Synthesis of 9-Halogenated 9-Deazaguanine N^7-(2′-Deoxyribonucleosides)

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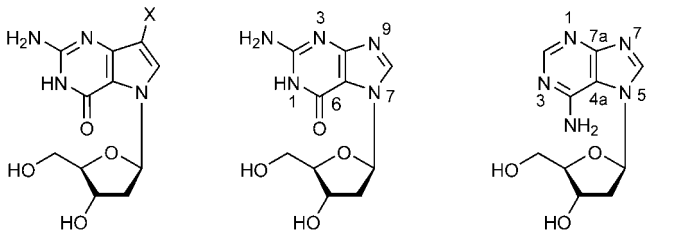
The syntheses of N^7-glycosylated 9-deazaguanine **1a** as well as of its 9-bromo and 9-iodo derivatives **1b**,**c** are described. The regioselective 9-halogenation with *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS) was accomplished at the protected nucleobase **4a** (2-{[(dimethylamino)methylidene]amino}-3,5-dihydro-3-[(pivaloyloxy)methyl]-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one). Nucleobase-anion glycosylation of **4a**–**c** with 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**5**) furnished the fully protected intermediates **6a**–**c** (*Scheme 2*). They were deprotected with 0.01M NaOMe yielding the sugar-deprotected derivatives **8a**–**c** (*Scheme 3*). At higher concentrations (0.1M NaOMe), also the pivaloyloxymethyl group was removed to give **7a**–**c**, while conc. aq. NH_3 solution furnished the nucleosides **1a**–**c**. In D_2O, the sugar conformation was always biased towards *S* (67–61%).

Introduction. – In the following, the synthesis of the 9-deazaguanine N^7-(2′-deoxyribonucleosides) **1a**–**c** is reported (purine numbering is used throughout, except for the *Tables* and the *Exper. Part*). The parent guanine 2′-deoxyribonucleoside **2** as well as the adenine 2′-deoxyribonucleoside **3** have been shown to form stable base pairs in duplex DNA [1][2] as well as in DNA triplexes [3–6]. Because of their unusual glycosylation site, these nucleosides show altered base-pairing behavior compared to the canonical DNA constituents dA and dG.



1a X = H
b X = Br
c X = I

2
purine numbering

3
systematic numbering

While compound **3** has already been incorporated into oligonucleotides [1], compound **2** has been introduced in duplex and triplex DNA [2–6]. Triplexes containing the 2′-deoxyguanosine derivative **2** show high third-strand-binding affinity specific to the dG · dC base pair. The base triplet formed between compound **2** and dG ·

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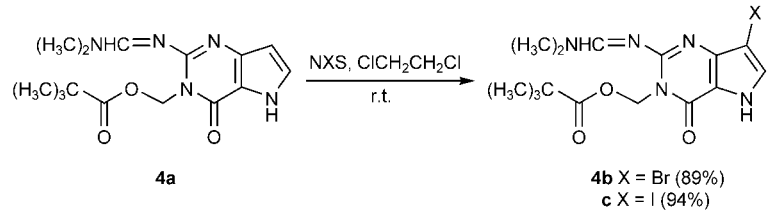
dC is structurally related to the $dCH^+ \cdot dG \cdot dC$ base triplet. Contrary to the latter being stable only under acidic conditions, the $\mathbf{2} \cdot dG \cdot dC$ triplet is stable in neutral medium.

Experiments with halogenated derivatives of 7-deazapurine nucleosides [7–10] or 8-aza-7-deazapurine nucleosides have shown that halogen substituents stabilize the DNA duplex structure [11][12]. As the equivalent position of the unusually glycosylated nucleoside **2** is N(9), halogen substituents cannot be introduced in a purine nucleoside. Therefore, 9-deazaguanine was chosen as nucleobase which is expected to be accessible for halogenation at the 9-position. The 9-alkyl-substituted derivatives of 9-deazaguanine show biological activity as purine nucleoside phosphorylase inhibitors [13–15]. Concerning the duplex and triplex stability, the 9-position is the only favorable site providing steric freedom when the nucleoside is a part of the second or third strand of DNA. For compound **1a**, a synthesis was already described [16]. Since this route was found to be laborious for halogenated derivatives, we now describe a protocol for the synthesis of the 9-deazaguanine N^7-(2′-deoxyribonucleoside) **1a** that includes the 9-bromo- and 9-iodonucleosides **1b**,**c**. It is supposed that compounds **1b**,**c** will stabilize triplex DNA compared to the nonhalogenated **1a**. Preliminary results of this work have been reported in a short communication [17].

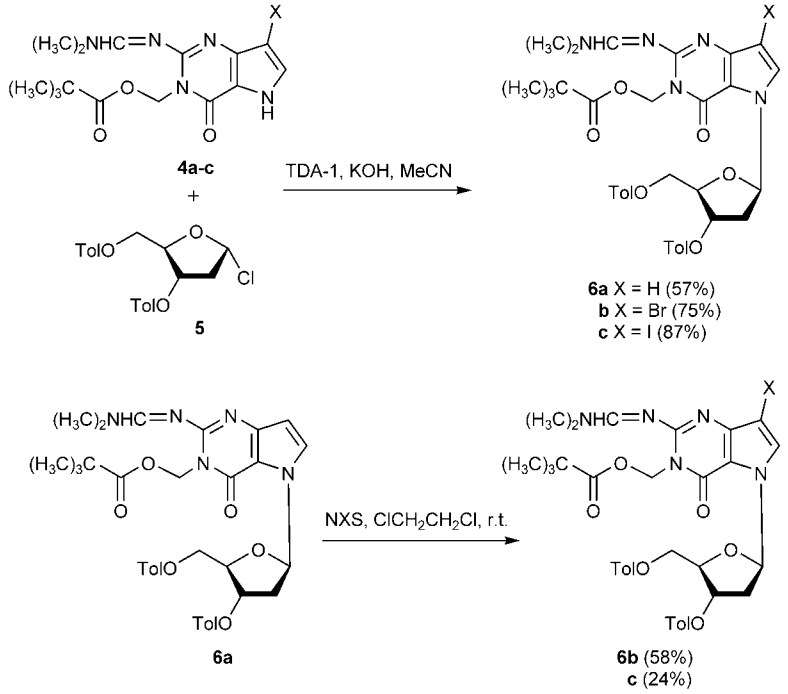
Results and Discussion. – 1. *Synthesis and Characterization*. The N^7-glycosylated 9-deaza-2′-deoxyguanosine **1a** was already synthesized by glycosylation of 2,6-dichloro-9-deazaguanine followed by nucleophilic displacement with aqueous NaOH solution and methanolic ammonia [16]. Later, a synthetic route was reported for the preparation of the protected 9-deazaguanine base **4a** [18]. Also an improved protocol was described [19] which in our hands did not lead to the expected compound; methylation of the heterocycle was observed at elevated temperatures. As compound **4a** is fully protected and carries protecting groups suitable for the glycosylation reaction as well as for oligonucleotide synthesis, it was used as starting material for the synthesis of 9-deazapurine 2′-deoxyribonucleoside **1a** and its 9-halogenated derivatives **1b**,**c**. From findings on 7-deazaguanine nucleosides, it was also anticipated that regioselective halogenation at position 9 will be possible when the amino group of the base is protected. Two synthetic routes were chosen for the synthesis of compounds **1b**,**c**: *i*) the halogenation of the nucleobase followed by glycosylation and *ii*) the halogenation of the fully protected nucleoside.

On the first route, the fully protected key intermediate **4a** was treated with an excess of *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) in dichloroethane at room temperature. The 9-bromo and 9-iodo derivatives **4b**,**c** were formed in a regioselective way in yields of 90–95% (*Scheme 1* and *Exper. Part*). Neither formation of another regioisomer nor of 7,8-dihalogenated derivatives were detected by TLC. Then, the stereoselective nucleobase-anion glycosylation was applied to compound **4a** as well as to the 9-halogenated derivatives **4b**,**c**. The reaction was performed with the protected nucleobases dissolved in MeCN and 2-deoxy-3,5-di-*O*-(*p*-totuoyl)-α-D-*erythro*-pentofuranosyl chloride (**5**); powdered KOH/TDA-1 (=tris[2-(2-methoxyethoxy)ethyl]amine) was used to generate the nucleobase anion (*Scheme 2*). The fully protected N^7-β-D-nucleosides **6a**–**c** were obtained in a stereoselective way. They were

Scheme 1



Scheme 2

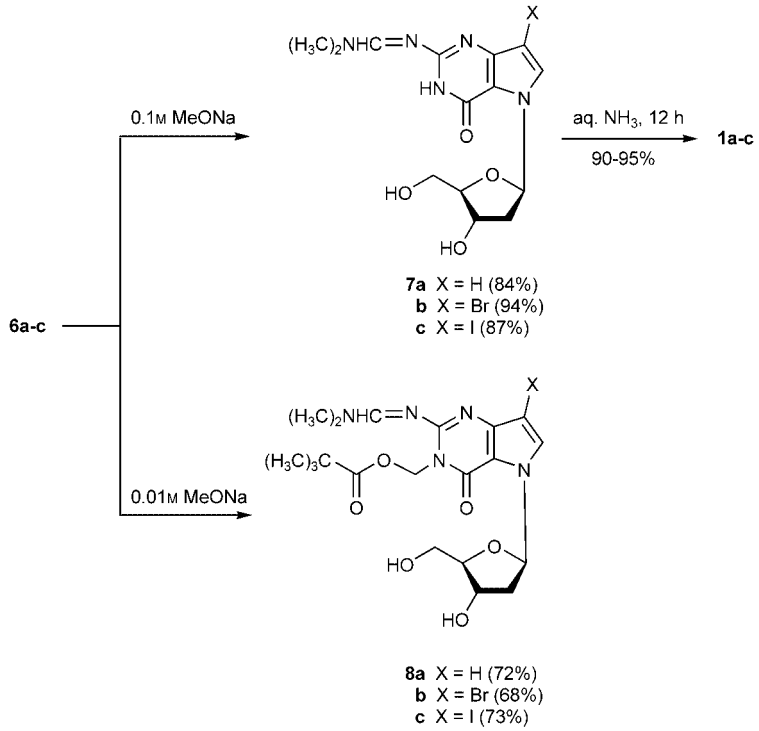


purified by flash column chromatography (FC) yielding **6a** (57%), **6b** (75%), and **6c** (87%) (see *Exper. Part*).

The halogenation reaction was also performed with the fully protected nucleoside **6a**. A suspension of **6a** was treated with NBS or NIS in dichloroethane at room temperature furnishing the halogenated nucleosides **6b**,**c** in 58 and 24% yield, respectively (see *Scheme 2* and *Exper. Part*). As the yield of the halogenation was low on the nucleoside level compared to that on the nucleobase, this route was abandoned.

The deprotection of **6a**–**c** was carried out with 0.1M NaOMe/MeOH at room temperature for 1 h resulting in the removal of the *p*-toluoyl groups protecting the sugar moiety as well as of the pivaloyloxymethyl group at the nucleobase (*Scheme 3*).

Scheme 3



The [(dimethylamino)methylidene]amino protecting groups are stable under these conditions. Compounds **7a**–**c** were isolated in yields of 84% for **7a**, 94% for **7b**, and 87% for **7c**. When the deprotection of **6a**–**c** was performed with 0.01M NaOMe/MeOH at room temperature for 1 h, only the *p*-toluoyl groups were removed furnishing nucleosides **8a**–**c** in good yields (72% for **1a**, 68% for **1b**, and 73% for **1c**). Both partially base-protected nucleosides **7a**–**c** as well as fully base-protected nucleosides **8a**–**c** can be used for further manipulation towards the synthesis of phosphoramidites. To test the suitability of the protecting groups, their hydrolysis was studied. The complete removal of all protecting groups of **7a**–**c** was accomplished in 25% aqueous NH_3 solution in a sealed vessel at 60° for 16 h furnishing the nucleosides **1a**–**c** in almost quantitative yields (see *Scheme 3* and *Exper. Part*).

The nucleosides described above as well as all synthetic intermediates were characterized by ^{1}H- and ^{13}C-NMR spectra and elemental analyses (*Table 1* and *Exper. Part*). The position of halogenation and the configuration of the anomeric center were confirmed by the ^{1}H-NOE difference spectra of **1a**–**c** (*Table 2* and discussion below the *Table*). According to a calibration graph [20], compounds **1a**–**c** prefer the *high-syn* conformation, which is reported for other 2′-deoxynucleosides [20][21]. Estimation of *syn*- and *anti*-conformer populations according to [20] gave an *anti*-rotamer population of 55% for **1a**, 65% for **1b**, and 75% for **1c**. This is in line with earlier findings reported for 7-deazapurine 2′-deoxyribonucleosides [22][23].

Table 1. *^{13}C-NMR Chemical Shifts* [ppm] *of 9-Deazapurine Nucleosides and Synthetic Precursors Measured in (D_6)DMSO at 23°*

	C(2)[a]) C(2)[b])	C (4)[a]) C(6)[b])	C(4a)[a]) C(5)[b])	C(6)[a]) C(8)[b])	C(7)[a]) C(9)[b])	C(7a)[a]) C(4)[b])	Me (Piv)	MeN	N=CH	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)	CH_2O	C=O
4a	152.9	154.0	113.4	128.2	101.7	144.0	26.6	34.2	156.6						654	176.6
b	153.6	153.8	113.4	127.7	88.8	141.2	26.6	34.4	156.7	–	–	–	–	–	65.4	176.6
c	153.4	153.6	113.7	132.1	57.6	144.6	26.7	34.5	156.7						65.5	176.7
6a	153.6	154.1	112.7	129.3	103.3	145.7	26.7	34.4	156.9	85.4	38.3	74.9	81.1	64.2	65.3	176.7
b	153.7	154.2	112.7	126.5	90.9	142.7	26.6	34.5	156.8	85.6	[c])	74.8	81.4	64.1	65.4	176.6
c	153.6	154.0	112.9	131.8	60.2	146.0	26.6	34.5	156.8	85.6	38.2	74.9	81.4	64.1	65.4	176.6
7a	154.4	155.0	113.8	127.3	102.5	146.8	–	34.4	157.0	85.3	41.0	70.7	87.1	61.8	–	–
b	154.7	155.0	113.8	126.4	89.9	143.7	–	34.4	157.0	85.5	41.1	70.4	87.3	61.5	–	–
c	154.7[d])	154.8[d])	114.0	130.8	59.1	147.0	–	34.5	157.0	85.6	41.2	70.5	87.3	61.6		
8a	153.4	154.0	112.5	128.5	102.7	145.2	26.7	34.4	156.8	85.2	41.0	70.6	87.2	61.7	65.4	176.7
b	153.7[d])	153.9[d])	112.4	127.5	89.9	142.2	26.6	34.5	156.8	85.5	41.1	70.3	87.3	61.4	65.3	176.6
c	153.7[d])	153.8[d])	112.8	132.0	59.2	145.7	26.7	34.6	156.9	85.7	41.3	70.4	87.4	61.5	65.5	176.7
1a	150.8	154.2	111.6	127.4	101.6	148.1				85.3	40.9	70.6	87.0	61.8	–	–
b	151.5	153.8	111.4	126.3	88.9	145.0				85.5	41.0	70.3	87.2	61.5	–	–
c	151.3	153.8	111.7	130.7	57.7	148.4				85.6	41.1	70.4	87.2	61.6		

[a]) Systematic numbering. [b]) Purine numbering. [c]) Overlapped with DMSO signal. [d]) Tentative.

Table 2. *NOE Data of 9-Deaza-2′-deoxyguanosine* (**1a**) *and of the 9-Halogenated Derivatives* **1b**,**c**[a])

	Proton irradiated	NOE observed ([%])
1a	H–C(6)	H–C(1′) (0), H–C(2′) (5)
	H–C(1′)	H–C(6) (1.1), H_α–C(2′) (5.4), H–C(4′) (1.5)
	H–C(7)	H–C(1′) (0), H–C(6) (5.7), H–C(2′) (0)
1b	H–C(6)	H–C(1′) (0.6), H–C(2′) (3.5), H–C(3′) (0.6), OH–C(5′) (0.5)
	H–C(1′)	H–C(6) (0), H_α–C(2′) (5.6), H–C(4′) (1.6)
1c	H–C(6)	H–C(1′) (0), H–C(2′) (2.9)
	H–C(1′)	H–C(6) (0), H_α–C(2′) (6.7), H–C(4′) (1.3)

[a]) Measured in (D_6)DMSO at 25°.

According to *Table 1*, the C(7) signals of **1b** and **1c** are shifted upfield compared to the nucleoside **1a** due to the halogen substituents attached (systematic numbering; (δ (CH) 101.6, δ (CBr) 88.9, and δ (CI) 57.7 ppm). In addition, a large ^1J(C(6), H–C(6)) coupling constant of 190.6 Hz and small ^2J(C(7), H–C(6)) and ^3J(C(6), H–C(1′)) coupling constants of 5.5 and 4.25 Hz, respectively, were obtained from the gated-decoupled ^{13}C-NMR spectrum of **1c** and suggest C(7) as the position of halogenation (systematic numbering). The β-D-configuration of the anomeric center of **1a**–**c** was confirmed by the irradiation of H–C(1′) resulting in NOEs at H–C(4′) ($\eta = 1.5\%$ for **1a**, $\eta = 1.6\%$ for **1b**, and $\eta = 1.3\%$ for **1c**).

The UV spectra of compounds **1b**,**c** and, for comparison, of **1a** measured in 0.1M sodium phosphate buffer (pH 7.0) show three distinct maxima at 232, 262, and 287 nm for **1a**, 235, 272, and 297 nm for **1b**, and 237, 276, and 299 nm for **1c**. This indicates that the 9-halogeno substituents induce a bathochromic shift. The nucleosides **1a**–**c** show two pK_a values between pH 3 and 11. The pK_a values for compound **1a** are 4.9 and 10.3, while the halogenated derivatives show lower values, 3.5 and 9.6 for **1b** and 3.5 and 9.7 for **1c**.

2. *Conformational Analyses of the 9-Deazaguanine* N^7*-Nucleosides* **1a**–**c**. Conformational analysis of the sugar moiety of nucleosides **1a**–**c** was performed with the program PSEUROT (version 6.3) [24][25]. Conformational changes of 9-substituted 9-deaza-2′-deoxyguanosine were studied on the basis of vicinal ^{1}H,^{1}H coupling constants. Calculations were performed with pseudorotational starting parameters recommended in the users manual of the program ($\Phi_{max} = 36°$ (both *N* and *S*)). The input contained the following ^{1}H,^{1}H-coupling constants: $J(1',2')$, $J(1',2'')$, $J(2',3')$, $J(2'',3')$, and $J(3',4')$ (see *Table 3*). During the iterations, either the puckering parameters (P, Φ_{max}) of the minor conformer (*N*) or the puckering amplitudes of both conformers were constrained. In all cases, the root-mean-square (r.m.s.) values were ≤ 0.4 Hz and the $|\Delta J_{max}| \leq 0.5$ Hz. From the conformer population shown in *Table 3*, some general trends can be deduced. The nonhalogenated compound **1a** shows a population of *ca.* 67% of the *S*-conformers; the conformation of the bromo and iodo derivatives **1b**,**c** are slightly shifted towards *N* (63 and 61% *S*, resp.). These values are *ca.* 10–15% higher than those found for 2′-deoxyguanosine. The data demonstrate that the higher the electron-withdrawing effect of the 9-substituent is, the more the $N \rightleftharpoons S$ equilibrium of the sugar moiety is biased towards the *N*-conformation [26][27]. This suggests that 9-substituents on pyrrolo[3,2-*d*]pyrimidine 2′-deoxyribonucleosides have a similar influence on the sugar puckering as electron-withdrawing 7-substituents in pyrrolo[2,3-*d*]pyrimidine 2′-deoxyribonucleosides [28][29].

Table 3. N/S-*Conformer Populations of the Sugar Moieties of 9-Deaza-2′-deoxyguanosine* **1a** *and of the Halogenated Derivatives* **1b**,**c** *Measured in* D_2O *at 298 K*

	^3J(H,H) [Hz][a]					Conformation	
	1′,2′	1′,2″	2′,3′	2″,3′	3′,4′	% *N*	% *S*
1a	6.85	6.54	6.75	3.84	3.84	33	67
1b	6.63	6.41	6.55	4.16	4.00	37	63
1c	6.65	6.29	6.13	4.24	4.07	39	61

[a]) 2′ and 2″ represent the 2 H–C(2′).

In conclusion, it was shown that bromo and iodo substituents can be regioselectively introduced at the 9-position of 9-deazapurine nucleosides. These compounds will be used in duplex- and triplex-forming DNA. Studies on the formation of triplexes containing **1a**–**c** (*Fig.*, motif **II**) are under investigation; such triplex structures (see **II**) are expected to be more stable than those formed by cytidine-containing oligonucleotides (see motif **I**).

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Experimental Part

General. All chemicals were purchased from *Aldrich*, *Sigma*, or *Fluka* (*Sigma-Aldrich Chemie GmbH*, Deisenhofen, Germany). Solvents were of laboratory grade. TLC: aluminium sheets, silica gel *60* F_{254}, 0.2-mm layer (*VWR*, Germany). Ion exchange: *Serdolit AD-4* resin, 0.1–0.2 mm (*Serva Electrophoresis GmbH*, Heidelberg, Germany). Column flash chromatography (FC): silica gel *60* (*VWR*, Germany) at 0.4 bar; sample

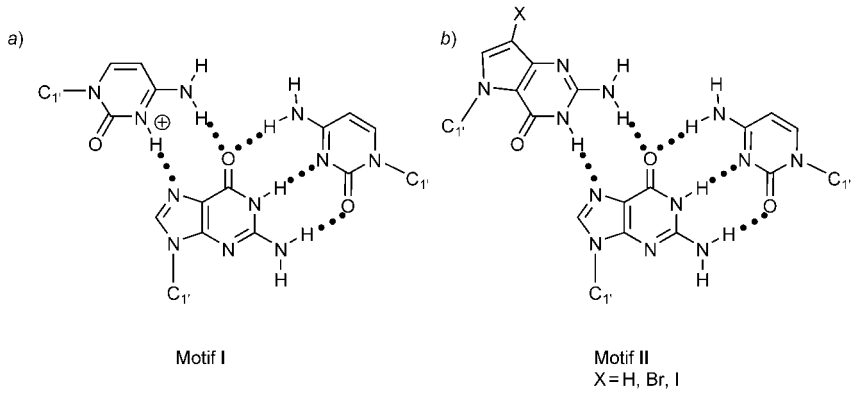

Figure. *Triplex formation* a) *by cytidine-containing oligonucleotides* (motif **I**) *and* b) *by oligonucleotides containing* **1a**–**c** (motif **II**)

collection with an *UltroRac-II* fractions collector (*LKB Instruments*, Sweden). UV Spectra: *U-3200* spectrometer (*Hitachi*, Tokyo, Japan); λ_{max} (ε) in nm. NMR Spectra: *Avance-250* or *AMX-500* spectrometers (*Bruker*, Karlsruhe, Germany), at 250.13 MHz for ^{1}H and ^{13}C; δ in ppm rel. to Me_4Si as internal standard, *J* values in Hz. Elemental analyses were performed by *Mikroanalytisches Laboratorium Beller* (Göttingen, Germany).

*7-Bromo-2-[[(dimethylamino)methylidene]amino}-3,5-dihydro-3-[(pivaloyloxy)methyl]-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one* (**4b**). To a suspension of 2-{[(dimethylamino)methylidene]amino}-3,5-dihydro-3-[(pivaloyloxy)methyl]-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (**4a**) [18] (1.0 g, 3.13 mmol) in 1,2-dichlorethane (50 ml) was added NBS (725 mg, 4.07 mmol) under stirring at r.t. Stirring was continued for another 10 min, and the mixture was poured into ice-water. The precipitate was filtered off *in vacuo* and washed with H_2O. The residue was dried and subjected to FC (silica gel, column 15 × 3 cm, stepwise gradient CH_2Cl_2/MeOH 98:2, 95:5): **4b** (1.12 g, 90%). Colorless solid. TLC (CH_2Cl_2/MeOH 95:5): R_f 0.5. UV (MeOH): 261 (21800), 303 (15600). ^{1}H-NMR ((D$_6$)DMSO): 12.24 (*s*, NH); 8.52 (*s*, N=CH); 7.47 (*s*, H–C(6)); 6.18 (*s*, CH_2O); 3.16, 2.98 (2*s*, Me_2N); 1.08 (*s*, 3 Me). Anal. calc. for $C_{15}H_{20}BrN_5O_3$ (398.26): C 45.24, H 5.06, N 17.59; found: C 45.36, H 5.02, N 17.50.

*2-[[(Dimethylamino)methylidene]amino}-3,5-dihydro-7-iodo-3-[(pivaloyloxy)methyl]-4*H*-pyrrolo[3,2-d]pyrimidin-4-one* (**4c**). As described for **4b**, with **4a** (1.0 g, 3.13 mmol) and NIS (855 mg, 3.80 mmol) in 1,2-dichlorethane (50 ml): **4c** (1.32 g, 95%). Colorless solid. TLC (CH_2Cl_2/MeOH 95:5): R_f 0.5. UV (MeOH): 263 (20600), 305 (15000). ^{1}H-NMR ((D$_6$)DMSO): 12.27 (*s*, NH); 8.51 (*s*, N=CH); 7.47 (*s*, H–C(6)); 6.17 (*s*, CH_2O); 3.16, 2.97 (2*s*, Me_2N); 1.08 (*s*, 3 Me). Anal. calc. for $C_{15}H_{20}IN_5O_3$ (445.26): C 40.46, H 4.53, N 15.73; found: C 40.32, H 4.41, N 15.61.

5-[2-Deoxy-3,5-di-O-(p-*toluoyl)-β*-D-erythro-*pentofuranosyl]-2-[[(dimethylamino)methylidene]amino}-3,5-dihydro-3-[(pivaloyloxy)methyl]-4*H*-pyrrolo[3,2-d]pyrimidin-4-one* (**6a**). To a suspension of powdered KOH (310 mg, 5.53 mmol) and TDA-1 (=tris[2-(2-methoxyethoxy)ethyl]amine; 70 µl, 0.22 mmol) in anh. MeCN (15 ml) was added **4a** (1 g, 3.13 mmol) while stirring at r.t. Stirring was continued for another 10 min, and 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-*α*-D-*erythro*-pentofuranosyl chloride (**5**; 1.46 g, 3.76 mmol) [30][31] was added in portions. After 30 min, insoluble material was filtered off, and the solvent was evaporated. The resulting foam was applied to FC (silica gel, column 12 × 4 cm, stepwise gradient CH_2Cl_2/MeOH 99:1, 98:2): **6a** (1.19 gm, 57%). Colorless foam. TLC (CH_2Cl_2/MeOH 98:2): R_f 0.3. UV (MeOH): 242 (33200), 307 (14600). ^{1}H-NMR ((D$_6$)DMSO): 8.56 (*s*, N=CH); 7.94–7.86 (*m*, 5 arom. H); 7.67 (*d*, *J* = 3.1, H–C(6)); 7.30 (*m*, 4 arom. H); 7.05 (*t*, *J* = 6.7, H–C(1′)); 6.23 (*d*, *J* = 3.0, H–C(7)); 6.17 (*s*, CH_2O); 5.63 (*m*, H–C(3′)); 4.54 (*m*, 2 H–C(5′), H–C(4′)); 3.14, 2.96 (2*s*, Me_2N); 2.64 (*m*, 2 H–C(2′)); 2.39, 2.37 (2*s*, 2 Me); 1.08 (*s*, 3 Me). Anal. calc. for $C_{36}H_{41}N_5O_8$ (671.74): C 64.37, H 6.15, N 10.43; found: C 64.40, H 6.20, N 10.40.

7-Bromo-5-[2-deoxy-3,5-di-O-(p-*toluoyl)-β*-D-erythro-*pentofuranosyl]-2-[[(dimethylamino)methylidene]-amino}-3,5-dihydro-3-[(pivaloyloxy)methyl]-4*H*-pyrrolo[3,2-d]pyrimidin-4-on*e (**6b**). *Method A:* As described for **6a**, with powdered KOH (140 mg, 2.5 mmol), TDA-1 (46 µl, 0.14 mmol), **4b** (600 mg, 1.51 mmol), and **5** (970 mg, 2.50 mmol) in anh. MeCN (10 ml): **6b** (850 mg, 75.1%). Colorless foam.

Method B: To a suspension of **6a** (400 mg, 0.60 mmol) in 1,2-dichlorethane (5 ml) was added NBS (116 mg, 0.65 mmol) under stirring at r.t. Stirring was continued for another 25 min, and the mixture was poured into ice-cold H_2O (100 ml). The precipitate was filtered off and dried under vacuum. The residue was applied to FC (silica gel, column 12 × 2 cm, stepwise gradient CH_2Cl_2/MeOH 99:1, 98:2): **6b** (260 mg, 58%). Colorless foam. TLC (CH_2Cl_2/MeOH 98:2): R_f 0.4. UV (MeOH): 240 (48500), 311 (22600). ^{1}H-NMR ((D$_6$)DMSO): 8.53 (*s*, N=CH); 7.93–7.86 (*m*, arom. H, H–C(6)); 7.35 (*m*, arom. H); 7.04 (*t*, *J* = 6.7, H–C(1′)); 6.15 (*s*, CH_2O); 5.64 (*m*, H–C(3′)); 4.54 (*m*, 2 H–C(5′), H–C(4′)); 3.17, 2.98 (2*s*, Me_2N); 2.75 (*m*, 2 H–C(2′′)); 2.39, 2.37 (2*s*, 2 Me); 1.08 (*s*, 3 Me). Anal. calc. for $C_{36}H_{40}BrN_5O_8$ (750.64): C 57.60, H 5.37, N 9.33; found: C 58.00, H 5.42, N 9.19.

5-[2-Deoxy-3,5-di-O-(p-*toluoyl)-β*-D-erythro-*pentofuranosyl]-2-{[(dimethylamino)methylidene]amino}-3,5-dihydro-7-iodo-3-[(pivaloyloxy)methyl]-4*H-*pyrrolo[3,2-*d*]pyrimidin-4-one* (**6c**). *Method A:* As described for **6a**, with powdered KOH (390 mg, 6.95 mmol), TDA-1 (140 µl, 0.44 mmol), **4c** (1 g, 2.25 mmol), and **5** (1.17 g, 3.0 mmol) in anh. MeCN (30 ml): **6c** (1.55 g, 87%). Colorless foam.

Method B: As described for **6b**, with **6a** (400 mg, 0.56 mmol) and NIS (184 mg, 0.87 mmol) in CH_2Cl_2 (5 ml): **6b** (115 mg, 24%). Colorless foam. TLC (CH_2Cl_2/MeOH 98:2): R_f 0.44. UV (MeOH): 240 (38500), 265 (22200), 312 (16400). ^{1}H-NMR ((D$_6$)DMSO): 8.52 (*s*, N=CH); 7.90 (*m*, arom. H, H–C(6)); 7.34 (*m*, arom. H); 7.03 (*t*, *J* = 6.9, H–C(1′)); 6.15 (*s*, CH_2O); 5.65 (*m*, H–C(3′)); 4.55 (*m*, 2 H–C(5′), H–C(4′)); 3.17, 2.98 (2*s*, Me_2N); 2.79 (*m*, H_α–C(2′)); 2.67 (*m*, H_β–C(2′)); 2.39, 2.37 (2*s*, 2 Me); 1.08 (*s*, 3 Me). Anal. calc. for $C_{36}H_{40}IN_5O_8$ (797.64): C 54.21, H 5.05, N 8.78; found: C 54.24, H 4.95, N 8.75.

5-[2-Deoxy-β-D-erythro-*pentofuranosyl]-2-{[(dimethylamino)methylidene]amino}-3,5-dihydro-4*H-*pyrrolo[3,2-*d*]pyrimidin-4-one* (**7a**). A soln. of **6a** (1.3 g, 1.94 mmol) in 0.1M NaOMe/MeOH (100 ml) was stirred for 1 h at r.t. Silica gel was added (5 g), and the solvent was evaporated. The mixture was applied to FC (silica gel, column 14 × 4 cm, CH_2Cl_2/MeOH 9:1): **7a** (520 mg, 84%). Colorless solid. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.25. UV (MeOH): 224 (10600), 254 (18700), 294 (15900). ^{1}H-NMR ((D$_6$)DMSO): 11.13 (*s*, NH); 8.53 (*s*, N=CH); 7.61 (*d*, *J* = 3.1, H–C(6)); 6.88 (*t*, *J* = 6.8, H–C(1′)); 6.16 (*d*, *J* = 3.1, H–C(7)); 5.24 (*d*, *J* = 3.9, OH–C(3′)); 4.92 (*t*, *J* = 5.4, OH–C(5′)); 4.28 (*m*, H–C(3′)); 3.78 (*m*, H–C(4′)); 3.52 (*m*, 2 H–C(5′)); 3.10, 2.98 (2*s*, Me_2N); 2.18 (*m*, 2 H–C(2′)). Anal. calc. for $C_{14}H_{19}N_5O_4$ (321.33): C 52.33, H 5.96, N 21.79; found: C 52.67, H 5.70, N 21.39.

7-Bromo-5-[2-deoxy-β-D-erythro-*pentofuranosyl]-2-{[(dimethylamino)methylidene]amino}-3,5-dihydro-4*H-*pyrrolo[3,2-*d*]pyrimidin-4-one* (**7b**). As described for **7a**, with **6b** (260 mg, 0.35 mmol) and 0.1M NaOMe/MeOH (30 ml): **7b** (130 mg, 94%). Colorless solid. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.34. UV (MeOH): 226 (15500), 260 (25000), 297 (21700). ^{1}H-NMR ((D$_6$)DMSO): 11.37 (*s*, NH); 8.50 (*s*, N=CH); 7.82 (*s*, H–C(6)); 6.88 (*t*, *J* = 6.7, H–C(1′)); 5.25 (*d*, *J* = 3.7, OH–C(3′)); 4.97 (*t*, *J* = 5.2, OH–C(5′)); 4.27 (*m*, H–C(3′)); 3.77 (*m*, H–C(4′)); 3.52 (*m*, 2 H–C(5′)); 3.15, 3.00 (2*s*, Me_2N); 2.24 (*m*, 2 H–C(2′)). Anal. calc. for $C_{14}H_{18}BrN_5O_4$ (400.23): C 42.01, H 4.53, N 17.50; found: C 42.30, H 4.60, N 17.35.

5-[2-Deoxy-β-D-erythro-*pentofuranosyl]-2-{[(dimethylamino)methylidene]amino}-3,5-dihydro-7-iodo-4*H-*pyrrolo[3,2-*d*]pyrimidin-4-one* (**7c**). As described for **7a**, with **6c** (1 g, 1.25 mmol) and 0.1M NaOMe/MeOH (80 ml): **7c** (485 mg, 87%). Colorless solid. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.42. UV (MeOH): 229 (8600), 263 (17000), 301 (16100). ^{1}H-NMR ((D$_6$)DMSO): 11.34 (*s*, NH); 8.50 (*s*, N=CH); 7.81 (*s*, H–C(6)); 6.88 (*t*, *J* = 6.6, 6.9, H–C(1′)); 5.24 (*d*, *J* = 3.7, OH–C(3′)); 4.96 (*t*, *J* = 5.2, OH–C(5′)); 4.28 (*m*, H–C(3′)); 3.78 (*m*, H–C(4′)); 3.52 (*m*, 2 H–C(5′)); 3.14, 3.01 (2*s*, Me_2N); 2.25 (*m*, 2 H–C(2′)). Anal. calc. for $C_{14}H_{18}IN_5O_4$ (447.23): C 37.60, H 4.06, N 15.66; found: C 37.68, H 4.10, N 15.28

5-[2-Deoxy-β-D-erythro-*pentofuranosyl]-2-{[(dimethylamino)methylidene]amino}-3,5-dihydro-3-[(pivaloyloxy)methyl]-4*H-*pyrrolo[3,2-*d*]pyrimidin-4-one* (**8a**). A soln. of **6a** (150 mg, 0.22 mmol) and 0.01M NaOMe/MeOH (15 ml) was stirred for 1 h at r.t. Silica gel (1 g) was added, and the solvent was evaporated. The mixture was applied to FC (silica gel, column 14 × 2 cm, CH_2Cl_2/$(CH_3)_2CO$ 98:2): **8a** (70 mg, 72%). Colorless solid. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.5. UV (MeOH): 262 (20900), 309 (16700). ^{1}H-NMR ((D$_6$)DMSO): 8.56 (*s*, N=CH); 7.72 (*s*, H–C(6)); 6.89 (*t*, *J* = 6.6, H–C(1′)); 6.20 (*s*, H–C(7)), 6.18 (*s*, CH_2O); 5.24 (*d*, *J* = 3.9, OH–C(3′)); 4.92 (*t*, *J* = 5.3, OH–C(5′)); 4.29 (*m*, H–C(3′)); 3.79 (*m*, H–C(4′)); 3.51 (*m*, 2 H–C(5′)); 3.14, 2.97 (2*s*, Me_2N); 2.27 (*m*, 2 H–C(2′)); 1.10 (*s*, 3 Me). Anal. calc. for $C_{20}H_{29}N_5O_6$ (435.47): C 55.16, H 6.71, N 16.08; found: C 54.78, H 6.36, N 16.10.

7-Bromo-5-[2-deoxy-β-D-erythro-*pentofuranosyl]-2-{[(dimethylamino)methylidene]amino}-3,5-dihydro-3-[(pivaloyloxy)methyl]-4*H-*pyrrolo[3,2-*d*]pyrimidin-4-one* (**8b**). As described for **8a**, with **6b** (150 mg, 0.20 mmol) and 0.01M NaOMe/MeOH: **8b** (70 mg, 68%). Colorless solid. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.48. UV (MeOH): 262 (20900), 309 (16700). ^{1}H-NMR ((D$_6$)DMSO): 8.52 (*s*, N=CH); 7.91 (*s*, H–C(6)); 6.87 (*t*, *J* = 6.6, H–C(1′)); 6.16 (*s*, CH_2O); 5.25 (*d*, *J* = 3.9, OH–C(3′)); 4.99 (*t*, *J* = 5.3, OH–C(5′)); 4.28 (*m*, H–C(3′));

3.79 (*m*, H–C(4′)); 3.53 (*m*, 2 H–C(5′)); 3.17, 2.98 (2*s*, Me_2N); 2.31–2.23 (*m*, 2 H–C(2′)); 1.09 (*s*, 3 Me). Anal. calc. for $C_{20}H_{28}BrN_5O_6$ (514.37): C 46.70, H 5.49, N 13.62; found: C 46.50, H 5.61, N 13.07.

*5-[2-Deoxy-β-*D-erythro-*pentofuranosyl]-2-{[(dimethylamino)methylidene]amino}-3,5-dihydro-7-iodo-3-[(pivaloyloxy)methyl]-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one* (**8c**). As described for **8a**, with **6c** (500 mg, 0.63 mmol) and 0.01M NaOMe/MeOH (35 ml): **8c** (256 mg, 73%). Colorless solid. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.52. UV (MeOH): 266 (21100), 312 (18700). ^{1}H-NMR ((D$_6$)DMSO): 8.51 (*s*, N=CH); 7.89 (*s*, H–C(6)); 6.86 (*t*, *J* = 6.6, H–C(1′)); 6.15 (*s*, CH_2O); 5.26 (*d*, *J* = 3.9, OH–C(3′)); 4.99 (*t*, *J* = 5.3, OH–C(5′)); 4.28 (*m*, H–C(3′)); 3.78 (*m*, H–C(4′)); 3.55 (*m*, 2 H–C(5′)); 3.16, 2.98 (2*s*, Me_2N); 2.36–2.22 (*m*, 2 H–C(2′)); 1.08 (*s*, 3 Me_3). Anal. calc. for $C_{20}H_{28}IN_5O_6$ (561.37): C 42.79, H 5.03, N 12.48; found: C 42.68, H 5.05, N 12.25.

*2-Amino-5-(2-deoxy-β-*D-erythro-*pentofuranosyl)-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one* (**1a**). Compound **7a** (700 mg, 2.18 mmol) was stirred in 25% aq. ammonia (50 ml) at 60° for 12 h in a sealed vessel. The solvent was evaporated, and the residue was dissolved in H_2O (50 ml) and chromatographed (*Serdolit AD-4* resin). The salt was washed off with distilled H_2O for 2 h, and the product was collected with MeOH/H_2O 1:5: **1a** (550 mg, 95%). Colorless solid. Crystallization from MeOH gave colorless crystals. M.p. 195–196°. TLC (CH_2Cl_2/MeOH 8:2): R_f 0.36. UV (0.1M sodium phosphate buffer pH 7.0): 232 (20000), 262 (8000), 287 (6200). ^{1}H-NMR ((D$_6$)DMSO): 10.60 (*s*, NH); 7.54 (*s*, H–C(6)); 6.79 (*m*, H–C(1′)); 6.01 (*s*, H–C(7)); 5.83 (*s*, NH_2); 5.21 (*s*, OH–C(3′)); 4.90 (*s*, OH–C(5′)); 4.27 (*m*, H–C(3′)); 3.70 (*m*, H–C(4′)); 3.47 (*m*, 2 H–C(5′)); 2.26 (*m*, H_β–C(2′)); 2.15 (*m*, H_α–C(2′)). Anal. calc. for $C_{11}H_{14}N_4O_4$ (266.25): C 49.62, H 5.30, N 21.04: found: C 49.65, H 5.27, N 20.87.

*2-Amino-7-bromo-5-(2-deoxy-β-*D-erythro-*pentofuranosyl)-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one* (**1b**). As described for **1a**, with **7b** (250 mg, 0.63 mmol) and 25% aq. ammonia (30 ml): **1b** (195 mg, 90%). M.p. > 210°. TLC (CH_2Cl_2/MeOH 8:2): R_f 0.7. UV (0.1M sodium phosphate buffer pH 7.0): 235 (21000), 272 (7300), 297 (6800). ^{1}H-NMR ((D$_6$)DMSO): 10.74 (*s*, NH); 7.54 (*s*, H–C(6)); 6.79 (*m*, H–C(1′)); 6.12 (*s*, NH_2); 5.21 (*d*, *J* = 3.3, OH–C(3′)); 4.93 (*d*, *J* = 4.9, OH–C(5′)); 4.25 (*m*, H–C(3′)); 3.76 (*m*, H–C(4′)); 3.53 (*m*, 2 H–C(5′)); 2.19 (*m*, H_β–C(2′)); 2.03 (*m*, H_α–C(2′)). Anal. calc. for $C_{11}H_{13}BrN_4O_4$ (345.15): C 38.28, H 3.80, N 16.23; found: C 38.38, H 3.75, N 16.36.

*2-Amino-5-(2-deoxy-β-*D-erythro-*pentofuranosyl)-3,5-dihydro-7-iodo-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one* (**1c**). As described for **1a**, with **7c** (220 mg, 0.49 mmol) and 25% aq. ammonia (30 ml): **1c** (180 mg, 93%). M.p. > 210°. TLC (CH_2Cl_2/MeOH 8:2): R_f 0.78. UV (0.1M sodium phosphate buffer pH 7.0): 237 (19700), 276 (7600), 299 (7000). ^{1}H-NMR ((D$_6$)DMSO): 10.74 (*s*, NH); 7.54 (*s*, H–C(6)); 6.79 (*m*, H–C(1′)); 6.12 (*s*, NH_2); 5.21 (*d*, *J* = 3.3, OH–C(3′)); 4.93 (*d*, *J* = 4.9, OH–C(5′)); 4.25 (*m*, H–C(3′)); 3.76 (*m*, H–C(4′)); 3.53 (*m*, 2 H–C(5′)); 2.26 (*m*, H_β–C(2′)); 2.05 (*m*, H_α–C(2′)). Anal. calc. for $C_{11}H_{13}IN_4O_4$ (392.15): C 33.69, H 3.34, N 14.29; found: 33.69, H 3.34, N 14.29.

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