

2-Amino-8-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-4(8*H*)-one: Synthesis and Conformation of a 5-Aza-7-deazaguanine Fluoronucleoside

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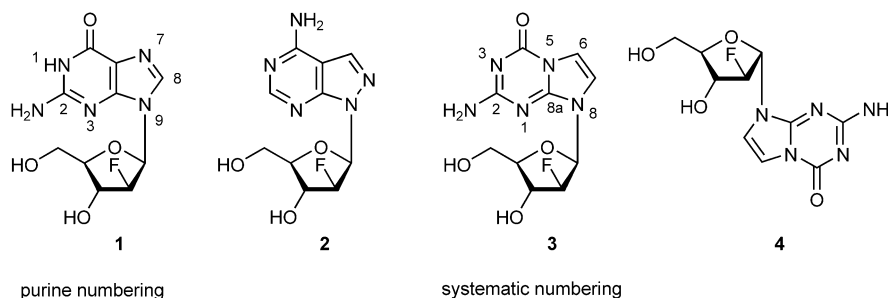
Nucleobase-anion glycosylation of 2-[(2-methyl-1-oxopropyl)amino]imidazo[1,2-*a*]-1,3,5-triazin-4(8*H*)-one (**6**) with 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro- α -D-arabinofuranosyl bromide (**8**) furnishes a mixture of the benzoyl-protected anomeric 2-amino-8-(2-deoxy-2-fluoro-D-arabinofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-4(8*H*)-ones **9/10** in a ratio of *ca.* 1:1. After deprotection, the inseparable anomeric mixture **3/4** was silylated. The obtained 5-*O*-[(1,1-dimethylethyl)diphenylsilyl] derivatives **11** and **12** were separated and desilylated affording the nucleoside **3** and its α -D anomer **4**. Similar to 2'-deoxy-2'-fluoroarabinoguanosine, the conformation of the sugar moiety is shifted from *S* towards *N* by the fluoro substituent in *arabino* configuration.

Introduction. – Naturally occurring organohalogen compounds are abundant in plants, microorganisms, and fungi [1]. However, only 13 F-containing natural products have been isolated. Their structures cover relatively simple molecules such as fluoroacetate, which was already found in 1943 [2], and more-complicated molecules such as the nucleoside nucleocidin [3]. Recently, 5-fluorouracil derivatives were detected in sponge [4].

It has been reported that an F-substituent strongly affects the chemical, physical, and biological properties of molecules [5]. F-Substitution at nucleosides can enhance biological activity and increase chemical or metabolic stability [6–8]. Owing to the small *Van der Waals* radius of the F-substituent that is comparable with that of a H-atom, the presence of an F-atom in a nucleoside does not lead to significant steric perturbations of the shape of the molecule. Thus, fluorinated nucleosides are isosteric to their natural counterparts. At the same time, the F-atom is the substituent with the highest electronegativity. Its incorporation gives rise to essential changes of the electronic properties of a heterocyclic base and/or the conformational behavior of the pentofuranose ring and, as a consequence, to changes of the biochemical properties of the modified nucleosides. Thus, C(2) fluorination of adenosine residues renders these analogues resistant towards deamination by adenosine deaminase (ADA) [8]. The 2'-deoxy-2'-fluoroguanosine, which may be considered as an analogue of guanosine and simultaneously of 2'-deoxyguanosine, shows high anti-influenza-virus activity as well as a higher metabolic stability regarding cleavage by purine nucleoside phosphorylase (PNP) [9].

Previously, several purine nucleosides containing the 2-deoxy-2-fluoro- β -D-arabinofuranosyl moieties such as the 2'-deoxyguanosine derivative **1** have been synthesized

[10]. These compounds have the potential to act as antiviral and antileukemic agents [9][11][12]. More recently, the synthesis of 1-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (**2**) has been reported, which shows activity against human cytomegalovirus and hepatitis-B virus, as well as against herpes-simplex virus [13].

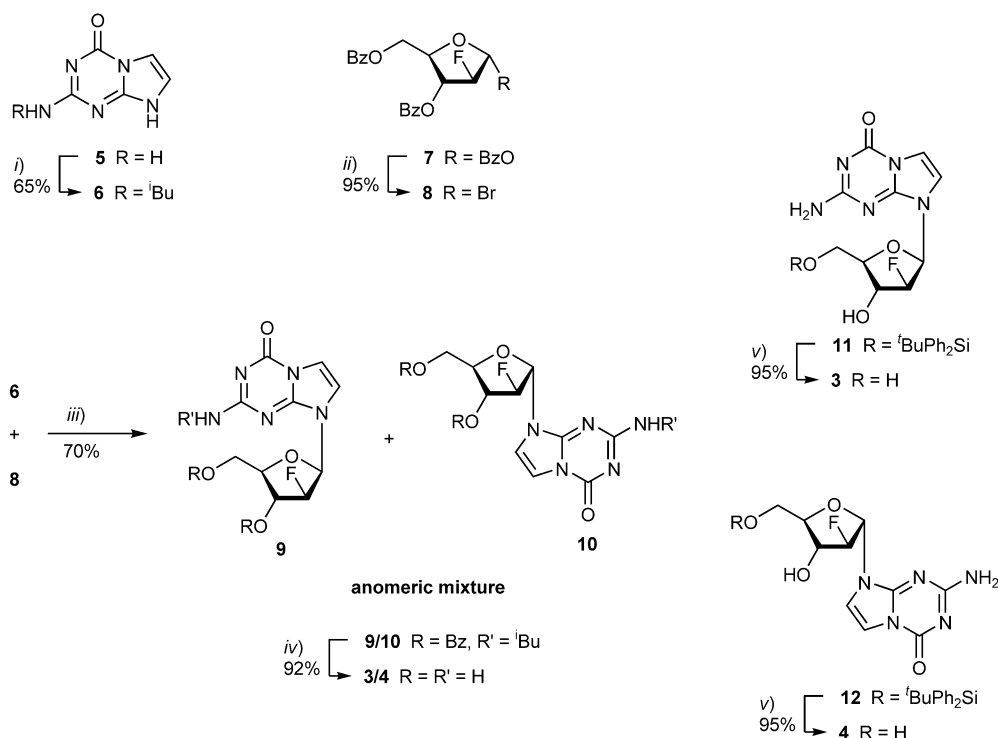


In nucleosides the most populated conformations of the furanose ring are North (*N*; C(3')-*endo*) and South (*S*; C(2')-*endo*). These conformations are dependent of various *gauche* and anomeric effects [14]. In 2'-deoxyribonucleosides, the 5'-OH and the 3'-OH groups prefer a *gauche* orientation resulting in an *S*-sugar pucker. In the case of 2'-deoxy-2'-fluoro- β -D-arabinonucleosides containing a modified nucleobase, the situation is more complex depending on the strong *gauche* effect of the highly electronegative F-atom and on the anomeric-effect influences of the modified base [15][16]. In continuation of our studies performed on pyrazolo[3,4-*d*]pyrimidine 2'-deoxy-2'-fluoro-D-arabinofuranonucleosides, we report on the synthesis and conformational properties of the of 2-aminoimidazo[1,2-*a*]-1,3,5-triazin-4(8*H*)-one nucleosides **3** and **4** containing the sugar moiety with the F-substituents in the 2'-'up' position (*arabino* configuration).

Results and Discussion. – *Synthesis.* Various synthetic routes have been developed to prepare 2'-deoxy-2'-fluoro- β -D-arabinofuranonucleosides [17][18]. The synthesis of the target molecules **3** and **4** was performed in a convergent way as it has been reported for the fluorinated nucleoside **2** [8]. Before glycosylation, 2-aminoimidazo[1,2-*a*]-1,3,5-triazin-4(8*H*)-one (**5**) was protected at the 2-amino group with an isobutyryl residue (\rightarrow **6**) [19] (*Scheme*). The condensation of **6** with the fluoroglycosyl bromide **8** was then performed under the conditions of nucleobase-anion glycosylation in MeCN in the presence of K₂CO₃ or DBU as base [13][20]. For this purpose, commercially available 1,3,5-tri-*O*-benzoyl-2-deoxy-2-fluoro- α -D-arabinofuranose (**7**) was readily transformed to 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro- α -D-arabinofuranosyl bromide (**8**) [21]. The glycosylation of **6** [19] with the fluoroglycosyl bromide **8** was finally carried out in MeCN, with TDA-1 (tris[2-(2-methoxyethoxy)ethyl]amine) as a catalyst and potassium carbonate as base. Compared to the glycosylation reaction of the same base with the 2-deoxy-3',5'-di-*O*-(*p*-toluoyl)- β -D-*erythro*-pentofuranosyl chloride [19], the reaction was prolonged (24 h). As a partial deprotection of the benzoyl group was observed, the reaction mixture was directly treated with ammonia-saturated MeOH to give an anomeric-nucleoside mixture **3/4** in 55% yield. However, application of the recently

suggested DBU salt glycosylation [13] for the same condensation of **6** with **8** gave also an anomer mixture of protected nucleosides **9/10**, but in higher yield (70%). At this stage, the ^1H -NMR spectra and HPLC profiles displayed a *ca.* 1:1 ratio (α/β -D) of the anomeric nucleosides (data not shown).

Scheme



i) Isobutyric anhydride, H₃PO₄, reflux, 1 h, 65%. ii) 30% HBr soln./AcOH, CH₂Cl₂, 18 h; r.t.; 95%. iii) DBU, MeCN, Ar, 24 h, r.t.; 70%. iv) NH₃ (g) in MeOH, 24 h, r.t.; 92%. v) Bu₄NF, THF, 0.5 h, r.t.; 95%.

The formation of the anomeric-nucleoside mixture obtained during nucleobase-anion glycosylation differs from the outcome of the reaction products of other nucleobases. In most other cases, a stereoselective reaction is observed when the fluoro- β -D-glycosyl bromide **8** is employed [22]. This was verified with pyrazolo[3,4-*d*]pyrimidines as well as with pyrimidine nucleosides [18]. As the nucleobase **6** yields also anomer mixtures when the stereochemically pure 2-deoxy-3',5'-di-*O*-(*p*-toluoyl)- β -D-*erythro*-pentofuranosyl chloride is employed, the formation of anomer mixtures is the result of the particular properties of the protected nucleobase **6**. The anomer mixture of the fluoronucleosides **9/10** was separable by anal. HPLC, but not on a preparative scale by silica-gel column chromatography. Thus, deprotection with ammonia-saturated MeOH was performed as described [23] resulting again in an inseparable mixture of the free nucleosides **3/4** (92% yield). To accomplish separation, the mixture **3/4** was transiently protected with the (*tert*-butyl)diphenylsilyl residue by

treatment with (*tert*-butyl)chlorodiphenylsilane/1*H*-imidazole at room temperature. The obtained anomer mixture **11/12** of the 5'-*O*-silylated compounds was now separable by column chromatography, and the individual anomers **11** (β -D) and **12** (α -D) were isolated in 28% and 27% yield, respectively. Final deprotection of **11** or **12** with Bu₄NF in THF furnished the nucleosides **3** and **4** (*Scheme*). The anomeric configuration of compounds **3**, **4**, **11**, and **12** was assigned from the ¹H- and ¹³C-NMR spectra (*Tables 1* and *2*, resp.)

The ¹H-NMR spectra of the β -D-anomers **3** and **11** show a shift of the H–C(2') and H–C(4') resonances to a higher field compared to the α -D-anomers **4** and **12** (*Table 1*). Regarding the ¹³C-NMR spectra, the C(1') and C(2') resonances are shifted downfield (4–5 ppm) passing from the β -D-anomers to the α -D-anomers (eclipsing interaction of the base and the F-atom). The same observation can be made with the C(4') resonances (3–4 ppm). The *J*(F,C(1')) coupling constants are decreased by 20 Hz and the *J*(F,C(2')) couplings are increased by 6–7 Hz when going from the α -D-anomers **4** and **12** to the β -D-anomers **3** and **11** (*Table 2*). These observations are in good agreement with data previously reported for other pairs of anomers [10]. Moreover, it was stated that the ⁵*J*(H–C(7),F) and ⁴*J*(C(7),F) long-range couplings are observed in the purine 2'-deoxy-2'-fluoro- β -D-arabinofuranonucleosides, but not in the α -D-anomers [10]. These long-range couplings are indicative for the physical proximity of the nuclei involved. In our case, the presence of the ⁵*J*(H–(7),F) and also ⁴*J*(C(7),F) long-range couplings unequivocally characterize the β -D-anomer structures of **3** and **11** (see *Table 2* and *Exper. Part*). In the case of the α -D-anomers **4** and **12**, the assignment of the chemical shifts of C(1') and C(4') (which are very close) was made unequivocally from the coupling constants (*Table 2*).

Table 1. ¹H-NMR Chemical Shifts and Coupling Constants of Sugar Moieties of Fluorinated Nucleosides^{a)}

	δ (H) [ppm]						<i>J</i> [Hz]							
	H–C(1')	H–C(2')	H–C(3')	H–C(4')	H–C(5')	H'–C(5')	<i>J</i> (1',2')	<i>J</i> (1',F)	<i>J</i> (2',3')	<i>J</i> (2',F)	<i>J</i> (3',4')	<i>J</i> (3',F)	<i>J</i> (4',5')	<i>J</i> (4',5'') ^{b)}
3	6.18	5.16	4.36	3.82	3.65	3.59	4.35	13.6	4.4	52.4	4.6	18.4	2.9	4.9
4	6.08	5.42	4.35	4.22	3.55	3.51	2.75	15.8	3.3	51.3	4.75	19.7	4.1	5.3
11	6.22	5.21	4.45	3.97	3.93	3.87	4.4	14.6	<i>ca.</i> 3.6	52.1	<i>ca.</i> 4.0	18.7	3.5	5.6
12	6.10	5.47	4.51	4.40	3.82	3.78	2.3	16.2	2.5	51.4	4.55	19.9	3.9	5.0

^{a)} Measured in (D₆)DMSO. ^{b)} 5'' is the short form of H'–C(5').

Table 2. ¹³C-NMR Chemical Shifts and *J*(F,C) [Hz] Coupling Constants of Nucleosides

	C(2) ^{c)}	C(4) ^{c)}	C(6) ^{c)}	C(7) ^{c)}	C(8a) ^{c)}	C(1')	C(2')	C(3')	C(4')	C(5')	C=O (Bz)
	C(2) ^{d)}	C(6) ^{d)}	C(7) ^{d)}	C(8) ^{d)}	C(4) ^{d)}						ⁱ Bu; ⁱ Bu
1 ^{a)}	149.93	165.34	108.29	115.41	150.25	81.00	95.27	73.21	86.66	60.60	
9/10 ^{b)}	150.18	161.35	109.69	117.60	150.54	83.01	94.91(9) 91.97(10)	81.71	84.81	63.62	177.27 35.21; 19.51
3 ^{a)}	149.86	165.31	108.25	115.35 (<i>J</i> = 3.1)	150.22	80.95 (<i>J</i> = 16.65)	95.23 (<i>J</i> = 190.9)	71.93 (<i>J</i> = 22.9)	83.47 (<i>J</i> = 5.75)	60.02	
4 ^{a)}	149.95	165.28	108.46	115.04	150.37	85.81 (<i>J</i> = 36.0)	99.41 (<i>J</i> = 183.95)	73.46 (<i>J</i> = 23.15)	86.58 (<i>J</i> = 4.5)	60.72	
11 ^{a)}	149.78	165.32	108.31	115.14 (<i>J</i> = 4.13)	150.36	80.89 (<i>J</i> = 16.5)	95.17 (<i>J</i> = 190.8)	72.42 (<i>J</i> = 23.3)	82.94 (<i>J</i> = 5.25)	63.22	26.61; 18.82
12 ^{a)}	149.89	165.27	108.49	114.94	150.28	86.26 (<i>J</i> = 36.4)	99.37 (<i>J</i> = 184.2)	73.19 (<i>J</i> = 24.0)	86.23 (<i>J</i> = 4.1)	62.85	26.56; 18.85

^{a)} Measured in (D₆)DMSO. ^{b)} Measured in CDCl₃. ^{c)} Systematic numbering. ^{d)} Purine numbering.

Conformation of the Sugar Moiety. The conformational analysis of the furanose rings of nucleosides **3** and **4** was performed with the PSEUROT program (version 6.3) [24] which calculates the best fits of the three experimental $J(\text{H,H})$ coupling constants ($^3J(1',2')$, $^3J(2',3')$, $^3J(3',4')$) and two experimental $J(\text{H,F})$ coupling constants ($^3J(1',\text{F})$, $^3J(3',\text{F})$) to the five conformational parameters (P (= phase angle of pseudorotation) and ψ_m (= degree of pucker) for both North (N) and South (S) conformers and corresponding mol fractions). The use of both $^3J(\text{H,H})$ and $^3J(\text{H,F})$ coupling constants permits a detailed conformational analysis of the pentofuranose rings because of the overwhelming increase of the number of experimental data points over the puckering parameters P and ψ_m [25]. The coupling constants were taken from well-resolved ^1H -NMR spectra measured in (D_6)DMSO containing one drop of D_2O . The use of D_2O or (D_6)DMSO alone did not permit to calculate all coupling constants due to signal overlap (Table 3). The resulting optimized geometries of N and S pseudorotamers are presented in Table 4.

Table 3. Pseudorotational Parameters^{a)} of Compounds **3**, **4**, and **13–15**^{b)} and Conformation^{a)} at the $\text{C}(4')\text{--C}(5')$ Bond of Nucleosides

	P	$\psi_{m(N)}$	P	$\psi_{m(S)}$	R.m.s.	$ \Delta J_{\text{max}} $	N [%]	S [%]	$\gamma^{(+)\text{g}}$ [%]	γ^t [%]	$\gamma^{(-)\text{g}}$ [%]
3 ^{c)} ^{d)}	– 13.3	36.0 ^{e)}	137.6	41.0 ^{e)}	0.250	0.76	50	50	58	32	10
4 ^{c)} ^{d)}	52.0	34.0 ^{e)}	213.1	41.0 ^{e)}	0.022	0.08	55	45	40	37	23
13 ^{c)} ^{f)}	19.0 ^{e)}	36.0 ^{e)}	163.5	31.7	0.184	0.300	37	63	48	33	19
14 ^{f)} ^{g)}	54.5	41.0 ^{e)}	181.0	41.0 ^{e)}	0.000	0.000	50	50			
15 ^{f)} ^{g)}	19.0	36.0 ^{e)}	156.0	36.0 ^{e)}	0.400	0.500	29	71	53	30	17

^{a)} P = phase angle of pseudorotation, ψ_m = degree of pucker; N = North-type conformation, S = South-type conformation, γ = torsion angle about $\text{C}(4')\text{--C}(5')$. ^{b)} **13** [26a]: 2-amino-8-(2-deoxy- β -D-erythro-pentofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-4(8*H*)-one; **14** [10]: 9-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)-guanine; **15**: 2'-deoxyguanosine. ^{c)} Results obtained with three coupling constants. ^{d)} (D_6)DMSO + $\epsilon\text{D}_2\text{O}$. ^{e)} Values fixed during the final calculations. ^{f)} D_2O . ^{g)} Results obtained with three coupling constants.

Table 4. Sugar Conformations of Nucleosides **3**, **4**, and **13–18**^{a)} in Solution

	Conformation		Conformation
3 ^{b)} ^{c)}	54% N	14 ^{d)} ^{e)}	50% N
4 ^{b)} ^{c)}	53% N	15 ^{d)} ^{e)}	29% N
13 ^{b)} ^{d)}	37% N	17 ^{b)} ^{c)}	98% N
16 ^{d)} ^{e)}	22% N	18 ^{d)} ^{e)}	37% N

^{a)} **13** [26a]: 2-amino-8-(2-deoxy- β -D-erythro-pentofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-4(8*H*)-one; **14** [10]: 9-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)guanine; **15**: 2'-deoxyguanosine; **16** [19]: 2-amino-8-(2-deoxy- α -D-erythro-pentofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-4(8*H*)-one; **17** [16]: 6-amino-3-bromo-1-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one; **18** [26b]: 6-amino-3-bromo-1-(2-deoxy- β -D-erythro-pentofuranosyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one. ^{b)} Data obtained with five coupling constants. ^{c)} (D_6)DMSO + D_2O . ^{d)} D_2O . ^{e)} Data obtained with three coupling constants.

In the case of the β -D-anomer **3**, the presence of the F-atom shifts the sugar population towards North conformers (54% N) in comparison with the 2-amino-8-(2-deoxy- β -D-erythro-pentofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-4(8*H*)-one (**13**; 37%) [26a]. The same observation can also be made in the case of 9-(2'-deoxy-2'-fluoro- β -

D-arabinofuranosyl)guanine (**14**; 50% *N*) [10] and 2'-deoxyguanosine (**15**; 29% *N*). Thus, the presence of the F-atom in an 'up' position (*arabino* configuration) enhances the population of the *N* conformers by 21% in the case of guanine nucleosides, and by 17% in the case of 5-aza-7-deazaguanine nucleosides. The *gauche* effect of the ring O-atom and of the F-atom seems to govern the overall sugar conformation. The same behavior was found for the α -D-anomer **4** (53% *N*) compared to 2-amino-8-(2-deoxy- α -D-*erythro*-pentofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-4(8*H*)-one (**16**; 22% *N*) [19]. The conformations at the C(4')–C(5') bond of **3** and **4**, taken from the *J*(H,H) coupling constants *J*(4',5'), and *J*(4',5''), were calculated according to *Westhof et al.* [27]. The values are similar to that of 2'-deoxyguanosine and 5-aza-7-deaza-2'-deoxyguanosine (**13**) (Table 3).

It is known that purine 2'-deoxy-2'-fluoro- β -D-arabinonucleosides exist in a *ca.* 1:1 mixture of *N* and *S* conformers [15]. The strong *gauche* effect of the highly electronegative F-atom leads to a high population of *S* conformers, but in terms of the anomeric effect, the *N* conformer is energetically favored. These different contributions lead to an almost equal population of conformers. This is also observed in our case. The sugar moiety of the β -D-fluoroarabinofuranoside **3** exists to 54% in the *N* conformation, a value which is comparable with that of compound **14** (50% *N*) [10].

Conclusion. – Even if it is known from purine 2'-fluororibonucleosides that the main sugar conformation is the North conformation [28], the situation is more complex for nucleosides with modified nucleobases [16][29]. Examples taken from the literature show normally a preferential South conformation in the case of 2'-fluoro 'up' arabinonucleosides [30]. However, from this study and from our recent findings [16], it is obvious that 2'-fluoro substituents in *arabino* configuration can also lead to sugar moieties with a preferential North conformation. The fluoronucleoside derivatives **3** and **4** were also evaluated *in vitro* for their activity against RNA virus (human immunodeficiency virus, HIV-I) and DNA viruses (BVDV, yellow fever virus YFV, Dengue virus (DENV-I), and West Nile virus (WNV)). No significant antiviral activity was observed.

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Experimental Part

General. Chemicals were purchased from *ACROS*, *Fluka*, or *Sigma-Aldrich*. The 1,3,5-tri-*O*-benzoyl-2-deoxy-2-fluoro- α -D-arabinofuranose (**7**) was a commercial product of *ICN Biomedicals GmbH*. Solvents: technical grade, distilled before use. Eluents (*v/v*) for TLC and chromatography: CH₂Cl₂/MeOH 98:2 (*A*), CH₂Cl₂/MeOH 95:5 (*B*), CH₂Cl₂/MeOH 9:1 (*C*), and CH₂Cl₂/MeOH 8:2 (*D*). Flash chromatography (FC): 0.4 bar, silica gel 60 *H* (*Merck*, Darmstadt, Germany). TLC: aluminium sheet, silica gel 60 *F*₂₅₄ (0.2 mm, *VWR*, Germany). M.p.: *Berl* block apparatus; uncorrected. UV Spectra: *UV-3000* spectrophotometer (*Hitachi*, Japan); in nm. NMR Spectra: *Bruker-AMX-500* NMR spectrometer at 303 K and at 500.13 MHz for ¹H, 125.13 MHz for ¹³C, and 235.36 MHz for ¹⁹F; chemical shift values δ in ppm rel. to internal SiMe₄ (¹H, ¹³C) or CFCl₃ (¹⁹F); coupling constants *J* in Hz; ¹H-NMR of **3** and **4** in (D₆)DMSO containing one drop of D₂O. Microanalyses were performed by *Mikroanalytisches Labor Beller*, Göttingen, Germany.

3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro- α -D-arabinofuranosyl Bromide (**8**) [21]. To a soln. of 1,3,5-tri-*O*-benzoyl-2-deoxy-2-fluoro- α -D-arabinofuranose (**7**) [21] (1.0 g, 2.15 mmol) in CH₂Cl₂ (5 ml), 30% HBr soln. in

AcOH (1.2 ml) was added. The mixture was stirred at r.t. for 16 h and evaporated. The oily residue was redissolved in CH_2Cl_2 (20 ml), the soln. washed with H_2O (5 ml) and sat. NaHCO_3 soln. (5 ml), dried (MgSO_4), and evaporated, and the obtained viscous syrup further dried under high vacuum for 18 h at r.t. and used in the next step without purification.

2-Amino-8-(2-deoxy-2-fluoro-D-arabinofuranosyl)imidazo[1,2-a]-1,3,5-triazin-4(8H)-ones (**3/4**). Compound **6** [19] (100 mg, 0.45 mmol) was dissolved in dry MeCN (12 ml) under gentle warming. After addition of K_2CO_3 (200 mg, 1.45 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1; 20.24 μl , 63.3 μmol), the soln. was stirred for 10 min at r.t. Then, **8** (200 mg, 0.43 mmol) was added, and stirring was continued for 24 h. The insoluble material was filtered off, the filtrate evaporated, and the residue redissolved in sat. NH_3/MeOH (40 ml) and stirred at r.t. for 24 h. The soln. was evaporated, and the residue applied to FC (silica gel, 10×6 cm column, C and D): inseparable anomer mixture **3/4** (67.5 mg, 55%). Colorless foam. For data of the separated anomers, see below. Anal. calc. for $\text{C}_{10}\text{H}_{12}\text{FN}_5\text{O}_4$ (285.23): C 42.11, H 4.24, N 24.55; found: C 41.96, H 4.14, N 24.38.

8-(3,5-Di-O-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl)-2-[(2-methyl-1-oxopropyl)amino]imidazo[1,2-a]-1,3,5-triazin-4(8H)-ones (**9/10**). To a suspension of **6** [19] (100 mg, 0.45 mmol) in dry MeCN (5 ml) under Ar was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 70 μl , 0.47 mmol) while stirring at r.t. Stirring was continued for 15 min. A soln. of **8** (200 mg, 0.43 mmol) in MeCN (1.5 ml) was added dropwise (5 min) to the mixture. Stirring was continued for 24 h at r.t. The solvent was evaporated, affording a syrup which was dissolved in eluent A, adsorbed on silica gel, and applied to FC (silica gel, 15×6 cm column, A and B): **9/10** (170 mg, 70%). Colorless foam. TLC (silica gel, B): R_f 0.60. UV (MeOH): 258 (13900). $^1\text{H-NMR}$ (CDCl_3): 1.23, 1.24, 1.26, 1.27 (4s, 12 H, 4 Me); 3.06 ('sept.', $J = 13.49, 26.97$, 2 H, CH); 4.82 (m, 6 H, H-C(4')(α/β), H-C(5')(α/β), H'-C(5')(α/β)); 5.42 (m, 1 H, H-C(2')(β)); 5.62, 5.70, 5.77 (3m, 3 H, H-C(3')(α/β), H-C(2')(α)); 6.61 (m, 1 H, H-C(1')(α)); 6.70 (m, 1 H, H-C(1')(β)); 7.45–7.56 (2m, 16 H, H-C(6)(α/β), H-C(7)(α/β), Ph); 8.09 (m, 8 H, Ph); 8.47 (s, 2 H, NH).

2-Amino-8-(2-deoxy-2-fluoro-D-arabinofuranosyl)imidazo[1,2-a]-1,3,5-triazin-4(8H)-ones (**3/4**) from **9/10**. The anomer mixture **9/10** (150 mg, 0.27 mmol) was stirred in sat. NH_3/MeOH (7 ml) at r.t. for 24 h. The soln. was evaporated, and the crude product was applied to FC (silica gel, 10×6 cm column, C and D): inseparable anomer mixture **3/4** (70 mg, 92%). Colorless foam.

2-Amino-8-[2-deoxy-5-O-[(1,1-dimethylethyl)diphenylsilyl]-2-fluoro- β -D-arabinofuranosyl]imidazo[1,2-a]-1,3,5-triazin-4(8H)-one (**11**) and 2-Amino-8-[2-deoxy-5-O-[(1,1-dimethylethyl)diphenylsilyl]-2-fluoro- α -D-arabinofuranosyl]imidazo[1,2-a]-1,3,5-triazin-4(8H)-one (**12**). The anomer mixture **3/4** (ca. 1:1; 235 mg, 0.83 mmol) in dry DMF (5 ml) was treated with *tert*-butylchlorodiphenylsilane (0.25 ml, 0.96 mmol) and 1H-imidazole (140 mg, 2.06 mmol) at r.t. while stirring. Stirring was continued for 48 h, and the solvent was evaporated. The residue was applied to FC (silica gel, 20×6 cm column, B and C). From the faster-migrating zone, the α -D-anomer **12** (114.5 mg, 27%) was obtained. Colorless crystals from MeOH. M.p. 194–195°. R_f (D) 0.54. UV (MeOH): 258 (14500). $^1\text{H-NMR}$ ($(\text{D}_6)\text{DMSO}$): 1.02 (s, 3 Me); 3.78, 3.82 (2dd, $J(5',5'') = 11.5$, $J(4',5'') = 5.0$, $J(4',5') = 3.9$, H-C(5'), H'-C(5'')); 4.40 (dd, $J(3',4') = 4.55$, H-C(4'')); 4.51 (dq, $J(2',3') = 2.52$, $J(3',F) = 19.9$, H-C(3'')); 5.47 (dt, $J(1',2') = 2.3$, $J(2',F) = 51.45$, H-C(2'')); 6.10 (m, $J(1',F) = 16.15$, OH-C(3'), H-C(1'')); 7.02 (br. d, NH_2); 7.40–7.50, 7.64–7.67 (2m, 4 H and 8 H, 2 Ph, H-C(6), H-C(7)). $^{19}\text{F-NMR}$ (D_6DMSO , CFCl_3): –188.70 (br. dt, $J(2',F) = 51.45$). Anal. calc. for $\text{C}_{26}\text{H}_{30}\text{FN}_5\text{O}_4\text{Si}$ (523.63): C 59.64, H 5.77, N 13.37; found: C 60.00, H 5.99, N 13.51.

From the slower-migrating zone, the β -D-anomer **11** (119 mg, 28%) was obtained. White powder. R_f (D) 0.50. UV (MeOH): 258 (14600). $^1\text{H-NMR}$ ($(\text{D}_6)\text{DMSO}$): 1.02 (s, 3 Me); 3.87, 3.93 (2dd, $J(5',5'') = 11.4$, $J(4',5'') = 5.6$, $J(4',5') = 3.5$, H-C(5'), H'-C(5'')); 3.97 (m, $J(3',4') \approx 4.0$, H-C(4'')); 4.45 (m, $J(2',3') \approx 3.6$, $J(3',F) = 18.7$, H-C(3'')); 5.21 (dt, $J(1',2') = 4.4$, $J(2',F) = 52.1$, H-C(2'')); 6.08 (d, $J = 4.85$, OH-C(3'')); 6.2 (dd, $J(1',F) = 14.6$, H-C(1'')); 7.06 (br. d, NH_2); 7.1 (t, $J(7,F) = 2.1$, H-C(7)); 7.3 (d, $J(6,7) = 2.4$, H-C(6)); 7.40–7.50, 7.63–7.66 (2m, 4 H and 6 H, 2 Ph). $^{19}\text{F-NMR}$ (D_6DMSO ; CFCl_3) –200.06 (br. dt, $J(2',F) = 52.1$). Anal. calc. for $\text{C}_{26}\text{H}_{30}\text{FN}_5\text{O}_4\text{Si}$ (523.63): C 59.64, H 5.77, N 13.37; found: C 59.93, H 6.01, N 13.24.

2-Amino-8-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)imidazo[1,2-a]-1,3,5-triazin-4(8H)-one (**3**). To a soln. of **11** (170 mg, 0.33 mmol) in THF (0.8 ml), a soln. of Bu_4NF in THF (1.2 ml) was added while stirring at r.t. for 0.5 h. The soln. was evaporated and applied to FC (silica gel): **3** (88 mg, 95%). Colorless powder. R_f (D) 0.59. UV (MeOH): 258 (14700). $^1\text{H-NMR}$ ($(\text{D}_6)\text{DMSO}$): 3.59 (dd, $J(4,5'') = 4.9$, $J(5',5'') = 12.05$, H'-C(5'')); 3.65 (dd, $J(4,5') = 2.9$, H-C(5'')); 3.82 ('q', $J(3,4') = 4.6$, H-C(4'')); 4.36 (dt, $J(2',3') = 4.4$, $J(3',F) = 18.4$, H-C(3'')); 5.16 (dt, $J(1',2') = 4.35$, $J(2',3') = 4.4$, $J(2',F) = 52.4$, H-C(2'')); 6.18 (dd, $J(1',2') = 4.35$, $J(1',F) = 13.6$, H-C(1'')); 9.25 (d, $J(6,7) = 10.9$, H-C(6)); 9.6 (m, $J(6,7) = 10.9$, $J(7,H) = 2.7$, H-C(7)). $^{19}\text{F-NMR}$ (D_6DMSO ; CFCl_3):

– 200.32 (br. *dt*, $J(1',F) = 13.6$, $J(2',F) = 52.4$, $J(3',F) = 18.4$). Anal. calc. for $C_{10}H_{12}FN_5O_4$ (285.23): C 42.11, H 4.24, N 24.55; found: C 42.07, H 4.40; N 24.06.

2-Amino-8-(2-deoxy-2-fluoro- α -D-arabinofuranosyl)imidazo[1,2-a]-1,3,5-triazin-4(8H)-one (4). As described for **3**, with **12** (120 mg, 0.23 mmol): **4** (62 mg, 95%). Colorless powder. R_f (*D*) 0.59. UV (MeOH): 258 (14600). 1H -NMR ((D_6)DMSO): 3.51 (*dd*, $J(4,5'') = 5.3$, $J(5',5'') = 12.2$, H–C(5'')); 3.55 (*dd*, $J(4,5') = 4.1$, $J(5',5'') = 12.2$, H–C(5'')); 4.22 (*'q'*, $J(3',4') = 4.8$, H–C(4'')); 4.35 (*m*, $J(3',4') = 4.75$, $J(3',F) = 19.7$, H–C(3'')); 5.42 (*dt*, $J(2',3') = 3.3$, $J(2',F) = 51.3$, H–C(2'')); 6.08 (*dd*, $J(1',2') = 2.8$, $J(1',F) = 15.8$, H–C(1'')); 7.35 (*d*, $J(6,7) = 2.7$, H–C(6)); 7.40 (*d*, $J(7,6) = 2.7$, H–C(7)). ^{19}F -NMR ((D_6)DMSO; $CFCl_3$): – 189.93 (br. *ddd*, $J(1',F) = 15.8$, $J(2',F) = 51.3$, $J(3',F) = 19.7$). Anal. calc. for $C_{10}H_{12}FN_5O_4$ (285.23): C 42.11, H 4.24, N 24.55; found: C 41.86, H 4.34, N 24.14.

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