7-Halogenated 7-Deaza-2′-deoxyinosines

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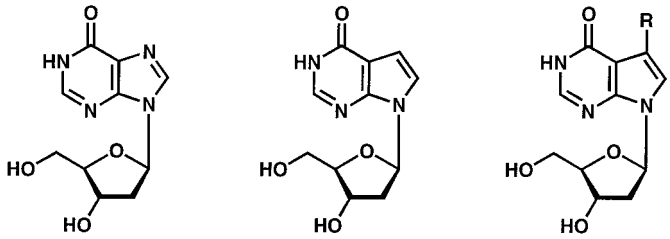
The synthesis of the 7-deaza-2′-deoxyinosine derivatives **3a**–**c** with chloro, bromo, and iodo substituents at position 7 is described. Glycosylation of the 7-halogenated 6-chloro-7-deazapurines **4a**–**c** or of the 7-halogenated 6-chloro-7-deaza-2-(methylthio)purines **9a**–**c** with 2-deoxy-3,5-di-*O*-(4-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**5**) furnished the intermediates **7a**–**c** and **11a**–**c**, respectively, which gave, upon deprotection, the desired nucleosides **3a**–**c**.

Introduction. – 2′-Deoxyinosine (**1**) is the classical universal nucleoside which shows ambiguous base pairing with the four natural components of DNA [1]. It is used for the synthesis of primers and probes in DNA technology [2–5]. Recently, it was found that 7-deaza-2′-deoxyinosine[1]) (**2**) is an efficient substitute of 2′-deoxyinosine [6].



1 **2** **3a** R = Cl, **b** R = Br, **c** R = I

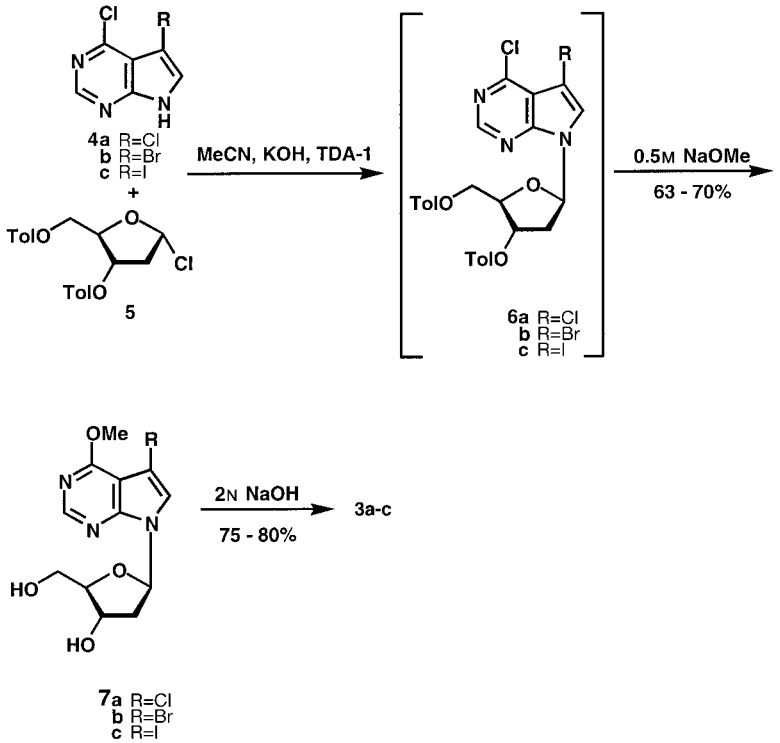
The present investigation is part of a study involving 7-deazapurine 2′-deoxyribonucleosides as substitutes of regular purine 2′-deoxynucleosides within DNA fragments. Earlier, various substituents such as halogeno, alkyl, alkynyl, or alkenyl groups were introduced at position 7 of 7-deaza-2′-deoxypurine nucleosides and incorporated later into oligonucleotides [7–11]. In the case of 7-deaza-2′-deoxyadenosine as well as 7-deaza-2′-deoxyguanosine, the 7-substitution led to a significant duplex stabilization with retention of the particular DNA structure [7–12]. Now, the synthesis of 7-chloro- (**3a**), 7-bromo- (**3b**), and 7-iodo-7-deaza-2′-deoxyinosine (**3c**) derivatives is described, which are the key intermediates for later studies on oligonucleotides.

Results and Discussion. – As nucleobase precursors of compounds **3a**–**c**, the 7-substituted 6-chloro-7-deazapurines[1]) **4a**–**c** [12][13] were chosen which have been

[1]) Purine numbering is used throughout the *General Part*; for systematic names, see *Exper. Part.*

used earlier in the synthesis of 7-substituted 7-deaza-2′-deoxyadenosine derivatives [12]. Stereoselective nucleobase-anion glycosylation of these aglycones with 2-deoxy-3,5-di-*O*-(4-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**5**) [14] was carried out as described before [12], with the exception that the intermediates **6a**–**c** were not isolated (*Scheme 1*). Now, a one-pot glycosylation of **4a**–**c** followed by simultaneous detoluoylation and Cl/OMe exchange at position 6 with 0.5M NaOMe/MeOH was performed, which yielded the corresponding 6-methoxy nucleosides **7a**–**c** directly and improved the former procedure significantly. Besides the easier workup, the total yield was increased by *ca.* 15% to 63–70%. Subsequent nucleophilic displacement of the MeO group by OH was performed with 2N aqueous NaOH giving the desired nucleosides **3a**–**c** (75–80% yield).

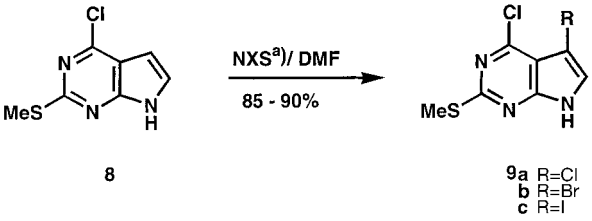
Scheme 1



Alternatively, we also investigated the possibility to incorporate the halogeno substituents at position 7 of the 6-chloro-7-deaza-2-(methylthio)purine **8**. We selected this substitution pattern because the nucleosides resulting after glycosylation can serve as universal intermediates also for the synthesis of 7-substituted 7-deazaadenine and 7-deazaguanine derivatives [15][16]. When compound **8** was treated with *N*-iodosuccinimide (NIS) in CH_2Cl_2 according to [13], a clean reaction was observed affording 7-substituted **9c** in 80% yield (*Scheme 2*). No formation of a 7,8-diiodo compound was detected (TLC or NMR monitoring of the crude reaction mixture). On the other hand, when compound **8** was brominated with *N*-bromosuccinimide (NBS) in the same

solvent, the formation of a mixture of three halogenated congeners took place (7-, 8-, and 7,8-dibromo-7-deaza-2-(methylthio)purines). However, exchange of CH_2Cl_2 by DMF overcame this problem and, therefore, DMF became the solvent of choice for this particular reaction. In this way, compounds **9a–c** were synthesized in 85–90% yield. The fact that the halogeno substituent was incorporated at the 7 position was established by ^{1}H- (see *Exper. Part*) and ^{13}C-NMR spectroscopy (see [17]).

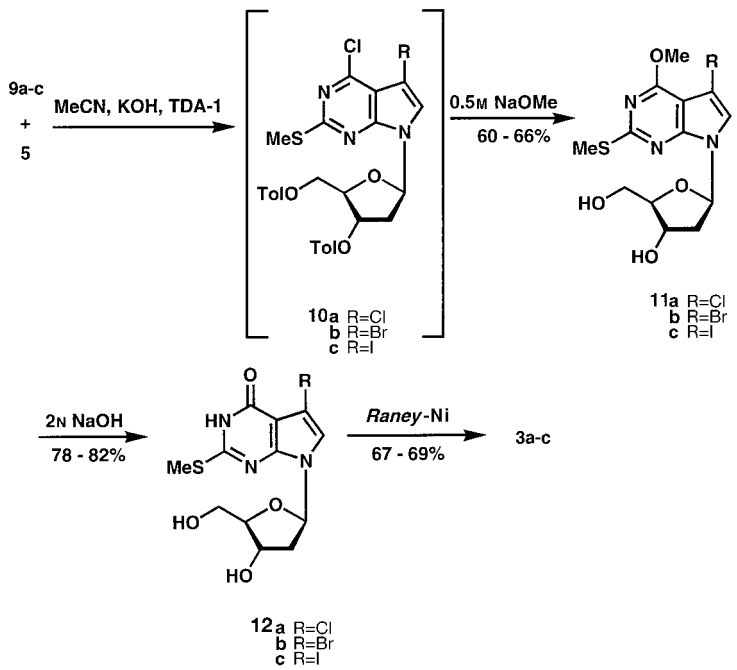
Scheme 2



[a]) NXS = *N*-chloro-, *N*-bromo, or *N*-iodosuccinimide

The subsequent glycosylation of the halogenated nucleobases **9a–c** was performed as described above without isolation of the intermediates **10a–c** (*Scheme 3*). The nucleosides **11a–c** were isolated in 60–66% total yield. Finally, the nucleophilic OMe/OH exchange reaction of **11a–c** was performed with 2N NaOH furnishing the nucleosides **12a–c** (78–82% yield). The latter were then desulfurized with *Raney*-Ni to give the nucleosides **3a–c**.

Scheme 3



All compounds were characterized by ^{1}H- and ^{13}C-NMR spectroscopy as well as by elemental analyses (*Table 1* and *Exper. Part*). According to *Table 1*, the C(7) signal of the 7-unsubstituted 7-deazapurine nucleoside **2** is shifted downfield upon chlorination and upfield upon bromination and iodination (**3a**: $\Delta\delta = -3.8$; **3b**: $\Delta\delta = +16.1$; **3c**: $\Delta\delta = +50.9$).

Table 1. *^{13}C-NMR Data of 7-Deaza-2′-deoxyinosines*[a])

	C(2)[b]) C(2)[c])	C(4)[b]) C(7a)[c])	C(5)[b]) C(4a)[c])	C(6)[b]) C(4)[c])	C(7)[b]) C(5)[c])	C(8)[b]) C(6)[c])	MeO	MeS	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)
2	143.7	147.4	108.4	158.2	102.5	120.7			83.2	40.2	71.0	87.4	62.0
3a	144.9	146.2	104.8	156.9	106.3	117.8			82.9	[d])	70.7	87.5	61.7
b	145.3	146.8	105.9	157.7	90.2	120.1			83.0	[d])	70.7	87.5	61.7
c	144.6	147.2	108.0	157.7	55.4	125.6			83.2	[d])	70.9	87.6	61.8
7a [12]	151.6	150.1	102.7	162.3	102.7	121.6	53.9		83.1	40.6	70.9	87.6	61.6
b	151.5	150.7	104.1	162.3	86.6	124.1	53.9		83.2	[d])	70.9	87.6	61.6
c	151.2	150.9	106.5	162.1	51.1	129.0	53.6		83.6	[d])	70.7	87.4	61.6
11a	161.4	150.8	99.3	164.0	102.9	119.9	53.8	13.5	82.7	[d])	70.7	87.4	61.6
b	161.4	151.3	100.7	163.8	86.9	122.4	53.8	13.5	82.7	[d])	70.7	87.4	61.6
c	161.6	152.1	103.4	163.4	51.6	127.6	53.7	13.6	82.8	[d])	70.8	87.4	61.7
12a	156.7[e])	146.3[e])	101.2	157.3[e])	106.3	116.6		12.7	82.6	[d])	70.7	87.4	61.6
b	156.4[e])	146.7[e])	102.3	157.4[e])	90.4	119.1		12.7	82.6	[d])	70.7	87.4	61.6
c	156.6[e])	146.5[e])	104.3	157.7[e])	55.3	123.9		12.7	82.7	[d])	70.7	87.3	61.6

[a]) Measured in (D_6)DMSO. [b]) Purine numbering. [c]) Systematic numbering. [c]) Superimposed by (D_6)DMSO. [e]) Tentative.

Next, the sugar conformation of the nucleoside **2** as well as of **3a**–**c** in solution was compared with that of the parent purine nucleoside **1**. For this purpose, vicinal ^3J(H,H) couplings (*Table 2*) of **1**, **2**, and **3a**–**c** were taken from well-resolved ^{1}H-NMR spectra measured in D_2O. The conformation in solution ($N \rightleftarrows S$) was deduced from the pseudorotational parameters P and Ψ_m by application of the PSEUROT program[2]). The data are listed in *Table 2*. The rotational equilibrium about the C(4′)–C(5′) bond was calculated according to *Westhof et al.* [19] using the vicinal ^{1}H,^{1}H couplings between H–C(4′) and H–C(5′) as well as H′–C(5′), respectively (*Table 2*). From these data, a slight trend can be deduced: while l_d (**1**) exhibits a γ^{g+} population of 52%, this population is reduced to 44–46% in the cases of the 7-deazapurine nucleosides **2** and **3a**–**c**. These findings are in line with those obtained for other 7-deazapurine 2′-deoxynucleosides as compared to their corresponding purine counterparts [20].

Table 2. *^{3}J(H,H) Coupling Constants of the Sugar Moieties and Conformer Populations of Nucleosides* **1**, **2**, *and* **3a**–**c**[a])

	^3J(H,H) [Hz]						Conformation				
	J(1′,2′)	J(1′,2″)	J(2′,3′)	J(2″,3′)	J(3′,4′)	J(4′,5′)	%N	%S	%γ^{g+}	%γ^{t}	%γ^{g-}
l_d (**1**)	6.80	6.55	6.40	3.80	3.55	3.60, 4.75	35	65	52	30	18
c^7l_d (**2**)	7.15	6.60	6.40	3.40	3.50	3.90, 5.00	31	69	46	33	21
$Cl^7c^7l_d$ (**3a**)	6.90	6.60	6.45	3.60	3.55	3.90, 5.10	33	67	45	34	21
$Br^7c^7l_d$ (**3b**)	6.90	6.60	6.45	3.65	3.55	3.95, 5.10	33	67	44	34	22
$I^7c^7l_d$ (**3c**)	6.90	6.60	6.40	3.70	3.60	3.95, 5.10	34	66	44	34	22

[a]) Solvent, D_2O; r.m.s. ≤ 0.18 Hz; $|\Delta J_{max}| \leq 0.3$ Hz; T 303 K.

[2]) Version 6.2; licensor: Prof. Dr. *C. Altona*, *Gorlaeus Laboratories*, Leiden, The Netherlands [18].

As it can be seen from *Table 2*, the $N \rightleftarrows S$ equilibrium of 7-deaza-2′-deoxyinosine (**2**) is slightly biased towards the *S*-conformation. This effect is again compensated in the cases of the 7-halogeno-substituted 7-deaza-2′-deoxyinosines **3a**–**c** which show almost the same conformational parameters as 2′-deoxyinosine (**1**).

In conclusion, the halogenation reaction of 6-chloro-7-deaza-2-(methylthio)purine (**8**) leads, in DMF, exclusively to the 7-halogenated products **9a**–**c**. These compounds are useful precursors for the synthesis of 7-chloro- (**3a**), 7-bromo- (**3b**), and 7-iodo-7-deaza-2′-deoxyinosine (**3c**) as well as for 7-halogenated 7-deazaadenosine or 7-deazaguanosine derivatives. The importance of these 7-substituted 7-deazapurine nucleosides for the synthesis of derivatives carrying a linker and a reporter group at this favourable position is, meanwhile, well-established [15][17][21]. As the 2- and 8-positions of the regular 2′-deoxyinosine are unfavourable for such purposes, compound **3c** is an ideal precursor for the synthesis of 7-deaza-2′-deoxyinosine derivatives, which carry a reporter group at the sterically unproblematic position 7, and which can act as ambiguous primers and probes in DNA technology.

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Experimental Part

General. See [9]. TLC: Aluminium sheets coated with a 0.2-mm layer of silica gel *60* F_{254} (*Merck*, Germany). Flash chromatography (FC): at 0.5 bar; silica gel *60 H* (*Merck*, Germany). Solvent systems for TLC and FC: CH_2Cl_2/MeOH 9:1 (*A*), CH_2Cl_2/MeOH 8:2 (*B*). UV Spectra: *Hitachi-150-20* spectrometer (*Hitachi*, Japan). NMR Spectra: *Bruker-Avance-DPX-250* and *-AMX-500* spectrometers; δ values in ppm rel. to Me_4Si as internal standard (^1H and ^{13}C). Elemental analyses were performed by *Mikroanalytisches Laboratorium Beller*, Göttingen, Germany.

*5-Chloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-4-methoxy-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**7a**). To a soln. of **4a** [12] (1 g, 5.3 mmol) in MeCN (40 ml), KOH (0.75 g, 13.4 mmol) and TDA-1 (=tris[2-(2-methoxyethoxy)-ethyl]amine; 125 µl, 0.4 mmol) were added. After stirring at r.t. for 15 min, 2-deoxy-3,5-di-*O*-(4-toluoyl)-α-D-*erythro*-pentofuranosyl chloride [14] (**5**; 3.0 g, 7.7 mmol) was added, and stirring was continued for another 15 min. Insoluble material was filtered off and the filtrate evaporated and suspended in 0.5M NaOMe (20 ml). The suspension was stirred overnight and then evaporated and the residue applied to FC (column 20 × 5 cm, *A*): **7a** (1.0 g, 63%). Colourless solid. TLC (silica gel, *A*): R_f 0.53. All anal. data were identical to those described [12].

*5-Bromo-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-4-methoxy-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**7b**). As described for **7a** with **4b** [12] (1.4 g, 6.0 mmol), MeCN (40 ml), KOH (0.95 g, 17 mmol), TDA-1 (200 µl, 0.6 mmol), **5** (2.5 g, 6.4 mmol), and 0.5M NaOMe (20 ml): **7b** (1.4 g, 68%). Colourless solid. TLC (silica gel, *A*): R_f 0.56. UV (MeOH): 265 (9100), 281 (9700). ^{1}H-NMR ((D$_6$)DMSO): 8.44 (*s*, H–C(2)); 7.84 (*s*, H–C(6)); 6.59 (*t*, *J* = 6.8, H–C(1′)); 5.27 (*d*, *J* = 3.9, OH–C(3′)); 4.96 (*t*, *J* = 5.3, OH–C(5′)); 4.34 (*m*, H–C(3′)); 4.04 (*s*, MeO); 3.82 (*d*, H–C(4′)); 3.51 (*m*, 2 H–C(5′)); 2.23 (*m*, H–C(2′)). Anal. calc. for $C_{12}H_{14}BrN_3O_4$ (344.17): C 41.88, H 4.10, N 12.21; found: C 41.81, H 4.08, N 12.13.

*7-(2-Deoxy-β-*D-erythro-*pentofuranosyl)-5-iodo-4-methoxy-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**7c**). As described for **7a**, with **4c** [12] (1.7 g, 6.0 mmol), MeCN (40 ml), KOH (0.95 g, 17 mmol), TDA-1 (200 µl, 0.6 mmol), **5** (2.5 g, 6.4 mmol), and 0.5M NaOMe (20 ml): **7c** (1.65 g, 70%). Colourless solid. TLC (silica gel, *A*): R_f 0.60. UV (MeOH): 260 (9400), 282 (10800). ^{1}H-NMR ((D$_6$)DMSO): 8.43 (*s*, H–C(2)); 7.84 (*s*, H–C(6)); 6.58 (*t*, *J* = 6.9, H–C(1′)); 5.26 (*d*, *J* = 4.0, OH–C(3′)); 4.96 (*t*, *J* = 5.3, OH–C(5′)); 4.35 (*m*, H–C(3′)); 4.05 (*s*, MeO); 3.83 (*d*, H–C(4′)); 3.56 (*m*, 2 H–C(5′)); 2.24 (*m*, H–C(2′)). Anal. calc. for $C_{12}H_{14}IN_3O_4$ (391.16): C 36.85, H 3.61, N 10.74; found: C 36.70, H 3.80, N 10.60.

*5-Chloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-3,7-dihydro-4*H-*pyrrolo[2,3-*d*]pyrimidin-4-one* (**3a**). *a*) A soln. of **7a** (1.0 g, 3.3 mmol) in 2M NaOH (20 ml) was heated under reflux for 5 h. After cooling to r.t., the soln. was neutralized with 1M AcOH to pH 7 yielding a solid which was filtered and washed with H_2O: **3a** (710 mg, 75%). Colourless solid. TLC (silica gel, *B*): R_f 0.52. UV (MeOH): 263 (9000), 282 (sh, 7600). ^{1}H-NMR ((D$_6$)DMSO): 12.10 (*s*, NH); 7.92 (*s*, H–C(2)); 7.49 (*s*, H–C(6)); 6.45 (*t*, *J* = 6.3, H–C(1′)); 5.27 (br. *s*, OH–C(3′)); 4.96 (br. *s*, OH–C(5′)); 4.30 (*m*, H–C(3′)); 3.79 (*d*, H–C(4′)); 3.50 (*m*, 2 H–C(5′)); 2.39

(*m*, H_β–C(2′)); 2.20 (*m*, H_α–C(2′)). Anal. calc. for $C_{11}H_{12}ClN_3O_4$ (285.69): C 46.25, H 4.23, N 14.71; found: C 46.36, H 4.24, N 14.62.

b) To a soln. of **12a** (1.65 g, 5 mmol) in *N,N*-dimethylacetamide (40 ml), *Raney*-Ni suspension (20 ml) was added. After heating under reflux for 1.5 h, the soln. was filtered through a 1-cm layer of silica gel and washed with hot *N,N*-dimethylacetamide (3 × 50 ml). The combined filtrates were evaporated: **3a** (970 mg, 68%). Anal. data: identical to those described above.

*5-Bromo-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-3,7-dihydro-4*H-*pyrrolo[2,3-*d*]pyrimidin-4-one* (**3b**). *a*) As described for **3a** (in *a*)), with **7b** (1.1 g, 3.3 mmol): **3b** (860 mg, 79%). Colourless solid. TLC (silica gel, *B*): R_f 0.64. UV (MeOH): 264 (10900), 287 (8700). ^{1}H-NMR ((D$_6$)DMSO): 12.10 (*s*, NH); 7.94 (*s*, H–C(2)); 7.50 (*s*, H–C(6)); 6.44 (*t*, *J* = 6.3, H–C(1′)); 5.27 (br. *s*, OH–C(3′)); 4.96 (br. *s*, OH–C(5′)); 4.32 (*d*, H–C(3′)); 3.81 (*d*, H–C(4′)); 3.52 (*m*, 2 H–C(5′)); 2.37 (*m*, H_β–C(2′)); 2.20 (*m*, H_α–C(2′)). Anal. calc. for $C_{11}H_{12}BrN_3O_4$ (330.14): C 40.02, H 3.66, N 12.73; found: C 40.01, H 3.75, N 12.65.

b) As described for **3a** (in *b*)), with **12b** (1.88 g, 5 mmol) in *N,N*-dimethylacetamide (40 ml) and *Raney*-Ni suspension (20 ml): **3b** (1.1 g, 67%). Anal. data: identical to those described above.

*7-(2-Deoxy-β-*D-erythro-*pentofuranosyl)-3,7-dihydro-5-iodo-4*H-*pyrrolo[2,3-*d*]pyrimidin-4-one* (**3c**). *a*) As described for **3a** (in *a*)), with **7c** (1.2 g, 3.3 mmol): **3c** (995 mg, 80%) after crystallization from MeCN. Colourless solid. TLC (silica gel, *B*): R_f 0.69. UV (MeOH): 265 (13100), 282 (12000). ^{1}H-NMR ((D$_6$)DMSO): 12.01 (*s*, NH); 7.92 (*s*, H–C(2)); 7.53 (*s*, H–C(6)); 6.42 (*t*, *J* = 6.3, H–C(1′)); 5.26 (*d*, *J* = 4.0, OH–C(3′)); 4.94 (*t*, *J* = 6.6, OH–C(5′)); 4.31 (br. *s*, H–C(3′)); 3.80 (*d*, H–C(4′)); 3.43 (*m*, 2 H–C(5′)); 2.38 (*m*, H_β–C(2′)); 2.20 (*m*, H_α–C(2′)). Anal. calc. for $C_{11}H_{12}IN_3O_4$ (377.13): C 35.03, H 3.21, N 11.14; found: C 35.09, H 3.43, N 10.93.

b) As described for **3a** (in *b*), with **12c** (2.1 g, 5 mmol) in *N,N*-dimethylacetamide (40 ml) and *Raney*-Ni suspension (20 ml): **3c** (1.3 g, 69%). Anal. data: identical to those described above.

*4,5-Dichloro-2-(methylthio)-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**9a**). To a soln. of **8** (1.0 g, 5 mmol) in DMF (20 ml), *N*-chlorosuccinimide (1.0 g, 7.2 mmol) was added. After stirring for 18 h at r.t., the solvent was evaporated. The residue was crystallized from MeOH: **9a** (1.0 g, 85%). Colorless solid. M.p. 220–221°. TLC (silica gel, *A*): R_f 0.81. UV (MeOH): 224 (29000), 255 (28200), 282 (8800). ^{1}H-NMR ((D$_6$)DMSO): 12.66 (br. *s*, NH); 7.68 (*d*, H–C(6)); 2.54 (*s*, Me). Anal. calc. for $C_7H_5Cl_2N_3S$ (234.10): C 35.91, H 2.15, N 17.95; found: C 36.00, H 2.13, N 17.89.

*5-Bromo-4-chloro-2-(methylthio)-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**9b**). As described for **9a**, with **8** (1 g, 5 mmol) and *N*-bromosuccinimide (1 g, 5.5 mmol): **9b** (1.25 g, 90%). Colourless solid. TLC (silica gel, *A*): R_f 0.86. UV (MeOH): 228 (16600), 255 (25200), 284 (5300). ^{1}H-NMR ((D$_6$)DMSO): 12.72 (br. *s*, NH); 7.72 (*d*, H–C(6)); 22.53 (*s*, Me). Anal. calc. for $C_7H_5BrClN_3S$ (278.55): C 30.18, H 1.81, N 15.08; found: C 30.14, H 1.92, N 14.97.

*4-Chloro-5-iodo-2-(methylthio)-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**9c**). As described for **9a**, with **8** (1.0 g, 5 mmol) and *N*-iodosuccinimide (1.2 g, 5.2 mmol): **9c** (1.46 g, 90%). Colourless solid. TLC (silica gel, *A*): R_f 0.84. UV (MeOH): 225 (17300), 261 (27100), 285 (7800). ^{1}H-NMR ((D$_6$)DMSO): 12.70 (br. *s*, NH); 7.72 (*s*, H–C(6)); 2.54 (*s*, Me). Anal. calc. for $C_7H_5ClIN_3S$ (325.55): C 25.83, H 1.55, N 12.91; found: C 25.98, H 1.59, N 12.77.

*5-Chloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-4-methoxy-2-(methylthio)-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**11a**). To a soln. of **9a** (234 mg, 1 mmol) in MeCN (30 ml), KOH (0.38 g, 6.8 mmol) and TDA-1 (30 µl, 0.1 mmol) were added. After stirring at r.t. for 15 min, 2-deoxy-3,5-di-*O*-(4-toluoyl)-*α*-D-*erythro*-pentofuranosyl chloride [14] (**5**; 0.6 g, 1.5 mmol) was added and stirring continued for another 15 min. Insoluble material was filtered off and the filtrate evaporated and suspended in 0.5M NaOMe (20 ml). The suspension was stirred for 24 h and then evaporated and the residue applied to FC (column 20 × 5 cm, *A*): **11a** (207 mg, 60%). Colourless solid. TLC (silica gel, *A*): R_f 0.49. UV (MeOH): 244 (19900), 285 (11500). ^{1}H-NMR ((D$_6$)DMSO): 7.63 (*s*, H–C(6)); 6.54 (*t*, *J* = 6.5, H–C(1′)); 5.28 (*d*, *J* = 4.0, OH–C(3′)); 4.91 (*t*, *J* = 5.2, OH–C(5′)); 4.34 (br. *s*, H–C(3′)); 4.03 (*s*, MeO); 3.82 (*d*, H–C(4′)); 3.56 (*m*, 2 H–C(5′)); 2.56 (*s*, MeS); 2.23 (*m*, H–C(2′)). Anal. calc. for $C_{13}H_{16}ClN_3O_4S$ (345.80): C 45.15, H 4.66, N 12.15; found: C 45.29, H 4.75, N 12.05.

*5-Bromo-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-4-methoxy-2-(methylthio)-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**11b**). As described for **11a** with **9b** (280 mg, 1.0 mmol), MeCN (30 ml), KOH (0.38 g, 6.8 mmol), TDA-1 (30 µl, 0.1 mmol), **5** (0.6 g, 1.5 mmol), and 0.5M NaOMe (20 ml): **11b** (234 mg, 60%). Colourless solid. TLC (silica gel, *A*): R_f 0.50. UV (MeOH): 245 (24200), 287 (13300). ^{1}H-NMR ((D$_6$)DMSO): 7.63 (*s*, H–C(6)); 6.54 (*t*, *J* = 6.2, H–C(1′)); 5.31 (*d*, *J* = 3.7, OH–C(3′)); 4.94 (*t*, *J* = 4.6, OH–C(5′)); 4.33 (br. *s*, H–C(3′)); 4.03 (*s*, MeO); 3.81 (*d*, H–C(4′)); 3.50 (*m*, 2 H–C(5′)); 2.56 (*s*, MeS); 2.23 (*m*, H–C(2′)). Anal. calc. for $C_{13}H_{16}BrN_3O_4S$ (390.26): C 40.01, H 4.13, N 10.77; found: C 40.31, H 4.40, N 10.78.

*7-(2-Deoxy-β-*D*-*erythro*-pentofuranosyl)-5-iodo-4-methoxy-2-(methylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**11c**). As described for **11a**, with **9c** (325 mg, 1.0 mmol), MeCN (30 ml), KOH (0.38 g, 6.8 mmol), TDA-1 (30 µl, 0.1 mmol), **5** (0.6 g, 1.5 mmol), and 0.5M NaOMe (20 ml): **11c** (288 mg, 66%). Yellow solid. TLC (silica gel, *A*): R_f 0.52. UV (MeOH): 248 (28500), 287 (12500). ^{1}H-NMR ((D$_6$)DMSO): 7.67 (*s*, H–C(6)); 6.51 (*t*, *J* = 6.0, H–C(1′)); 5.27 (*d*, *J* = 4.2, OH–C(3′)); 4.89 (*t*, *J* = 5.4, OH–C(5′)); 4.33 (*m*, H–C(3′)); 4.03 (*s*, MeO); 3.81 (*d*, H–C(4′)); 3.54 (*m*, 2 H–C(5′)); 2.56 (*s*, MeS); 2.22 (*m*, H–C(2′)). Anal. calc. for $C_{13}H_{16}IN_3O_4S$ (437.26): C 35.71, H 3.69, N 9.61; found: C 35.88, H 3.51, N 9.78.

*5-Chloro-7-(2-deoxy-β-*D*-*erythro*-pentofuranosyl)-3,7-dihydro-2-(methylthio)-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one* (**12a**). A soln. of **11a** (1.7 g, 5 mmol) in 2M NaOH (25 ml) was heated under reflux for 3 h. After cooling to r.t., the soln. was neutralized with 1M AcOH to pH 7 yielding a solid which was filtered off and washed with H_2O: **12a** (1.3 g, 78%). Colourless solid. TLC (silica gel, *B*): R_f 0.70. UV (MeOH): 275 (10000). ^{1}H-NMR ((D$_6$)DMSO): 12.39 (*s*, NH); 7.37 (*s*, H–C(6)); 6.43 (*t*, *J* = 6.6, H–C(1′)); 5.30 (br. *s*, OH–C(3′)); 4.94 (br. *s*, OH–C(5′)); 4.32 (br. *s*, H–C(3′)); 3.80 (*d*, H–C(4′)); 3.51 (*m*, 2 H–C(5′)); 2.53 (*s*, MeS); 2.41 (*m*, H_β–C(2′)); 2.20 (*m*, H_α–C(2′)). Anal. calc. for $C_{12}H_{14}ClN_3O_4S$ (331.77): C 43.44, H 4.25, N 12.67; found: C 43.25, H 4.27, N 12.49.

*5-Bromo-7-(2-deoxy-β-*D*-*erythro*-pentofuranosyl)-3,7-dihydro-2-(methylthio)-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one* (**12b**). As described for **12a**, with **11b** (1.9 g, 5 mmol) and 2M NaOH (20 ml): **12b** (1.55 g, 82%). Colourless solid. TLC (silica gel, *B*): R_f 0.71. UV (MeOH): 276 (16100). ^{1}H-NMR ((D$_6$)DMSO): 12.34 (*s*, NH); 7.41 (*s*, H–C(6)); 6.45 (*t*, *J* = 6.2, H–C(1′)); 5.30 (br. *s*, OH–C(3′)); 4.95 (br. *s*, OH–C(5′)); 4.32 (br. *s*, H–C(3′)); 3.80 (*d*, H–C(4′)); 3.51 (*m*, 2 H–C(5′)); 2.53 (*s*, MeS); 2.40 (*m*, H_β–C(2′)); 2.20 (*m*, H_α–C(2′)). Anal. calc. for $C_{12}H_{14}BrN_3O_4S$ (376.22): C 38.31, H 3.75, N 11.17; found: C 38.62, H 3.92, N 10.92.

*7-(2-Deoxy-β-*D*-*erythro*-pentofuranosyl)-3,7-dihydro-5-iodo-2-(methylthio)-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one* (**12c**). As described for **12a**, with **11c** (2.2 g, 5 mmol) and 2M NaOH (20 ml): **12c** (1.7 g, 80%). Colourless solid. TLC (silica gel, *B*): R_f 0.75. UV (MeOH): 276 (16100). ^{1}H-NMR ((D$_6$)DMSO): 12.34 (*s*, NH); 7.37 (*s*, H–C(6)); 6.42 (*t*, *J* = 6.5, H–C(1′)); 5.26 (br. *s*, OH–C(3′)); 4.93 (br. *s*, OH–C(5′)); 4.31 (br. *s*, H–C(3′)); 3.79 (*d*, H–C(4′)); 3.52 (*m*, 2 H–C(5′)); 2.51 (*s*, MeS); 2.17 (*m*, H–C(2′)). Anal. calc. for $C_{12}H_{14}IN_3O_4S$ (423.22): C 34.06, H 3.33, N 9.93; found: C 34.35, H 3.38, N 9.75.

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