (145 mg, 83%). Colorless crystals. M.p. 177° (dec.). TLC (SiO_2, CH_2Cl_2/MeOH 10:1): R_f 0.36. UV (MeOH): 281 (5800). ^{1}H-NMR ((D$_6$)DMSO): 2.14–2.19 (*m*, H_α–C(2′)); 2.37–2.45 (*m*, H_β–C(2′)); 3.45–3.58 (*m*, 2 H–C(5′)); 3.79–3.80 (*m*, H–C(4′)); 4.30–4.31 (*m*, H–C(3′)); 4.94 (*t*, *J* = 5.3, OH–C(5′)); 5.29 (*d*, *J* = 3.9, OH–C(3′)); 6.40 (*t*, *J* = 6.7, H–C(1′)); 7.24 (br. *s*, NH_2); 7.64 (*s*, H–C(6)). Anal. calc. for $C_{11}H_{12}BrClN_4O_3$ (363.59): C 36.34, H 3.33, N 15.41; found: C 36.41, H 3.20, N 15.41.

*2-Chloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-5-iodo-7*H-*pyrrolo[2,3-*d*]pyrimidin-4-amine* (**6e**). As described for **6a**, with **13e** (350 mg, 0.53 mmol) and NH_3/MeOH (80 ml). FC yielded a colorless solid which was recrystallized from MeOH/CH_2Cl_2: **6e** (180 mg, 83%). Colorless crystals. M.p. 173° (dec.). TLC (SiO_2, CH_2Cl_2/MeOH 10:1): R_f 0.36. UV (MeOH): 283 (10500). ^{1}H-NMR ((D$_6$)DMSO): 2.14–2.18 (*m*, H_α–C(2′)); 2.40–2.45 (*m*, H_β–C(2′)); 3.45–3.56 (*m*, 2 H–C(5′)); 3.79–3.80 (*m*, H–C(4′)); 4.30–4.31 (*m*, H–C(3′)); 4.93 (*t*, *J* = 5.0, OH–C(5′)); 5.28 (*d*, *J* = 4.0, OH–C(3′)); 6.38 (*t*, *J* = 6.8, H–C(1′)); 7.22 (br. *s*, NH_2); 7.67 (*s*, H–C(6)). Anal. calc. for $C_{11}H_{12}ClIN_4O_3$ (410.60): C 32.18, H 2.95, N 13.65; found: C 32.20, H 2.80, N 13.65.

*4-Amino-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-5-fluoro-3,7-dihydro-2*H-*pyrrolo[2,3-*d*]pyrimidin-2-one* (**4b**). A soln. of **6b** (91 mg, 0.3 mmol) in 0.1% aq. NH_3 soln. (200 ml) was irradiated in a quartz reactor for 1 h. The soln. was concentrated to 20 ml and subjected to a *Serdolit-AD-4* column (20 × 2 cm).

The resin was washed with H_2O (200 ml) followed by H_2O/i-PrOH 9:1 (200 ml). The nucleoside-containing fractions were combined and evaporated to give **4b** (30 mg, 35%). Brownish solid. TLC (SiO_2, i-PrOH/H_2O/NH_3OH (25%) 7:2:1): R_f 0.63. UV (MeOH): 225 (19100), 258 (5600), 290 (4100). ^{1}H-NMR ((D$_6$)DMSO): 2.00–2.07 (*m*, H$_\alpha$–C(2′)); 2.20–2.27 (*m*, H$_\beta$–C(2′)); 3.47–3.50 (*m*, 2 H–C(5′)); 3.73–3.74 (*m*, H–C(4′)); 4.24–4.25 (*m*, H–C(3′)); 4.99 (br. *s*, OH–C(5′)); 5.21 (br. *s*, OH–C(3′)); 6.27 (*t*, *J* = 6.4, H–C(1′)); 6.87 (*s*, H–C(6)); 7.39 (br. *s*, NH_2); 7.67 (*s*, H–C(6)); 10.81 (br. *s*, NH). ^{19}F-NMR ((D$_6$)DMSO): −167.73. ESI-TOF-MS: 285.0996 ($[M+1]^+$, $C_{11}H_{14}FN_4O_4^+$; calc. 285.0999).

*7-(2-Deoxy-β-*D*-*erythro*-pentofuranosyl)-2,4-dimethoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**9a**). A suspension of **13a** [25] (370 mg, 0.68 mmol) in 0.5M MeONa (10 ml) was introduced into an autoclave and stirred at 60° overnight. The clear mixture was concentrated and the residue subjected to FC (SiO_2, 10 × 2.5 cm column, CH_2Cl_2/MeOH 20:1): **9a** (160 mg, 79%). Colorless solid. Anal. data: identical to those published earlier [37].

*5-Chloro-7-(2-deoxy-β-*D*-*erythro*-pentofuranosyl)-2,4-dimethoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**9c**). As described for **9a**, with **13c** (350 mg, 0.61 mmol) and 0.5M MeONa (20 ml). FC gave **9c** as colorless solid (180 mg, 89%). TLC (SiO_2, CH_2Cl_2/MeOH 20:1): R_f 0.24. UV (MeOH): 223 (27200), 264 (5900), 274 (6100). ^{1}H-NMR ((D$_6$)DMSO): 2.14–2.19 (*m*, H$_\alpha$–C(2′)); 2.42–2.51 (*m*, H$_\beta$–C(2′)); 3.47–3.54 (*m*, 2 H–C(5′)); 3.79–3.80 (*m*, H–C(4′)); 3.91 (*s*, MeO); 4.00 (*s*, MeO); 4.33 (*s*, H–C(3′)); 4.93 (*t*, *J* = 5.4, OH–C(5′)); 5.30 (*d*, *J* = 4.0, OH–C(3′)); 6.47 (*t*, *J* = 6.7, H–C(1′)); 7.55 (*s*, H–C(6)). Anal. calc. for $C_{13}H_{16}ClN_3O_5$ (329.74): C 47.35, H 4.89, N 12.74; found: C 47.41, H 4.80, N 12.65.

*7-(2-Deoxy-β-*D*-*erythro*-pentofuranosyl)-5-fluoro-2,4-dimethoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**9b**) *and 5-Chloro-7-(2-deoxy-β-*D*-*erythro*-pentofuranosyl)-2,4-dimethoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**9c**). As described for **9a**, with **13b**/**13c** (600 mg) and 0.5M MeONa (20 ml). FC resulted in two colorless compounds. The slower-migrating zone gave **9b** (232 mg) as colorless solid. TLC (SiO_2, CH_2Cl_2/MeOH 20:1): R_f 0.24. UV (MeOH): 223 (29200), 269 (20100). ^{1}H-NMR ((D$_6$)DMSO): 2.14–2.20 (*m*, H$_\alpha$–C(2′)); 2.37–2.46 (*m*, H$_\beta$–C(2′)); 3.47–3.53 (*m*, 2 H–C(5′)); 3.79–3.81 (*m*, H–C(4′)); 3.91 (*s*, MeO); 4.00 (*s*, MeO); 4.31–4.33 (*m*, H–C(3′)); 4.92 (*t*, *J* = 5.3, OH–C(5′)); 5.29 (*d*, *J* = 3.8, OH–C(3′)); 6.52 (*t*, *J* = 6.2, H–C(1′)); 7.33 (*d*, *J* = 1.8, H–C(6)). ^{19}F-NMR ((D$_6$)DMSO): −167.73. Anal. calc. for $C_{13}H_{16}FN_3O_5$ (313.28): C 49.84, H 5.15, N 13.41; found: C 49.73, H 5.10, N 13.33.

The faster-migrating zone gave **9c** (80 mg). Anal. data: identical to those reported above.

*5-Bromo-7-(2-deoxy-β-*D*-*erythro*-pentofuranosyl)-2,4-dimethoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**9d**). As described for **9a**, with **13d** (200 mg, 0.32 mmol) and 0.5M MeONa (20 ml). FC gave **9d** as colorless solid (100 mg, 83%). TLC (SiO_2, CH_2Cl_2/MeOH 20:1): R_f 0.25. UV (MeOH): 223 (27200), 261 (6100), 275 (6300). ^{1}H-NMR ((D$_6$)DMSO): 2.13–2.21 (*m*, H$_\alpha$–C(2′)); 2.49–2.53 (*m*, H$_\beta$–C(2′)); 3.46–3.58 (*m*, 2 H–C(5′)); 3.80–3.82 (*m*, H–C(4′)); 3.92 (*s*, MeO); 4.01 (*s*, MeO); 4.39 (*s*, H–C(3′)); 4.94 (*t*, *J* = 5.1, OH–C(5′)); 5.29 (*d*, *J* = 3.6, OH–C(3′)); 6.50 (*t*, *J* = 8.4, H–C(1′)); 7.59 (*s*, H–C(6)). Anal. calc. for $C_{13}H_{16}BrN_3O_5$ (374.19): C 41.73, H 4.31, N 11.23; found: C 41.82, H 4.22, N 11.22.

*7-(2-Deoxy-β-*D*-*erythro*-pentofuranosyl)-5-iodo-2,4-dimethoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**9e**). As described for **9a**, with **13e** (240 mg, 0.36 mmol) and 0.5M MeONa (20 ml). FC gave **9e** as colorless solid (140 mg, 92%). TLC (SiO_2, CH_2Cl_2/MeOH 20:1): R_f 0.25. UV (MeOH): 223 (33400), 262 (7300), 275 (7700). ^{1}H-NMR ((D$_6$)DMSO): 2.14–2.19 (*m*, H$_\alpha$–C(2′)); 2.45–2.55 (*m*, H$_\beta$–C(2′)); 3.43–3.54 (*m*, 2 H–C(5′)); 3.80–3.82 (*m*, H–C(4′)); 3.92 (*s*, MeO); 4.01 (*s*, MeO); 4.34–4.35 (*m*, H–C(3′)); 4.94 (*t*, *J* = 5.2, OH–C(5′)); 5.30 (*d*, *J* = 3.7, OH–C(3′)); 6.46 (*t*, *J* = 6.7, H–C(1′)); 7.61 (*s*, H–C(6)). Anal. calc. for $C_{13}H_{16}IN_3O_5$ (421.19): C 37.07, H 3.83, N 9.98; found: C 37.06, H 4.33, N 9.85.

*2-Chloro-7-(2-deoxy-β-*D*-*erythro*-pentofuranosyl)-4-methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**10a**) and *2,4-Dichloro-7-(2-deoxy-β-*D*-*erythro*-pentofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**14**). A suspension of **13a** [25] (300 mg, 0.56 mmol) in NH_3/MeOH (30 ml, sat. at 0°) was stirred at r.t. overnight. The clear mixture was concentrated, and the residue subjected to FC (SiO_2, 10 × 2.5 cm column, CH_2Cl_2/MeOH 20:1 to afford two compounds. The faster-migrating zone yielded **10a** as colorless solid which was recrystallized from MeOH/CH_2Cl_2: **10a** (80 mg, 48%). Colorless crystals. M.p. 185°. TLC (SiO_2, CH_2Cl_2/MeOH 15:1): R_f 0.29. UV (MeOH): 225 (21300), 270 (8500). ^{1}H-NMR ((D$_6$)DMSO): 2.19–2.28 (*m*, H$_\alpha$–C(2′)); 2.44–2.55 (*m*, H$_\beta$–C(2′)); 3.49–3.61 (*m*, 2 H–C(5′)); 3.83–3.84 (*m*, H–C(4′)); 4.05 (*s*, MeO); 4.35–4.36 (*m*, H–C(3′)); 4.97 (*t*, *J* = 5.4, OH–C(5′)); 5.36 (*d*, *J* = 4.2, OH–C(3′)); 6.50 (*t*, *J* = 7.0,

H–C(1′)); 6.61 (*d*, *J* = 3.6, H–C(5′)); 7.67 (*d*, *J* = 3.7, H–C(6)). Anal. calc. for $C_{12}H_{14}ClN_3O_4$ (299.71): C 48.09, H 4.71, N 14.02; found: C 47.99, H 4.70, N 14.10.

The second zone yielded **14** as colorless solid (50 mg, 30%) which was recrystallized from MeOH. M.p. 164°. TLC (SiO_2, CH_2Cl_2/MeOH 15:1): R_f 0.28. UV (MeOH): 231 (29400), 282 (4800). ^{1}H-NMR ((D$_6$)DMSO): 2.26–2.32 (*m*, H$_\alpha$–C(2′)); 2.46–2.57 (*m*, H$_\beta$–C(2′)); 3.51–3.63 (*m*, 2 H–C(5′)); 3.85–3.86 (*m*, H–C(4′)); 4.37–4.38 (*m*, H–C(3′)); 5.00 (*t*, *J* = 5.2, OH–C(5′)); 5.39 (*d*, *J* = 4.2, OH–C(3′)); 6.53 (*t*, *J* = 6.8, H–C(1′)); 6.78 (*d*, *J* = 3.7, H–C(5)); 8.00 (*d*, *J* = 3.7, H–C(6)). Anal. calc. for $C_{11}H_{11}Cl_2N_3O_3$ (304.13): C 43.44, H 3.65, N 13.82; found: C 43.40, H 3.60, N 13.95.

*2,5-Dichloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-4-methoxy-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**10c**). As described for **10a**, with **13c** (250 mg, 0.43 mmol) and NH_3/MeOH (30 ml). FC resulted in a colorless solid which was recrystallized from CH_2Cl_2/MeOH: **10c** (124 mg, 86%). Colorless needles. M.p. 160°. TLC (SiO_2, CH_2Cl_2/MeOH 15:1): R_f 0.29. UV (MeOH): 227 (24100), 281 (6500). ^{1}H-NMR ((D$_6$)DMSO): 2.18–2.27 (*m*, H$_\alpha$–C(2′)); 2.41–2.46 (*m*, H$_\beta$–C(2′)); 3.45–3.61 (*m*, 2 H–C(5′)); 3.82–3.83 (*m*, H–C(4′)); 4.07 (*s*, MeO); 4.33–4.34 (*m*, H–C(3′)); 4.96 (*t*, *J* = 5.3, OH–C(5′)); 5.33 (*d*, *J* = 4.2, OH–C(3′)); 6.49 (*t*, *J* = 6.8, H–C(1′)); 7.86 (*s*, H–C(6)). Anal. calc. for $C_{12}H_{13}Cl_2N_3O_4$ (334.15): C 43.13, H 3.92, N 12.58; found: C 43.10, H 3.86, N 12.50.

*2-Chloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-5-fluoro-4-methoxy-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**10b**) *and 2,5-Dichloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-4-methoxy-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**10c**). As described for **10a**, with **13b**/**13c** (270 mg) and NH_3/MeOH (30 ml). FC afforded two colorless compounds. The slower-migrating zone gave **10b** as colorless solid (101 mg) which was recrystallized from CH_2Cl_2/MeOH. Needles. M.p. 157°. TLC (SiO_2, CH_2Cl_2/MeOH 15:1): R_f 0.27. UV (MeOH): 225 (22800), 273 (26100). ^{1}H-NMR ((D$_6$)DMSO): 2.22–2.26 (*m*, H$_\alpha$–C(2′)); 2.39–2.44 (*m*, H$_\beta$–C(2′)); 3.49–3.55 (*m*, 2 H–C(5′)); 3.80–3.83 (*m*, H–C(4′)); 4.05 (*s*, MeO); 4.32–4.33 (*m*, H–C(3′)); 4.93 (*s*, OH–C(5′)); 5.31 (*d*, *J* = 3.7, OH–C(3′)); 6.52 (*t*, *J* = 6.0, H–C(1′)); 7.65 (*s*, H–C(6)). ^{19}F-NMR ((D$_6$)DMSO): –167.07. Anal. calc. for $C_{12}H_{13}ClFN_3O_4$ (317.70): C 45.37, H 4.12, N 13.23; found: C 45.36, H 4.07, N 13.12.

The faster-migrating zone yielded **10c** as colorless solid (35 mg). Anal. data: identical to those reported above.

*5-Bromo-2-chloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-4-methoxy-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**10d**). As described for **10a**, with **13d** (300 mg, 0.48 mmol) and NH_3/MeOH (35 ml). FC yielded a colorless solid which was recrystallized from CH_2Cl_2/MeOH: **10d** (163 mg, 89%). Colorless needles M.p. 165°. TLC (SiO_2, CH_2Cl_2/MeOH 15:1): R_f 0.31. UV (MeOH): 228 (26600), 281 (6900). ^{1}H-NMR ((D$_6$)DMSO): 2.18–2.25 (*m*, H$_\alpha$–C(2′)); 2.42–2.49 (*m*, H$_\beta$–C(2′)); 3.52–3.62 (*m*, 2 H–C(5′)); 3.81–3.83 (*m*, H–C(4′)); 4.06 (*s*, MeO); 4.32–4.33 (*m*, H–C(3′)); 4.96 (*t*, *J* = 4.9, OH–C(5′)); 5.32 (*d*, *J* = 3.4, OH–C(3′)); 6.48 (*t*, *J* = 6.6, H–C(1′)); 7.88 (*s*, H–C(6)). Anal. calc. for $C_{12}H_{13}BrClN_3O_4$ (378.61): C 38.07, H 3.46, N 11.10; found: C 38.45, H 3.80, N 11.00.

*2-Chloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-5-iodo-4-methoxy-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**10e**). As described for **10a**, with **13e** (400 mg, 0.60 mmol) and NH_3/MeOH (40 ml). FC resulted in a colorless solid which was recrystallized from CH_2Cl_2/MeOH: **10e** (204 mg, 80%). Colorless crystals M.p. 168° (dec.). TLC (SiO_2, CH_2Cl_2/MeOH 15:1): R_f 0.31. UV (MeOH): 232 (25000), 284 (5800). ^{1}H-NMR ((D$_6$)DMSO): 2.18–2.23 (*m*, H$_\alpha$–C(2′)); 2.42–2.49 (*m*, H$_\beta$–C(2′)); 3.41–3.59 (*m*, 2 H–C(5′)); 3.82–3.83 (*m*, H–C(4′)); 4.06 (*s*, MeO); 4.32–4.33 (*m*, H–C(3′)); 4.96 (*t*, *J* = 4.9, OH–C(5′)); 5.31 (*d*, *J* = 3.8, OH–C(3′)); 6.46 (*t*, *J* = 6.7, H–C(1′)); 7.88 (*s*, H–C(6)). Anal. calc. for $C_{12}H_{13}ClIN_3O_4$ (424.96): C 33.86, H 3.08, N 9.87; found: C 33.69, H 3.15, N 9.85.

*7-(2-Deoxy-β-*D-erythro-*pentofuranosyl)-3,7-dihydro-2-methoxy-4*H-*pyrrolo[2,3-*d*]pyrimidin-4-one* (**17a**). A suspension of **9a** (100 mg, 0.35 mmol) in 2N NaOH (8 ml) was stirred under reflux for 3 h. The clear soln. was cooled, diluted with H_2O (10 ml), and neutralized with 1N aq. AcOH. The soln. was concentrated, and the residue subjected to FC (SiO_2, 8 × 2.5 cm column, CH_2Cl_2/MeOH 20:1 → 10:1). The obtained colorless solid was recrystallized from MeOH: **17a** (85 mg, 89%). Colorless crystals. M.p. 205° (dec.). TLC (SiO_2, CH_2Cl_2/MeOH 10:1): R_f 0.35. UV (MeOH): 255 (9500), 272 (sh, 6600). ^{1}H-NMR ((D$_6$)DMSO): 2.15–2.20 (*m*, H$_\alpha$–C(2′)); 2.32–2.40 (*m*, H$_\beta$–C(2′)); 3.44–3.56 (*m*, 2 H–C(5′)); 3.79–3.80 (*m*, H–C(4′)); 3.91 (*s*, MeO); 4.33–4.34 (*m*, H–C(3′)); 4.90 (br. *s*, OH–C(5′));

5.30 (br. *s*, OH–C(3′)); 6.34–6.39 (*m*, H–C(1′), H–C(5)); 7.13 (*d*, *J* = 3.6, H–C(6)); 11.84 (br. *s*, NH). Anal. calc. for $C_{12}H_{15}N_3O_5$ (281.26): C 51.24, H 5.38, N 14.94; found: C 51.33, H 3.35, N 15.00.

*7-(2-Deoxy-β-*D-erythro-*pentofuranosyl)-5-fluoro-3,7-dihydro-2-methoxy-4*H-*pyrrolo[2,3-*d*]pyrimidin-4-one* (**17b**). As described for **17a**, with **9b** (125 mg, 0.40 mmol) and 2N NaOH (10 ml). FC afforded a colorless solid which was recrystallized from MeOH: **17b** (108 mg, 90%). Colorless crystals M.p. 140° (dec.). TLC (SiO_2, CH_2Cl_2/MeOH 10:1): R_f 0.33. UV (MeOH): 255 (10000), 275 (sh, 6800). ^{1}H-NMR ((D$_6$)DMSO): 2.12–2.18 (*m*, H_α–C(2′)); 2.32–2.40 (*m*, H_β–C(2′)); 3.44–3.50 (*m*, 2 H–C(5′)); 3.77–3.78 (*m*, H–C(4′)); 3.90 (*s*, MeO); 4.29–4.30 (*m*, H–C(3′)); 4.90 (*t*, *J* = 4.9, OH–C(5′)); 5.29 (*d*, *J* = 3.3, OH–C(3′)); 6.36 (*t*, *J* = 6.9, H–C(1′)); 7.06 (*s*, H–C(6)); 12.00 (br. *s*, NH). ^{19}F-NMR ((D$_6$)DMSO): –166.54. Anal. calc. for $C_{12}H_{14}FN_3O_5$ (299.26): C 48.16, H 4.72, N 14.04; found: C 48.26, H 4.62, N 14.00.

*5-Chloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-3,7-dihydro-2-methoxy-4*H-*pyrrolo[2,3-*d*]pyrimidin-4-one* (**17c**). As described for **17a**, with **9c** (100 mg, 0.30 mmol) and 2N NaOH (10 ml). FC afforded a colorless solid which was recrystallized from MeOH: **17c** (85 mg, 90%). Colorless crystals M.p. 205° (dec.). TLC (SiO_2, CH_2Cl_2/MeOH 10:1): R_f 0.35. UV (MeOH): 258 (8800). ^{1}H-NMR ((D$_6$)DMSO): 2.16–2.18 (*m*, H_α–C(2′)); 2.35–2.44 (*m*, H_β–C(2′)); 3.43–3.50 (*m*, 2 H–C(5′)); 3.77–3.78 (*m*, H–C(4′)); 3.90 (*s*, MeO); 4.29–4.30 (*m*, H–C(3′)); 4.92 (*t*, *J* = 4.9, OH–C(5′)); 5.29 (*d*, *J* = 3.2, OH–C(3′)); 6.36 (*t*, *J* = 6.9, H–C(1′)); 7.27 (*s*, H–C(6)); 12.00 (br. *s*, NH). Anal. calc. for $C_{12}H_{14}ClN_3O_5$ (315.71): C 45.65, H 4.47, N 13.31; found: C 45.51, H 4.70, N 13.15.

*5-Bromo-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-3,7-dihydro-2-methoxy-4*H-*pyrrolo[2,3-*d*]pyrimidin-4-one* (**17d**). As described for **17a**, with **9d** (150 mg, 0.40 mmol) and 2N NaOH (12 ml). FC afforded a colorless solid which was recrystallized from MeOH: **17d** (125 mg, 87%). Colorless crystals M.p. 212° (dec.). TLC (SiO_2, CH_2Cl_2/MeOH 10:1): R_f 0.38. UV (MeOH): 259 (9500), 276 (sh, 7600). ^{1}H-NMR ((D$_6$)DMSO): 2.14–2.18 (*m*, H_α–C(2′)); 2.39–2.45 (*m*, H_β–C(2′)); 3.48–3.54 (*m*, 2 H–C(5′)); 3.79–3.80 (*m*, H–C(4′)); 3.91 (*s*, MeO); 4.30–4.31 (*m*, H–C(3′)); 4.93 (*t*, *J* = 5.1, OH–C(5′)); 5.29 (*d*, *J* = 3.5, OH–C(3′)); 6.36 (*t*, *J* = 7.0, H–C(1′)); 7.32 (*s*, H–C(6)); 12.00 (br. *s*, NH). Anal. calc. for $C_{12}H_{14}BrN_3O_5$ (360.16): C 40.02, H 3.92, N 11.67; found: C 40.10, H 3.65, N 11.65.

*7-(2-Deoxy-β-*D-erythro-*pentofuranosyl)-3,7-dihydro-5-iodo-2-methoxy-4*H-*pyrrolo[2,3-*d*]pyrimidin-4-one* (**17e**). As described for **13a**, with **9e** (210 mg, 0.5 mmol) and 2N NaOH (20 ml). FC afforded a colorless solid which was recrystallized from MeOH: **17e** (150 mg, 74%). Colorless crystals. M.p. 196° (dec.). TLC (SiO_2, CH_2Cl_2/MeOH 10:1): R_f 0.41. UV (MeOH): 261 (8400), 277 (sh, 6800). ^{1}H-NMR ((D$_6$)DMSO): 2.15–2.18 (*m*, H_α–C(2′)); 2.40–2.49 (*m*, H_β–C(2′)); 3.45–3.54 (*m*, 2 H–C(5′)); 3.79–3.80 (*m*, H–C(4′)); 3.90 (*s*, MeO); 4.31–4.32 (*m*, H–C(3′)); 4.92 (*t*, *J* = 5.2, OH–C(5′)); 5.29 (*d*, *J* = 3.6, OH–C(3′)); 6.36 (*dd*, *J* = 6.1, 7.9, H–C(1′)); 7.34 (*s*, H–C(6)); 11.96 (br. *s*, NH). Anal. calc. for $C_{12}H_{14}IN_3O_5$ (407.16): C 35.40, H 3.47, N 10.32; found: C 35.36, H 3.58, N 10.15.

*7-(2-Deoxy-β-*D-erythro-*pentofuranosyl)-5-fluoro-1*H-*pyrrolo[2,3-*d*]*pyrimidine-2,4(3*H,*7*H)-*dione* (**5b**). *From* **17b**. To a soln. of **17b** (100 mg, 0.33 mmol) in MeCN (20 ml) were added NaI (60 mg, 0.4 mmol) and Me_3SiCl (76 µl, 0.6 mmol) at r.t. while stirring. Stirring was continued for 1 h. The reaction was stopped by addition of MeOH (5 ml), and the soln. was concentrated. The residue was subjected to FC (SiO_2, 2 × 10 cm column, CH_2Cl_2/MeOH 20:1 and 10:1): **5b** (63 mg, 66%). Pale yellow solid.

From **18**. As described above, with **18** (80 mg, 0.27 mmol), MeCN (20 ml), NaI (30 mg, 0.2 mmol), and Me_3SiCl (40 µl, 0.31 mmol). FC afforded compound **5b** (52 mg, 68%). Pale yellow solid. TLC (SiO_2, CH_2Cl_2/MeOH 20:1 → 10:1): R_f 0.18. UV (0.1M NaH_2PO_4 buffer, pH 7.0): 253 (8400), 285 (5300). ^{1}H-NMR ((D$_6$)DMSO): 2.14–2.26 (*m*, 2 H–C(2′)); 3.46–3.56 (*m*, 2 H–C(5′)); 3.80 (*d*, *J* = 2.6, H–C(4′)); 4.28–4.29 (*m*, H–C(3′)); 5.26 (*d*, *J* = 3.5, OH–C(3′)); 5.38 (br. *s*, OH–C(5′)); 6.11 (*t*, *J* = 6.8, H–C(1′)); 6.89 (*s*, H–C(6)); 10.76 (*s*, NH); 11.85 (br. *s*, NH). ^{19}F-NMR ((D$_6$)DMSO): –167.28. ESI-TOF-MS: 308.0656 ($[M+Na]^+$, $C_{11}H_{12}FN_3NaO_5^+$; calc. 308.0659).

*5-Chloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-1*H-*pyrrolo[2,3-*d*]*pyrimidine-2,4(3*H,*7*H)-*dione* (**5c**). As described for **5b**, with **17c** (80 mg, 0.25 mmol), MeCN (20 ml), NaI (40 mg, 0.26 mmol), and Me_3SiCl (70 µl, 0.55 mmol). FC resulted in **5c** (50 mg, 65%). Pale yellow solid. TLC (SiO_2, CH_2Cl_2/MeOH 10:1): R_f 0.19. UV (0.1M NaH_2PO_4 buffer, pH 7.0): 256 (8000), 285 (5100). ^{1}H-NMR ((D$_6$)DMSO): 2.11–2.32 (*m*, 2 H–C(2′)); 3.52–3.62 (*m*, 2 H–C(5′)); 3.81–3.82 (*m*, H–C(4′)); 4.29–

4.30 (*m*, H–C(3′)); 5.29 (*d*, *J* = 3.5, OH–C(3′)); 6.13 (*t*, *J* = 6.8, H–C(1′)); 7.10 (*s*, H–C(6)); 10.76 (*s*, NH); 11.58 (br. *s*, NH). ESI-TOF-MS: 324.0361 ($[M+Na]^+$, $C_{11}H_{12}ClN_3NaO_5^+$; calc. 324.0363).

*7-(2-Deoxy-β-*D-erythro-*pentofuranosyl)-5-fluoro-7*H-*pyrrolo[2,3-*d*]pyrimidine-2,4-diamine* (**7b**) *and 4-Chloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-5-fluoro-7*H-*pyrrolo[2,3-*d*]pyrimidin-2-amine* (**8**). A suspension of **15** [14] (800 mg, 1.28 mmol) in NH_3/MeOH (150 ml; sat. at 0°) was introduced into an autoclave and stirred at 70° for 5 d. The clear soln. was concentrated and the residue subjected to FC (SiO_2, 13 × 2.5 cm column, CH_2Cl_2/MeOH 20:1 → 10:1): **16** [38] (80 mg, 21%), **8**, and **7b**. The slowest-migrating zone gave **7b** as a pale yellow solid (120 mg, 33%) which was recrystallized from MeOH/CH_2Cl_2: light yellow crystals. M.p. 180° (dec.). TLC (SiO_2, CH_2Cl_2/MeOH 5:1): R_f 0.45. UV (MeOH): 233 (19100), 266 (10500), 289 (sh, 6900). ^{1}H-NMR ((D$_6$)DMSO): 1.99–2.05 (*m*, H_α–C(2′)); 2.23–2.34 (*m*, H_β–C(2′)); 3.34–3.47 (*m*, 2 H–C(5′)); 3.71–3.72 (*m*, H–C(4′)); 4.24–4.25 (*m*, H–C(3′)); 4.96 (*s*, OH–C(5′)); 5.18 (*d*, *J* = 3.6, OH–C(3′)); 5.79 (*s*, NH_2); 6.38 (*t*, *J* = 6.9, H–C(1′)); 6.54 (*s*, NH_2); 6.82 (*s*, H–C(6)). ^{19}F-NMR ((D$_6$)DMSO): –168.15 (F–C(5)). Anal. calc. for $C_{11}H_{14}FN_5O_3$ (283.26): C 46.64, H 4.98, N 24.72; found: C 46.72, H 5.02, N 24.58.

The second migrating zone yielded **8** as colorless solid (100 mg, 26%). Recrystallization from MeOH/CH_2Cl_2 gave colorless crystals. M.p. 165°. TLC (SiO_2, CH_2Cl_2/MeOH 10:1): R_f 0.30. UV (MeOH): 233 (19100), 285 (7500). ^{1}H-NMR ((D$_6$)DMSO): 2.08–2.14 (*m*, H_α–C(2′)); 2.30–2.36 (*m*, H_β–C(2′)); 3.46–3.51 (*m*, 2 H–C(5′)); 3.74–3.79 (*m*, H–C(4′)); 4.28–4.30 (*m*, H–C(3′)); 4.92 (*t*, *J* = 5.4, OH–C(5′)); 5.26 (*d*, *J* = 3.7, OH–C(3′)); 6.45 (*t*, *J* = 6.9, H–C(1′)); 6.94 (*s*, NH_2); 7.32 (*d*, *J* = 1.77, H–C(6)). ^{19}F-NMR ((D$_6$)DMSO): –170.23. Anal. calc. for $C_{11}H_{12}ClFN_4O_3$ (302.69): C 43.65, H 4.00, N 18.51; found: C 43.97, H 3.72, N 18.21.

*7-(2-Deoxy-β-*D-erythro-*pentofuranosyl)-5-fluoro-3,7-dihydro-4-methoxy-2*H-*pyrrolo[2,3-*d*]pyrimidin-2-one* (**18**). To a soln. of **16** [14] (150 mg, 0.5 mmol) in 10% aq. AcOH soln. (25 ml), a soln. of $NaNO_2$ (83 mg, 1.2 mmol) in H_2O (4 ml) was added dropwise while stirring. Stirring was continued for 20 min. The soln. was neutralized with 2N NaOH under cooling and concentrated. The residue was subjected to FC (SiO_2, 8 × 2.5 cm column, CH_2Cl_2/MeOH 20:1 → 10:1): **18** (94 mg, 63%). Colorless solid. TLC (SiO_2, CH_2Cl_2/MeOH 10:1): R_f 0.29. UV (MeOH): 222 (24300), 248 (5200), 285 (5900). ^{1}H-NMR ((D$_6$)DMSO): 2.13–2.17 (*m*, H_α–C(2′)); 2.26–2.33 (*m*, H_β–C(2′)); 3.49–3.53 (*m*, 2 H–C(5′)); 3.75–3.78 (*m*, H–C(4′)); 3.97 (*s*, MeO); 4.28–4.30 (*m*, H–C(3′)); 5.25 (br. s, OH–C(3′), OH–C(5′)); 6.41 (*t*, *J* = 6.6, H–C(1′)); 7.19 (*s*, H–C(6)). ^{19}F-NMR ((D$_6$)DMSO): –167.78. Anal. calc. for $C_{12}H_{14}FN_3O_5$ (299.26): C 48.16, H 4.72, N 14.04; found: C 47.98, H 4.71, N 13.98.

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