

## Synthesis of Potentially Antiviral 2',3'-Dideoxy-2'-fluoro-3'-(hydroxyamino)nucleosides

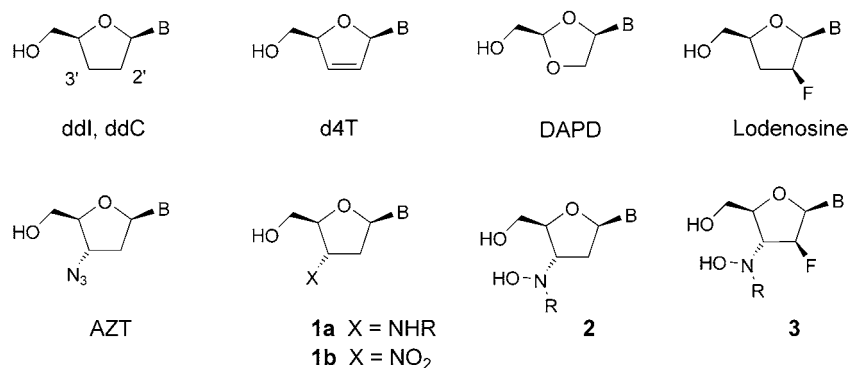
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A series of novel 3'-(alkyl(hydroxy)amino)-2'-fluoronucleoside analogs were prepared *via* conjugate addition of *N*-methylhydroxylamine to various 2-fluorobutenolides. The adducts **13a** and **16** were obtained as single isomers under absolute control of stereochemistry. The crucial *N*-demethylation of **23–25** was readily achieved by means of DDQ oxidation, followed by nitron/oxime exchange reaction. By this procedure, a variety of alkyl groups could be efficiently introduced at the 3'-N-atom of the nucleoside analogs, some of which might display potentially interesting anti-HIV properties.

**Introduction.** – Structural modifications of nucleoside analogs have been successful in the search for effective antiviral agents against human immunodeficiency virus (HIV) [1–3]. Of particular interest is the alteration of the 2'- and 3'-OH groups of ribose rings, particularly the 2',3'-dideoxynucleoside analogs termed ddI, ddC, d4T, DAPD, and lodenosine [4–7]. It has been established that the 3'-position of 2'-deoxynucleoside analogs can tolerate various differently sized substituents, including N-containing moieties, and still maintain their antiviral activities, *e.g.*, AZT, **1a**, and **1b** [8–11]. An interesting new class of nucleoside analogs of types **2** and **3** (R = Me) possess 3'-(hydroxyamino) substituents [12][13].

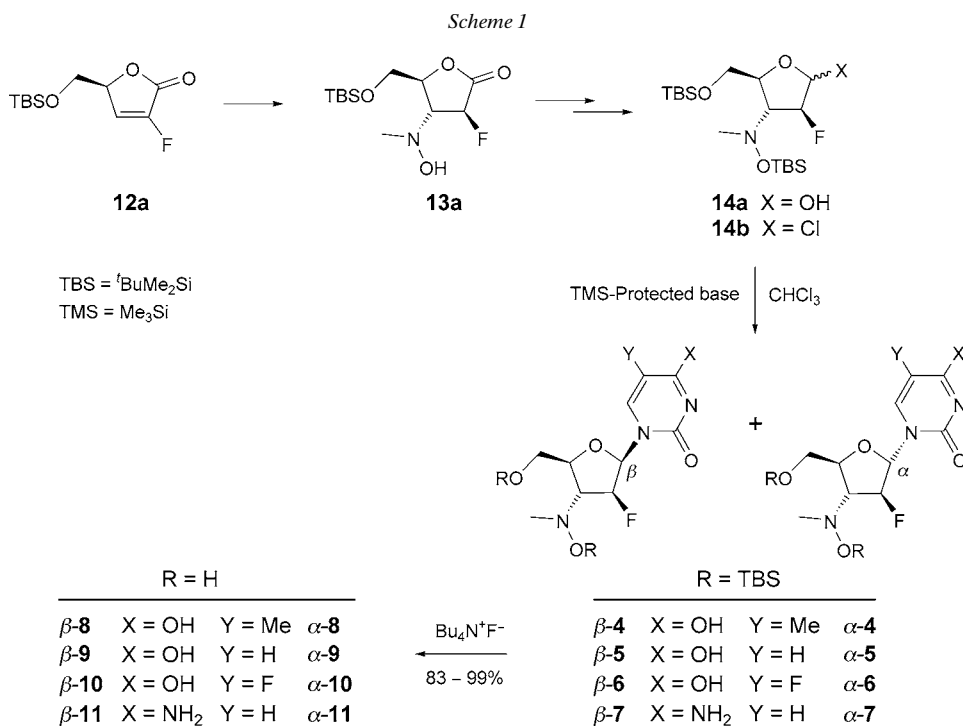


Compounds of type **3** differ from those of type **2** by an additional F-atom at the 2' $\beta$ -position and by different *N*-alkyl groups. It is known that the 2'-F-atom can stabilize glycosyl bonds under both hydrolytic and enzymatic conditions [14]. As shown by

structure/activity-relationship studies, 2' $\beta$ -configured compounds typically exhibit excellent antiviral activities [15] (in contrast to most 2' $\alpha$ -isomers), as exemplified by 2'-1-(2'-deoxy-2'-fluoro- $\beta$ -L-arabinofuranosyl)uracil (L-FMAU) [16] and 1-(2',3'-di-deoxy-2'-fluoro- $\beta$ -D-pentofuranosyl)cytosine (F-ddA, lodenosine) [17][18].

Although nucleosides **3** with *N*-Me groups (*R* = Me) have been prepared by hydroxylamine-concerted addition [19], a variety of compounds with other alkyl substituents were required for antiviral studies [13]. Many synthetic approaches have been made to introduce such *N*-alkyl groups into compounds of type **3**, but without much success. Here, we report a strategy for the stereoselective preparation of 2'-fluoro-3'-(hydroxyamino)nucleosides of type **3**. The main feature of the procedure reported is that the different *N*-alkyl groups can be introduced *via* a common intermediate at a late stage of the synthesis; moreover, our approach allows for efficient preparation of many related derivatives required to study structure/activity relationships.

**Results and Discussion.** – To access the *N*-methylated nucleoside analogs **4–11**, the TBS-protected<sup>1)</sup> compound **12a** was prepared and converted to **13a** and **14a** (Scheme 1) [13]. Since the acetate derivative of **14a** (*X* = OAc) failed to give the coupling product with nucleoside bases in the presence of catalytic amounts of TMSOTf, the

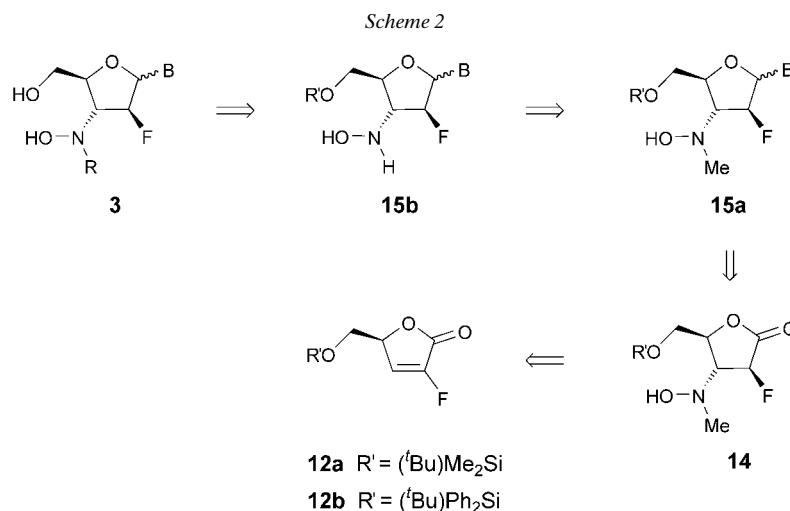


<sup>1)</sup> For abbreviations, see the *General* section in the *Exper. Part*.

corresponding chloride **14b** was selected as an alternative intermediate, which was easily prepared from **14a** with MsCl and 1 equiv. of Et<sub>3</sub>N (plus a catalytic amount of Bu<sub>3</sub>N). Glycosyl chloride **14b** was coupled with silylated uracil, thymine, 5-fluorouracil, and cytosine by refluxing in CHCl<sub>3</sub> to afford the protected nucleosides **4–7** (generally as *ca.* 1:1 mixtures of  $\alpha/\beta$ -anomers). Then, the two TBS groups were removed with Bu<sub>4</sub>N<sup>+</sup>F<sup>–</sup> (TBAF) in anhydrous THF to afford **8–11** (83–99%), which, except for **8**, were separated into the corresponding 1' $\alpha$ - and 1' $\beta$ -isomers by column chromatography (SiO<sub>2</sub>).

The configuration at the anomeric center was derived from the chemical shift of H–C(4'). The  $\beta$ -configuration of the F-atom in 2'-position was confirmed by both <sup>1</sup>H- and <sup>13</sup>C-NMR analyses. A long-range coupling between H–C(6) and the F-atom, with  $J(2'\text{-F}, \text{H}-\text{C}(6)) = 1\text{--}2\text{ Hz}$  was observed. Also, the coupling constants observed for C(1') and the F-atom are known to be considerably larger for the  $\alpha$ -isomer ( $J(\text{F}, \text{C}(1')) = 35\text{--}37\text{ Hz}$ ) than for the  $\beta$ -isomer ( $J(\text{F}, \text{C}(1')) = 16\text{--}18\text{ Hz}$ ) [20].

We next developed a retrosynthetic strategy to access 2'-fluoro-3'-(hydroxyamino) nucleosides of type **3** with *N*-alkyl substituents other than Me (*Scheme 2*). The addition of various *N*-alkyl hydroxylamines to the 2-fluorobutenolactone **12a** was not investigated since the preparation of the corresponding starting materials would have required great synthetic efforts. An efficient method would be to demethylate **15a** to **15b** as a key intermediate<sup>2)</sup>. This compound could then be derivatized to access a large series of products of type **3** by only a few chemical steps.



The synthesis started from the TBDPS-protected<sup>1)</sup> butenolide **12b** (*Scheme 3*). Conjugate addition of *N*-methylhydroxylamine afforded the adduct **16** as a single isomer in 65% yield. The latter was protected with TBSCl ( $\rightarrow$  **17**), reduced with DIBAL ( $\rightarrow$  **18**), and chlorinated with MsCl to afford the intermediate **19**, which was then reacted with different silylated bases to the protected nucleosides **20–22** (as *ca.*

<sup>2)</sup> Direct addition of NH<sub>2</sub>OH to **12a** afforded only low yields (<20%) of **15b**.

1:1 mixtures of  $\alpha/\beta$ -anomers). The *O*-TBS group was selectively removed with 48% HF in MeCN to yield the *N*-methyl derivatives **23–25**.

The unique properties of hydroxylamines allow the potential replacement of *N*-Me groups (which can be regarded as ‘unusual’ *N*-protecting groups), by other alkyl groups, *i.e.*, by the sequential oxidation of the *N*-Me group, followed by alkyl exchange and reduction. In a first attempt, **23–25** were subjected to HgO-promoted oxidation [21] to the corresponding nitron intermediates. However, these were contaminated with Hg-containing compounds, even after column-chromatographic purification. Finally, DDQ-mediated oxidation of **23–25** afforded the pure intermediate nitrones (structures not shown), in which the *N*-Me group was selectively converted to an  $N=CH_2$  group, which was removed with  $NH_2OH \cdot HCl$  by means of an exchange reaction (MeOH, 50°), affording the hydroxylamines **26–28**.

In the next step, compounds **26–28** were reductively alkylated to **29–35** (65–93%) by condensation with different aldehydes (butanal, 2-methylpropanal, cyclohexanecarboxaldehyde), followed by *in situ* reduction with  $NaBH_3CN$  (Scheme 4). Then, TBDPS deprotection with TBAF finally afforded the desired nucleosides **36–42** in 70–96% yield.

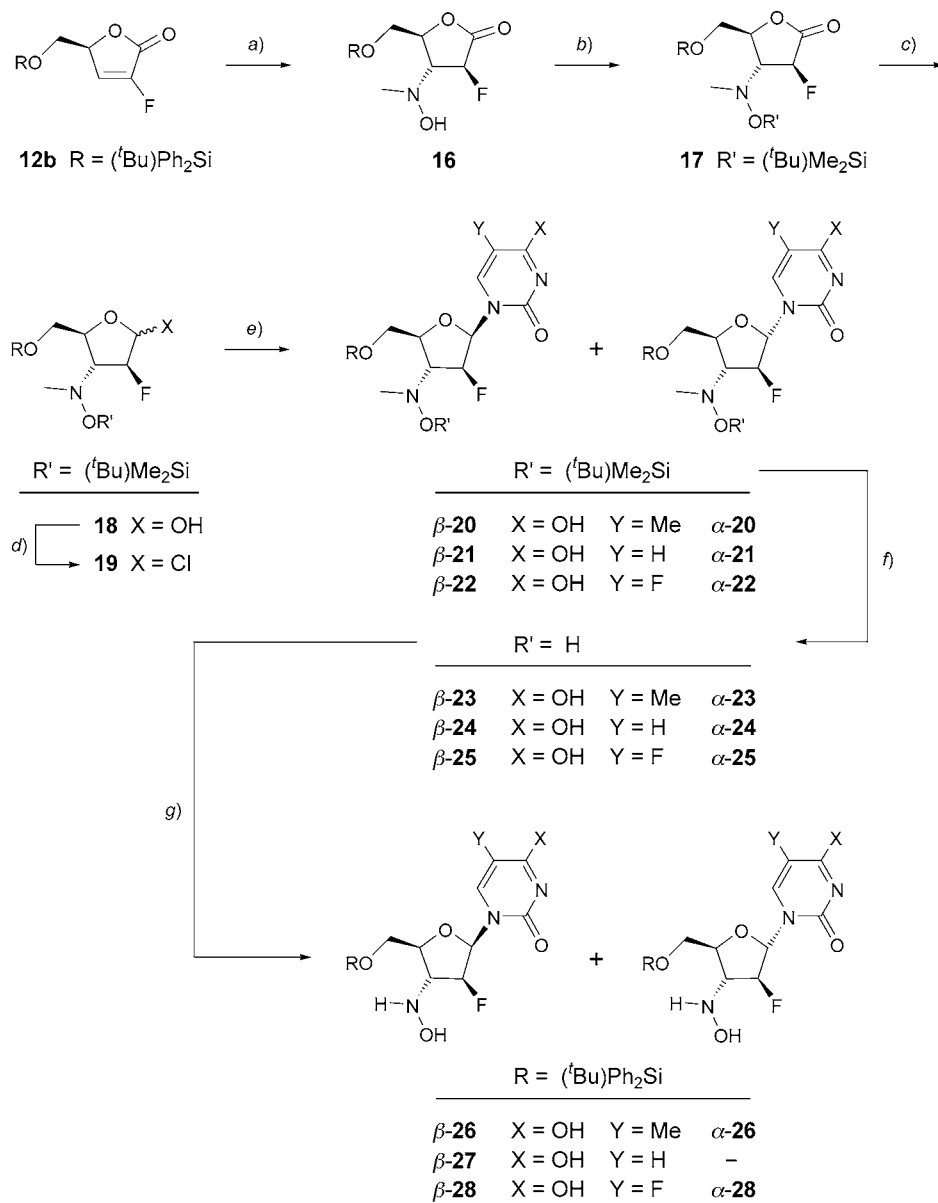
**Conclusions.** – We have developed a route towards the efficient synthesis of a variety of new *N*-alkylated 2',3'-dideoxy-2'-fluoro-3'-(hydroxyamino)nucleoside analogs by stereoselective addition to  $\alpha,\beta$ -unsaturated lactones (furan-1-ones). The compounds prepared were required to study their anti-HIV<sub>LAI</sub> and anti-HSV-1 activities. The two anomeric cytosine derivatives  $\alpha$ -**13** and  $\beta$ -**13**, indeed, showed significant anti-HIV<sub>LAI</sub> activities *in vitro*; and  $\alpha$ -**13** displayed an acceptably low cytotoxicity [19]. These compounds represent the first examples of nucleoside analogs with vicinal fluoro and amino functionalities at the 2'- and 3'-positions, respectively, of the dideoxyribose moiety and will certainly open up the way to further potentially biorelevant compounds of this type.

#### Experimental Part

**General.** Abbreviations: DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DIBAL,  $(^iBu)_2AlH$ ; Ms,  $MeSO_2$ ; TBAF,  $Bu_4N^+F^-$ ; TBDPS,  $(^iBu)Ph_2Si$ ; TBS,  $(^iBu)Me_2Si$ ; Tf,  $F_3CSO_2$ ; TMS,  $Me_3Si$ . All reagents and solvents were purchased from Aldrich, Fisher, or Acros Chimica, and were used without further purification unless otherwise stated. Thin layer chromatography (TLC) was performed on Merck silica gel 60  $F_{254}$  (0.25 mm; glass plates). Column and flash chromatography (CC and FC, resp.) were performed on Mallinckrodt silica gel 60 (230–400 mesh).  $^1H$ - and  $^{13}C$ -NMR spectra were recorded on a Varian-200 spectrometer (200 and 50 MHz, resp.) at ambient temp.; chemical shifts  $\delta$  in ppm rel. to  $SiMe_4$  ( $=0$  ppm), coupling constants  $J$  in Hz.

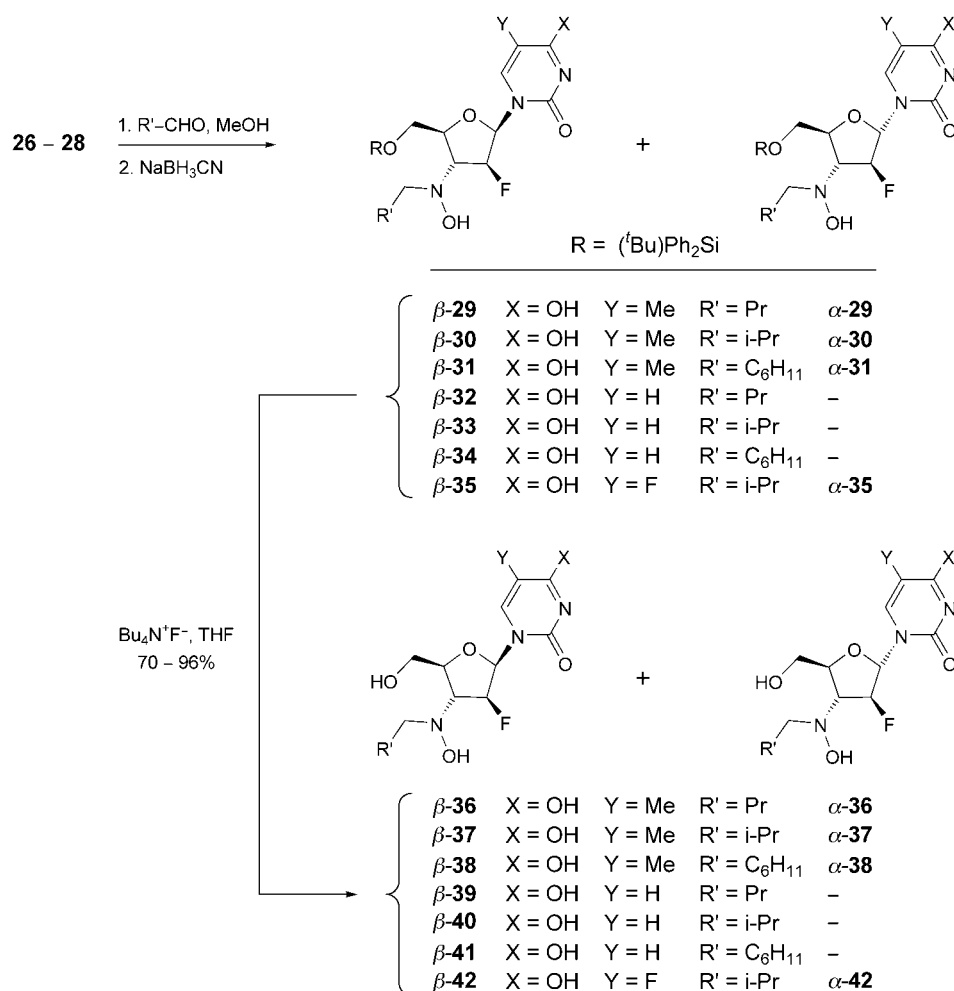
5-*O*-[*tert*-Butyl]dimethylsilyl]-2,3-dideoxy-2'-fluoro-3'-[hydroxy(methyl)amino]-D-arabino-1,4-lactone (**13a**). To a soln. of *N*-methylhydroxylamine hydrochloride (12.53 g, 150 mmol) in EtOH (300 ml) was added EtONa (10.20 g, 150 mmol) portionwise. The resulting mixture was stirred at r.t. for 10 min, and 5-[[*tert*-butyl]dimethylsilyl]oxy]methyl]-3-fluorofuran-2(5H)one (**12a**; 7.38 g, 30 mmol) was added. The resulting soln. was refluxed for 5 h and concentrated under reduced pressure. Then,  $H_2O$  (100 ml) was added to the residue, and the resulting soln. was extracted with  $CH_2Cl_2$ . The org. layer was washed with brine, dried ( $Na_2SO_4$ ), filtered, and concentrated. The residue was purified by FC ( $SiO_2$ ; AcOEt/petroleum ether 1:3): 6.08 g (69%) of **13a**. Oil.  $^1H$ -NMR ( $CDCl_3$ ): 6.30 (br. s, OH); 5.53 (*dd*,  $J=7.2$ , 51.4, H–C(2)); 4.51 (*dt*,  $J=7.2$ , 2.4, H–C(4)); 3.85 (*m*, H–C(3), 2 H–C(5)); 2.78 (*s*, MeN); 0.89 (*s*, *t*-Bu); 0.08 (*s*,  $Me_2Si$ ).  $^{13}C$ -NMR ( $CDCl_3$ ): 88.1, 84.3 (C(2)); 79.4, 79.3 (C(4)); 69.2, 68.8 (C(5)); 62.4 (C(3)); 47.5 (MeN); 26.3 ( $Me_3C$ ); –4.8, –4.9 ( $Me_2Si$ ). Anal. calc. for  $C_{12}H_{24}FNO_4Si$ : C 49.12, H 8.24, N 4.77; found: C 49.23, H 8.30, N 4.81.

Scheme 3



- a)  $\text{MeN}(\text{H})\text{OH} \cdot \text{HCl}$ , EtOH, EtONa; 65%. b)  $(t\text{Bu})\text{Me}_2\text{SiCl}$ , imidazole, DMF; 89%. c) DIBAL,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ$ .  
 d)  $\text{MeSO}_2\text{Cl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{Bu}_3\text{N}$  (cat.),  $\text{CH}_2\text{Cl}_2$ ,  $-40^\circ \rightarrow \text{r.t.}$  e)  $\text{Me}_3\text{Si}$ -protected base,  $\text{CHCl}_3$ ; 65–70% (from **17**).  
 f) 48% HF, MeCN; 97–99%. g) 1. DDQ/ $\text{CH}_2\text{Cl}_2$ ; 2.  $\text{H}_2\text{NOH} \cdot \text{HCl}$ , MeOH; 48–57% (2 steps).

Scheme 4



5-O-[(*tert*-Butyl)dimethylsilyl]-2,3-dideoxy-2-fluoro-3-[hydroxy(methyl)amino]- $\alpha,\beta$ -D-arabino-1,4-lactol (**14a**). A mixture of **13a** (5.50 g, 18.7 mmol), TBSCl (3.10 g, 20.6 mmol), and imidazole (2.80 g, 41.2 mmol) in anhyd. DMF (90 ml) was stirred under Ar gas at r.t. overnight. After addition of H<sub>2</sub>O, the resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The org. layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The residue was purified by FC (SiO<sub>2</sub>; AcOEt/petroleum ether 5:95) to afford 5-O-[(*tert*-butyl)dimethylsilyl]-2,3-dideoxy-2-fluoro-3-[(*tert*-butyl)dimethylsilyl]oxy(methyl)amino]arabino-1,4-lactone (intermediate; not shown in Scheme 1); 7.10 g (93%). Oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 5.50 (br., H–C(2)); 4.38 (br. s, H–C(4)); 3.80 (*m*, H–C(3), 2 H–C(5)); 2.69 (*s*, MeN); 0.85 (*s*, 2 *t*-Bu); 0.08 (*m*, 2 Me<sub>2</sub>Si). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 78.6, 78.5 (C(4)); 70.1, 69.7 (C(5)); 61.1 (C(3)); 47.7 (MeN); 26.4, 26.3 (2 Me<sub>3</sub>C); 18.8, 18.2 (2 Me<sub>3</sub>C); –3.9, –4.1, –4.8, –4.9 (2 Me<sub>2</sub>Si).

To a soln. of the above *O*-protected lactone (5.45 g, 13.5 mmol) in anhyd. CH<sub>2</sub>Cl<sub>2</sub> (80 ml) was added DIBAL (14.9 ml, 1.0M soln. in hexane) at –78° under Ar gas, and the mixture was stirred at this temp. for 1 h. Then, the mixture was quenched with MeOH (10 ml) and sat. aq. NH<sub>4</sub>Cl soln. The mixture was filtered over *Celite* to remove solid materials, and the filtrate was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The org. layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated: 5.07 g (93%) of **14a**. Colorless oil, which was directly used in the next step without further purification.

**Synthesis of Nucleosides 4–7 (General Procedure A; GPA):** MsCl (149 mg, 1.3 mmol) was added dropwise at  $-40^\circ$  under Ar gas to a soln. of crude **14a** (409 mg, 1 mmol), Et<sub>3</sub>N (162 mg, 1.6 mmol), and Bu<sub>3</sub>N (37 mg, 0.2 mmol) in anh. CH<sub>2</sub>Cl<sub>2</sub> (1 ml). After stirring at r.t. for 1 h, the resulting mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with H<sub>2</sub>O and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to afford the crude chloro derivative **14b** (yellowish oil), which was refluxed overnight in the presence of a TMS-protected nucleoside base (3 mmol) in EtOH-free CHCl<sub>3</sub> (5 ml). Then, H<sub>2</sub>O was added, and the resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The org. layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The residue was purified by FC (SiO<sub>2</sub>; AcOEt/petroleum ether 1:3  $\rightarrow$  1:1).

**1-[5'-O-[(tert-Butyl)dimethylsilyl]-3'-[[[(tert-butyl)dimethylsilyl]oxy](methyl)amino]-2',3'-dideoxy-2'-fluoro- $\alpha,\beta$ -D-arabinofuranosyl]thymine ( $\alpha,\beta$ -4).** GPA: 70% (anomeric mixture). White solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 9.97 (*m*, NH); 7.38 (*s*, H-C(6) ( $\beta$ )); 7.11 (*s*, H-C(6) ( $\alpha$ )); 6.17 (*dd*, *J* = 4.4, 14.0, H-C(1') ( $\alpha$ )); 6.02 (*dd*, *J* = 3.7, 19.7, H-C(1') ( $\beta$ )); 5.55 (*br.*, H-C(2')); 4.21 (*br. s*, H-C(4') ( $\alpha$ )); 3.75 (*m*, H-C(3'), 2 H-C(5'), H-C(4') ( $\beta$ )); 2.65 (*s*, MeN); 1.89 (*s*, Me-C(5)); 0.89, 0.88 (2*s*, 2 *t*-Bu); 0.11 (*m*, 2 Me<sub>2</sub>Si). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 164.8, 164.5 (C(4)); 150.9, 150.8 (C(2)); 137.5, 135.3 (C(6)); 111.8, 110.0 (C(5)); 89.1, 85.0 (C(2')); 88.7 (C(1')); 81.8, 81.7 (C(4')); 74.8, 74.3, 74.0, 73.6 (C(5')); 47.8 (MeN); 26.5, 26.4, 18.9, 19.2, 13.0 (2 *t*-Bu); -3.8, -4.0, -4.7, -4.8 (2 Me<sub>2</sub>Si).

**1-[5'-O-[(tert-Butyl)dimethylsilyl]-3'-[[[(tert-butyl)dimethylsilyl]oxy](methyl)amino]-2',3'-dideoxy-2'-fluoro- $\alpha,\beta$ -D-arabinofuranosyl]uracil ( $\alpha,\beta$ -5).** GPA: 68% (anomeric mixture). White solid.

**Data of  $\beta$ -5:** <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 10.00 (*br. s*, NH); 7.63 (*d*, *J* = 7.3, H-C(6)); 6.09 (*dd*, *J* = 3.7, 17.6, H-C(1')); 5.66 (*d*, *J* = 8.1, H-C(5)); 5.55 (*br.*, H-C(2')); 3.80 (*m*, H-C(4'), 2 H-C(5')); 3.50 (*dd*, *J* = 5.1, 26.3, H-C(3')); 2.69 (*s*, MeN); 0.88 (*s*, 2 *t*-Bu); 0.15 (*m*, 2 Me<sub>2</sub>Si). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 164.1 (C(4)); 150.7 (C(2)); 141.8 (C(6)); 101.9 (C(5)); 85.1, 84.9 (C(2)); 74.5 (C(1')); 74.1 (C(4')); 62.8 (C(5')); 47.7 (MeN); 26.5, 26.4, 18.8, 18.2 (2 *t*-Bu); -3.8, -4.0, -4.8, -4.9 (2 Me<sub>2</sub>Si).

**Data of  $\alpha$ -5:** <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 9.50 (*s*, NH); 7.35 (*d*, *J* = 8.1, H-C(6)); 6.17 (*dd*, *J* = 3.9, 14.6, H-C(1')); 5.75 (*d*, *J* = 8.1, H-C(5)); 5.55 (*br.*, H-C(2')); 4.23 (*br. s*, H-C(4')); 3.88 (*dd*, *J* = 2.6, 11.4, 1 H-C(5')); 3.74 (*dd*, *J* = 3.4, 11.4, 1 H-C(5')); 3.62 (*dt*, *J* = 5.4, 25.0, H-C(3')); 2.68 (*s*, MeN); 0.90, 0.87 (2*s*, 2 *t*-Bu); 0.15 (*m*, 2 Me<sub>2</sub>Si). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 163.8 (C(4)); 150.7 (C(2)); 139.8 (C(6)); 103.3 (C(5)); 90.2, 89.8 (C(2')); 82.5, 82.4 (C(1')); 74.4 (C(4')); 74.0 (C(5')); 47.9 (MeN); 26.5, 26.4, 18.9, 18.2 (2 *t*-Bu); -3.9, -4.0, -4.7, -4.8 (2 Me<sub>2</sub>Si).

**1-[5'-O-[(tert-Butyl)dimethylsilyl]-3'-[[[(tert-butyl)dimethylsilyl]oxy](methyl)amino]-2',3'-dideoxy-2'-fluoro- $\alpha,\beta$ -D-arabinofuranosyl]-5-fluorouracil ( $\alpha,\beta$ -6).** GPA: 66% (anomeric mixture). White solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 9.62 (*br. s*, NH); 7.79 (*d*, *J* = 6.2, H-C(6) ( $\beta$ )); 7.41 (*d*, *J* = 6.1, H-C(6) ( $\alpha$ )); 6.07 (*dd*, *J* = 3.1, 17.3, H-C(1')); 5.55 (*br.*, H-C(2')); 3.90 (*m*, H-C(4'), 2 H-C(5')); 3.55 (*dd*, *J* = 4.6, 25.3, H-C(3')); 2.63 (*s*, MeN); 0.89, 0.88 (2*s*, 2 *t*-Bu); 0.11 (*s*, 2 Me<sub>2</sub>Si). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 157.3, 157.0 (C(4)); 149.3, 142.7 (C(2)); 138.0 (C(6)); 126.5, 125.8, 124.3, 123.6 (C(5)); 85.3, 82.6 (C(2')); 85.0, 82.5 (C(1')); 74.4 (C(4')); 74.0 (C(5')); 47.7 (MeN); 26.5, 26.4, 18.9, 18.3 (2 *t*-Bu); -3.8, -4.0, -4.8, -4.9 (2 Me<sub>2</sub>Si).

**1-[5'-O-[(tert-Butyl)dimethylsilyl]-3'-[[[(tert-butyl)dimethylsilyl]oxy](methyl)amino]-2',3'-dideoxy-2'-fluoro- $\alpha,\beta$ -D-arabinofuranosyl]cytosine ( $\alpha,\beta$ -7).** GPA: 65% (anomeric mixture). White solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.65 (*dd*, *J* = 1.4, 7.5, H-C(6) ( $\beta$ )); 7.37 (*d*, *J* = 7.4, H-C(6) ( $\alpha$ )); 6.10 (*m*, H-C(1')); 5.78, 5.70 (2*d*, *J* = 7.3 and 7.4, H-C(5)); 5.40 (*br.*, H-C(2')); 4.22 (*br. s*, H-C(4') ( $\alpha$ )); 3.81 (*m*, H-C(4') ( $\beta$ ), 2 H-C(5')); 3.49 (*m*, H-C(3')); 2.63 (*m*, MeN); 0.85 (*m*, 2 *t*-Bu); 0.05 (*s*, 2 Me<sub>2</sub>Si). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 166.5, 166.3 (C(4)); 156.2, 155.9 (C(2)); 142.8, 140.6 (C(6)); 95.2, 94.2, 92.0, 91.3 (C(5)); 86.1, 83.9 (C(2')); 85.6, 83.4 (C(1')); 75.4, 74.9 (C(4')); 60.3 (C(3')); 48.0 (MeN); 26.6, 26.5, 18.7, 18.2 (2 *t*-Bu); -3.8, -3.9, -4.6, -4.7 (2 Me<sub>2</sub>Si).

**Synthesis of Nucleosides 8–11 (General Procedure B; GPB):** Compounds **4–7** were treated with TBAF (2.5 equiv.) in anh. THF for 2 h at r.t. The resulting mixture was directly (without evaporation of the solvent) purified by CC (SiO<sub>2</sub>).

**1-[2',3'-Dideoxy-2'-fluoro-3'-[hydroxy(methyl)amino]- $\alpha,\beta$ -D-arabinofuranosyl]thymine ( $\alpha,\beta$ -8).** GPB, with  $\alpha,\beta$ -4: 96% (anomeric mixture). White solid. <sup>1</sup>H-NMR ((D<sub>6</sub>)DMSO): 11.46, 11.42 (2*s*, NH); 8.45 (*dd*, *J* = 1.5, 4.7, NOH); 7.64 (*s*, H-C(6) ( $\beta$ )); 7.46 (*s*, H-C(6) ( $\alpha$ )); 6.00 (*m*, H-C(1')); 5.23 (*m*, H-C(2')); 5.09 (*m*, C(5')-OH); 4.39 (*m*, H-C(4') ( $\alpha$ )); 4.02 (*m*, H-C(4') ( $\beta$ )); 3.60 (*m*, H-C(3'), 2 H-C(5')); 2.63, 2.59 (2*s*, MeN); 1.79 (*s*, Me-C(5)). Anal. calc. for C<sub>11</sub>H<sub>16</sub>FN<sub>3</sub>O<sub>5</sub> · 0.3 H<sub>2</sub>O: C 44.83, H 5.68, N 14.26; found: C 45.08, H 5.81, N 14.30.

**1-[2',3'-Dideoxy-2'-fluoro-3'-[hydroxy(methyl)amino]- $\alpha,\beta$ -D-arabinofuranosyl]uracil ( $\alpha,\beta$ -9).** GPB, with  $\beta$ -5 and  $\alpha$ -5: 99% of  $\beta$ -9 and 92% of  $\alpha$ -9, resp. White solids.

**Data of  $\beta$ -9:** <sup>1</sup>H-NMR ((D<sub>6</sub>)DMSO): 11.46 (*s*, NH); 8.49 (*s*, NOH); 7.76 (*d*, *J* = 8.1, H-C(6)); 5.95 (*dd*, *J* = 4.0, 19.3, H-C(1')); 5.66 (*d*, *J* = 8.1, H-C(5)); 5.40 (*d*, *J* = 53.3, H-C(2')); 5.08 (*t*, *J* = 6.1, C(5')-OH); 4.06

(*m*, H–C(4')); 3.60 (*m*, H–C(3'), 2 H–C(5')); 2.65 (*s*, MeN). <sup>13</sup>C-NMR ((D<sub>6</sub>)DMSO): 163.2 (C(4)); 150.3 (C–(2)); 141.8, 141.7 (C(6)); 101.1 (C(5)); 93.9, 90.2 (C(2')); 84.2, 83.9 (C–(1')); 79.8 (C(4')); 73.0, 72.5 (C(5')); 61.5 (C(3')); 46.7 (MeN). Anal. calc. for C<sub>10</sub>H<sub>14</sub>FN<sub>3</sub>O<sub>5</sub>·0.5 H<sub>2</sub>O: C 42.26, H 5.32, N 14.78; found: C 42.53, H 5.05, N 14.37.

Data of **α-9**: <sup>1</sup>H-NMR ((D<sub>6</sub>)DMSO): 11.41 (*s*, NH); 8.42 (*s*, NOH); 7.58 (*d*, *J* = 8.1, H–C(6)); 6.05 (*dd*, *J* = 2.8, 16.2, H–C(1')); 5.65 (*dd*, *J* = 1.3, 8.0, H–C(5)); 5.42 (*dt*, *J* = 51.6, 2.8, H–C(2')); 5.09 (*t*, *J* = 5.8, C(5')–OH); 4.39 (*m*, H–C(4')); 3.60 (*m*, H–C(3'), H–C(5')); 2.68 (*s*, MeN). <sup>13</sup>C-NMR ((D<sub>6</sub>)DMSO): 163.4 (C(4)); 150.7 (C(2)); 140.6 (C(6)); 101.9 (C(5)); 98.9, 95.2 (C(2')); 89.9, 89.2 (C(1')); 83.6, 83.5 (C(4')); 73.9, 73.4 (C(5')); 62.5 (C(3')); 46.9 (MeN). Anal. calc. for C<sub>10</sub>H<sub>14</sub>FN<sub>3</sub>O<sub>5</sub>·0.2 H<sub>2</sub>O: C 43.08, H 5.21, N 15.07; found: C 43.41, H 5.26, N 14.79.

1-[2',3'-Dideoxy-2'-fluoro-3'-[hydroxy(methyl)amino]-α,β-D-arabinofuranosyl]-5-fluorouracil (**α,β-10**). GPB, with **α,β-6**: 99% (anomeric mixture). White solid. The two anomers were partially separated by FC (SiO<sub>2</sub>).

Data of **β-10**: <sup>1</sup>H-NMR (CD<sub>3</sub>OD): 8.08 (*dd*, *J* = 1.8, 6.9, H–C(6)); 6.04 (*ddd*, *J* = 1.6, 3.9, 18.0, H–C(1')); 5.45 (*dt*, *J* = 1.8, 52.8, H–C(2')); 4.15 (*m*, H–C(4')); 3.92 (*dd*, *J* = 2.8, 12.4, H–C(5')); 3.76 (*dd*, *J* = 4.4, 12.4, H–C(5')); 3.48 (*ddd*, *J* = 1.7, 6.2, 27.1, H–C(3')); 2.72 (*s*, MeN). <sup>13</sup>C-NMR (CD<sub>3</sub>OD): 150.7 (C(4)); 143.8 (C(2)); 139.2 (C(6)); 128.1, 127.4 (C(5)); 95.1, 91.4 (C(2')); 86.5, 86.2 (C(1')); 81.5 (C(4')); 74.6, 74.1 (C(5')); 63.1 (C(3')); 47.4 (MeN). Anal. calc. for C<sub>10</sub>H<sub>13</sub>F<sub>2</sub>N<sub>3</sub>O<sub>5</sub>·0.6 H<sub>2</sub>O: C 39.50, H 4.71, N 13.82; found: C 39.23, H 4.70, N 13.99.

Data of **α-10**: <sup>1</sup>H-NMR (CD<sub>3</sub>OD): 7.87 (*d*, *J* = 6.6, H–C(6)); 6.10 (*dt*, *J* = 1.6, 15.8, H–C(1')); 5.46 (*dt*, *J* = 2.3, 50.9, H–C(2')); 4.51 (*m*, H–C(4')); 3.80 (*dd*, *J* = 4.0, 11.8, H–C(5')); 3.70 (*dd*, *J* = 5.3, 12.1, H–C(5')); 3.43 (*ddd*, *J* = 2.6, 5.1, 24.5, H–C(3')); 2.70 (*s*, MeN). <sup>13</sup>C-NMR (CD<sub>3</sub>OD): 163.6 (C(4)); 151.0 (C(2)); 144.2 (C(6)); 126.9, 126.2 (C(5)); 100.2, 96.5 (C(2')); 92.8, 92.0 (C(1')); 86.0 (C(4')); 75.7, 75.3 (C(5')); 64.2 (C(3')); 47.6 (MeN). Anal. calc. for C<sub>10</sub>H<sub>13</sub>F<sub>2</sub>N<sub>3</sub>O<sub>5</sub>·0.2 H<sub>2</sub>O: C 40.46, H 4.55, N 14.16; found: C 40.61, H 4.37, N 14.43.

1-[2',3'-Dideoxy-2'-fluoro-3'-[hydroxy(methyl)amino]-α,β-D-arabinofuranosyl]cytosine (**α,β-11**). GPB, with **α,β-7**; followed by separation by FC (SiO<sub>2</sub>): 47% of **β-11** and 36% of **α-11**. White solids.

Data of **β-11**: <sup>1</sup>H-NMR ((D<sub>6</sub>)DMSO): 8.47 (*s*, NOH); 7.69 (*d*, *J* = 6.3, H–C(6)); 7.22 (*m*, NH<sub>2</sub>); 5.93 (*dd*, *J* = 3.4, 20.2, H–C(1')); 5.75 (*d*, *J* = 7.5, H–C(5)); 5.33 (*md*, *J* = 53.0, H–C(2')); 5.02 (*t*, *J* = 5.9, C(5')–OH); 4.01 (*m*, H–C(4')); 3.65 (*m*, 2 H–C(5')); 3.35 (*m*, H–C(3')); 2.63 (*s*, MeN). <sup>13</sup>C-NMR ((D<sub>6</sub>)DMSO): 165.9 (C(4)); 153.8 (C(2)); 142.3 (C(6)); 93.9, 93.8 (C(5)); 89.9, 85.2 (C(2')); 84.9 (C(1')); 79.5 (C(4')); 73.6, 73.2 (C(5')); 61.8 (C(3')); 46.7 (MeN). Anal. calc. for C<sub>10</sub>H<sub>15</sub>FN<sub>4</sub>O<sub>4</sub>·0.8 H<sub>2</sub>O: C 41.61, H 5.80, N 19.41; found: C 41.78, H 5.62, N 19.57.

Data of **α-11**: <sup>1</sup>H-NMR ((D<sub>6</sub>)DMSO): 8.37 (*s*, NOH); 7.54 (*d*, *J* = 7.5, H–C(6)); 7.19 (*m*, NH<sub>2</sub>); 6.01 (*dd*, *J* = 2.4, 16.6, H–C(1')); 5.74 (*d*, *J* = 7.5, H–C(5)); 5.33 (*d*, *J* = 51.7, H–C(2')); 5.06 (*t*, *J* = 5.5, C(5')–OH); 4.34 (*m*, H–C(4')); 3.49 (*m*, H–C(3'), 2 H–C(5')); 2.54 (*s*, MeN). <sup>13</sup>C-NMR ((D<sub>6</sub>)DMSO): 166.0 (C(4)); 155.4 (C(2)); 141.2 (C(6)); 99.3, 95.6 (C(2')); 94.3 (C(5)); 90.6, 89.9 (C(1')); 83.3 (C(4')); 74.1, 73.6 (C(5')); 62.5 (C(3')); 47.0 (MeN). Anal. calc. for C<sub>10</sub>H<sub>15</sub>FN<sub>4</sub>O<sub>4</sub>·0.2 H<sub>2</sub>O: C 43.23, H 5.59, N 20.16; found: C 43.43, H 5.57, N 19.97.

5-O-[(*tert*-Butyl)diphenylsilyl]-2,3-dideoxy-2-fluoro-3-[hydroxy(methyl)amino]-D-arabino-1,4-lactone (**16**). Prepared from **12b** in analogy to **13a**: Yield: 65% of **16**. Oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.69 (*m*, 4 arom. H); 7.42 (*m*, 6 arom. H); 5.92 (*br. s*, OH); 5.57 (*dd*, *J* = 7.3, 50.9, H–C(2)); 4.51 (*m*, H–C(4)); 3.95 (*m*, H–C(3), 2 H–C(5)); 2.78 (*s*, MeN); 1.08 (*s*, *t*-Bu). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 170.4; 170.0; 136.2; 136.0; 133.3; 132.9; 130.4; 128.3; 88.1; 84.2; 79.3; 79.1; 69.4; 69.1; 63.3; 47.5; 27.3; 19.9.

5-O-[(*tert*-Butyl)diphenylsilyl]-3-([(*tert*-butyl)dimethylsilyl]oxy)(methyl)amino)-2,3-dideoxy-2-fluoro-D-arabino-1,4-lactone (**17**). From **16** by standard silylation methodology (TBSCl, imidazole, DMF): 89% of **17**. Oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.71 (*m*, 4 arom. H); 7.45 (*m*, 6 arom. H); 4.47 (*br. s*, H–C(4)); 3.95 (*m*, H–C(3), 2 H–C(5)); 2.72 (*s*, MeN); 1.09 (*s*, *t*-Bu); 0.90 (*s*, *t*-Bu); 0.12 (*m*, 2 MeSi). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 170.4, 170.0 (C(1)); 136.2, 136.0, 133.3, 132.9, 130.4, 128.3 (2 Ph); 78.7, 78.6 (C–(4)); 70.4, 70.0 (C(5)); 62.5 (C(3)); 47.8 (MeN); 27.3, 26.5, 19.9, 18.3 (2 *t*-Bu); –3.9, –4.0 (Me<sub>2</sub>Si).

1-[5'-O-[(*tert*-Butyl)diphenylsilyl]-3'-([(*tert*-butyl)dimethylsilyl]oxy)(methyl)amino)-2',3'-dideoxy-2'-fluoro-α,β-D-arabinofuranosyl]thymine (**α,β-20**). Prepared, in analogy to **α,β-4**, from **17** in three steps: 70% (anomeric mixture). White solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 9.60 (*m*, NH); 7.76–7.33 (*m*, 10 arom. H, H–C(6)); 6.28 (*dd*, *J* = 4.2, 14.2, H–C(1') (α)); 6.10 (*dd*, *J* = 3.7, 20.1, H–C(1') (β)); 4.32 (*br. s*, H–C(4') (α)); 3.85 (*m*, H–C(3'), 2 H–C(5'), H–C(4') (β)); 2.67 (*s*, MeN); 1.95, 1.79 (2*s*, Me–C(5)); 1.12 (*s*, *t*-Bu); 0.90 (*m*, *t*-Bu); 0.14 (*m*, Me<sub>2</sub>Si). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 164.6, 164.4 (C(4)); 150.8 (C(2)); 137.6 (C(6)); 136.1, 135.9, 133.6, 133.4, 130.4,



130.3, 128.3, 128.2 (2 Ph); 111.8, 110.2 (C(5)); 85.1, 84.8 (C(2')); 81.9, 81.8 (C(1')); 74.9, 74.5 (C(4')); 74.2, 73.8 (C(5')); 47.9 (MeN); 27.4, 26.6, 26.5, 20.0, 18.3 (2 *t*-Bu); 12.8 (Me–C(5)); –3.7, –3.9 (Me<sub>2</sub>Si).

*1-[5'-O-[(tert-Butyl)diphenylsilyl]-3'-([[(tert-butyl)dimethylsilyl]oxy](methylamino)-2',3'-dideoxy-2'-fluoro- $\alpha,\beta$ -D-arabinofuranosyl]uracil ( $\alpha,\beta$ -21).* Prepared, in analogy to **5**, from **17** in three steps: 68% (anomeric mixture). The mixture was separated by FC (SiO<sub>2</sub>).

*Data of  $\beta$ -21:* <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 10.12 (br. s, NH); 7.70 (*m*, 4 arom. H); 7.45 (*m*, 6 arom. H, H–C(6)); 6.12 (*dd*, *J* = 4.0, 18.7, H–C(1')); 5.58 (*d*, *J* = 8.4, H–C(5)); 3.95 (*m*, H–C(4'), 2 H–C(5')); 3.63 (*dd*, *J* = 5.6, 26.3, H–C(3')); 2.69 (*s*, MeN); 1.11, 0.93 (2*s*, 2 *t*-Bu); 0.18 (*m*, Me<sub>2</sub>Si). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 164.2 (C(4)); 150.9 (C(2)); 141.8, 136.1 (C(5)); 136.0, 133.5, 133.3, 130.4, 128.3 (2 Ph); 102.0 (C(6)); 85.2, 84.9 (C(1')); 74.8 (C(4')); 74.3 (C(5')); 47.8 (MeN); 27.4, 26.6, 19.9, 19.3 (2 *t*-Bu); –3.7, –4.0 (Me<sub>2</sub>Si).

*Data of  $\alpha$ -21:* <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 9.88 (*s*, NH); 7.71 (*m*, 4 arom. H); 7.42 (*m*, 6 arom. H, H–C(6)); 6.25 (*dd*, *J* = 3.7, 14.6, H–C(1')); 5.78 (*d*, *J* = 8.0, H–C(5)); 4.32 (br. *s*, H–C(4')); 3.89 (*m*, 2 H–C(5')); 3.68 (*dd*, *J* = 4.3, 6.4, H–C(3')); 2.65 (*s*, MeN); 1.12, 0.88 (2*s*, 2 *t*-Bu); 0.12 (*m*, Me<sub>2</sub>Si). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 163.9 (C(4)); 150.8 (C(2)); 139.9 (C(5)); 136.1, 136.0, 133.5, 133.3, 130.3, 128.3 (2 Ph); 103.3 (C(6)); 90.3, 89.6 (C(2')); 82.6, 82.4 (C(1')); 74.6 (C(4')); 74.2 (C(5')); 64.8 (C(3')); 47.9 (MeN); 27.4, 26.6, 26.5, 19.9, 18.3 (2 *t*-Bu); –3.9 (Me<sub>2</sub>Si).

*1-[5'-O-[(tert-Butyl)diphenylsilyl]-3'-([[(tert-butyl)dimethylsilyl]oxy](methylamino)-2',3'-dideoxy-2'-fluoro- $\alpha,\beta$ -D-arabinofuranosyl]-5-fluorouracil ( $\alpha,\beta$ -22).* Prepared, in analogy to  $\alpha,\beta$ -6, from **17** in three steps: 65% (anomeric mixture). White solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.80–7.35 (*m*, 10 arom. H, H–C(6)); 6.22 (*m*, H–C(1')); 4.41 (br. *s*, ½ H–C(4')); 4.16–3.52 (*m*, H–C(3'), ½ H–C(4'), 2 H–C(5')); 2.69 (*s*, MeN); 1.15, 0.95 (2*s*, 2 *t*-Bu); 0.21 (*m*, Me<sub>2</sub>Si). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 157.9, 157.8, 157.4, 157.3 (C(4)); 149.6 (C(2)); 143.7, 142.9 (C(5)); 138.9, 138.2 (C(6)); 136.1, 136.0, 133.5, 133.3, 130.5, 130.4, 128.4, 128.3 (2 Ph); 85.4, 85.1 (C(2')); 82.8, 82.7 (C(1')); 74.8 (C(4')); 74.3 (C(5')); 48.0 (MeN); 27.5, 26.6, 19.9, 18.3 (2 *t*-Bu); –3.7, –3.9 (Me<sub>2</sub>Si).

*Synthesis of Nucleosides 23–25 (General Procedure C; GPC).* To a soln. of **20–22** (1 mmol) in MeCN (10 ml) was added 48% HF in H<sub>2</sub>O (36  $\mu$ l), and the resulting mixture was stirred at r.t. for 1 h. Then, H<sub>2</sub>O (10 ml) was added, and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The org. layer was washed with sat. aq. NaHCO<sub>3</sub> soln. and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude products **23–25**, resp., were purified by FC (SiO<sub>2</sub>).

*1-[5'-O-[(tert-Butyl)diphenylsilyl]-2',3'-dideoxy-2'-fluoro-3'-[hydroxy(methylamino)- $\alpha,\beta$ -D-arabinofuranosyl]thymine ( $\alpha,\beta$ -23).* GPC, with  $\alpha,\beta$ -20: 99% (anomeric mixture). White solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 10.85, 10.70 (2 br. *s*, NH); 7.71 (*m*, 4 arom. H); 7.41 (*m*, 6 arom. H, H–C(6)); 6.12 (*m*, H–C(1')); 5.50 (*m*, H–C(2')); 4.52 (*m*, H–C(4') ( $\alpha$ )); 4.24 (*m*, H–C(4') ( $\beta$ )); 3.82 (*m*, H–C(3'), 2 H–C(5')); 2.78 (*s*, MeN); 1.91, 1.75 (2*s*, Me–C(5)); 1.11 (*s*, *t*-Bu). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 165.2, 165.1 (C(4)); 151.5, 151.2 (C(2)), 138.2, 136.9 (C(6)); 136.1, 135.9, 133.6, 133.5, 133.3, 130.5, 130.3, 128.3, 128.2 (2 Ph); 111.3, 110.3 (C(5)); 100.6, 96.2, 94.7, 90.3 (C(2')); 85.2, 84.9, 83.3, 83.2 (C(1')); 79.5, 77.8 (C(4')); 73.9, 73.4 (C(5')); 65.8, 63.9 (C(3')); 47.0 (MeN); 27.5, 20.0, 19.9 (*t*-Bu); 12.9, 12.7 (C(5)–Me).

*1-[5'-O-[(tert-Butyl)diphenylsilyl]-2',3'-dideoxy-2'-fluoro-3'-[hydroxy(methylamino)- $\alpha,\beta$ -D-arabinofuranosyl]uracil ( $\alpha,\beta$ -24).* GPC, with  $\beta$ -21 and  $\alpha$ -21: 99% of  $\beta$ -24 and 98% of  $\alpha$ -24, resp. White solids.

*Data of  $\beta$ -24:* <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 10.68 (br. *s*, NH); 7.68 (*m*, 4 arom. H, H–C(6)); 7.42 (*m*, 6 arom. H); 6.21 (*dd*, *J* = 3.6, 19.0, H–C(1')); 5.57 (*d*, *J* = 8.1, H–C(5)); 5.50 (*dd*, *J* = 3.0, 52.0, H–C(2')); 4.29 (*m*, H–C(4')); 4.07 (*dd*, *J* = 3.4, 11.4, H–C(5')); 3.92 (*dd*, *J* = 6.0, 11.7, H–C(5')); 3.69 (*dd*, *J* = 4.9, 25.6, H–C(3')); 2.76 (*s*, MeN); 1.11 (*s*, *t*-Bu). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 164.5 (C(4)); 151.0 (C(2)); 142.2 (C(6)); 136.1, 136.0, 133.6, 133.3, 130.4, 128.4 (2 Ph); 102.0 (C(5)); 94.5, 90.8 (C(2')); 85.4, 85.0 (C(1')); 79.6 (C(4')); 73.8, 73.4 (C(5')); 64.3 (C(3')); 46.9 (MeN); 27.5, 19.9 (*t*-Bu).

*Data of  $\alpha$ -24:* <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 11.11 (br. *s*, NH); 7.72 (*m*, 4 arom. H); 7.40 (*m*, 6 arom. H, H–C(6)); 6.05 (*dd*, *J* = 1.7, 14.7, H–C(1')); 5.71 (*d*, *J* = 8.1, H–C(5)); 5.59 (*m*, H–C(2')); 4.60 (*m*, H–C(4')); 3.87 (*m*, H–C(3'), 2 H–C(5')); 2.76 (*s*, MeN); 1.12 (*s*, *t*-Bu). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 165.1 (C(4)); 151.3 (C(2)); 141.5 (C(6)); 136.1, 136.0, 133.5, 130.4, 128.3 (2 Ph); 102.2 (C(5)); 99.5, 95.7 (C(2')); 92.5, 91.7 (C(1')); 83.8 (C(4')); 74.2, 73.7 (C(5')); 65.5 (C(3')); 47.0 (MeN); 27.5, 19.9 (*t*-Bu).

*[5'-O-[(tert-Butyl)diphenylsilyl]-2',3'-dideoxy-2'-fluoro-3'-[hydroxy(methylamino)- $\alpha,\beta$ -D-arabinofuranosyl]-5-fluorouracil ( $\alpha,\beta$ -25).* GPC, with  $\alpha,\beta$ -22: 97% (anomeric mixture). White solid. The anomers were separated by FC (SiO<sub>2</sub>).

*Data of  $\beta$ -25:* <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.72 (*m*, 4 arom. H); 7.40 (*m*, 6 arom. H, H–C(6)); 6.14 (*d*, *J* = 17.7, H–C(1')); 5.49 (*dd*, *J* = 1.7, 52.9, H–C(2')); 4.30 (*m*, H–C(4')); 3.98 (*m*, 2 H–C(5')); 3.65 (*dd*, *J* = 5.0, 26.6, H–C(3')); 2.71 (*s*, MeN); 1.11 (*s*, *t*-Bu). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 158.3, 157.7 (C(4)); 149.7 (C(2)); 142.9, 138.2

(C(5)); 136.1, 136.0, 133.3, 133.2, 130.5, 128.4 (2 Ph); 126.8, 126.1 (C(6)); 94.7, 90.9 (C(2')); 85.6, 85.2 (C(1')); 79.7 (C(4')); 73.7, 73.3 (C(5')); 64.2 (C(3')); 46.8 (MeN); 27.4, 19.9 (*t*-Bu).

**Data of  $\alpha$ -25:**  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 7.78–7.33 (*m*, 10 arom. H, H–C(6), OH); 5.90 (*d*,  $J = 14.3$ , H–C(1')); 5.59 (*d*,  $J = 50.7$ , H–C(2')); 4.61 (*m*, H–C(4')); 3.81 (*m*, H–C(3'), H–C(5')); 2.71 (*s*, MeN); 1.12 (*s*, *t*-Bu).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ): 158.7, 158.1 (C(4)); 149.8 (C(2)); 142.9, 138.2 (C(5)); 136.1, 133.4, 130.4, 126.4, 125.7 (2 Ph); 128.3 (C(6)); 99.3, 95.6 (C(2')); 93.0, 92.3 (C(1')); 83.3 (C(4')); 74.0, 73.5 (C(5')); 65.3 (C(3')); 46.9 (MeN); 27.5, 19.9 (*t*-Bu).

**Synthesis of Nucleosides 26–28 (General Procedure D; GPD).** To a soln. of **23–25** (1 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 ml) was added a soln. of DDQ (272 mg, 1.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 ml) in small portions, and the resulting mixture was stirred at r.t. for 30 min. Then, the mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (10 ml), washed successively with sat. aq.  $\text{NaHCO}_3$  soln., brine, and  $\text{H}_2\text{O}$ , dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated. The resulting crude nitrone intermediate was purified by FC (short column of  $\text{SiO}_2$ ;  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  1:9). To this nitrone in MeOH (10 ml) was added  $\text{NH}_2\text{OH} \cdot \text{HCl}$  (104 mg, 1.5 mmol), the resulting mixture was warmed to  $50^\circ$  and stirred for 1 h at this temp. The solvent was evaporated, the residue, dissolved in  $\text{CH}_2\text{Cl}_2$  (20 ml), was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated to give the crude products **26–28**, resp., which were purified by FC ( $\text{SiO}_2$ ).

**1-[5'-O-[(tert-Butyl)diphenylsilyl]-2',3'-dideoxy-2'-fluoro-3'-(hydroxyamino)- $\alpha$ , $\beta$ -D-arabinofuranosyl]thymine ( $\alpha,\beta$ -26):** GPD, with  $\alpha,\beta$ -23: 51% (two steps; anomeric mixture). White solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 10.38 (br. *s*, NH); 7.75–7.30 (*m*, 10 arom. H, H–C(6)); 6.20 (*m*, H–C(1') ( $\beta$ )); 5.82 (*m*, H–C(1') ( $\alpha$ )); 5.39 (*m*, H–C(2')); 4.48 (*m*, H–C(4') ( $\alpha$ )); 4.00 (*m*, H–C(4') ( $\beta$ ), H–C(3'), 2 H–C(5')); 1.85 (*s*, Me–C(5) ( $\alpha$ )); 1.69 (*s*, Me–C(5) ( $\beta$ )); 1.10 (*s*, *t*-Bu).

**1-[5'-O-[(tert-Butyl)diphenylsilyl]-2',3'-dideoxy-2'-fluoro-3'-(hydroxyamino)- $\beta$ -D-arabinofuranosyl]uracil ( $\beta$ -27):** GPD, with  $\beta$ -24: 57% (two steps). White solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 10.05 (br. *s*, NH); 7.70–7.30 (*m*, 10 arom. H, H–C(6)); 6.20 (*d*,  $J = 19.5$ , H–C(1')); 5.56 (*d*,  $J = 8.1$ , H–C(5)); 5.40 (*m*, H–C(2')); 4.01 (*m*, H–C(3'), H–C(4'), 2 H–C(5')); 1.08 (*s*, *t*-Bu).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ): 164.5 (C(4)); 151.0 (C(2)); 142.2 (C(6)); 136.1, 136.0, 133.4, 133.2, 130.5, 128.3 (2 Ph); 102.1 (C(5)); 95.2, 91.4 (C(2')); 85.7, 85.5 (C(1')); 80.1 (C(4')); 67.9, 67.5 (C(5')); 64.1 (C(3')); 27.4, 19.9 (*t*-Bu).

**1-[5'-O-[(tert-Butyl)diphenylsilyl]-2',3'-dideoxy-2'-fluoro-3'-(hydroxyamino)- $\beta$ -D-arabinofuranosyl]-5-fluorouracil ( $\beta$ -28):** GPD, with  $\beta$ -25: 53% (2 steps). White solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 7.72–7.31 (*m*, 10 arom. H, H–C(6), OH); 6.17 (*d*,  $J = 18.7$ , H–C(1')); 5.35 (*d*,  $J = 53.0$ , H–C(2')); 3.95 (*m*, H–C(3'), H–C(4'), 2 H–C(5')); 1.11 (*s*, *t*-Bu).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ): 158.2, 157.7 (C(4)); 149.7 (C(2)); 143.0, 138.3 (C(5)); 136.1, 136.0, 133.2, 130.5, 128.4, 126.7 (2 Ph); 125.9 (C(6)); 95.5, 91.7 (C(2')); 85.7, 85.5 (C(1')); 80.6 (C(4')); 68.1, 67.6 (C(5')); 64.0 (C(3')); 27.4, 19.8 (*t*-Bu).

**1-[5'-O-[(tert-Butyl)diphenylsilyl]-2',3'-dideoxy-2'-fluoro-3'-(hydroxyamino)- $\alpha$ -D-arabinofuranosyl]-5-fluorouracil ( $\alpha$ -28):** GPD, with  $\alpha$ -25: 48% (2 steps). White solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 7.72–7.31 (*m*, 10 arom. H, H–C(6)); 5.92 (*d*,  $J = 15.4$ , H–C(1')); 5.44 (*d*,  $J = 48.8$ , H–C(2')); 4.37 (*m*, H–C(4')); 3.90 (*m*, H–C(3'), 2 H–C(5')); 1.11 (*s*, *t*-Bu).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ): 158.8, 158.3 (C(4)); 149.5 (C(2)); 142.7, 138.0 (C(5)); 136.1, 133.5, 133.4, 130.4, 126.8, 126.0 (2 Ph); 128.3 (C(6)); 99.6, 96.0 (C(2')); 93.5, 92.7 (C(1')), 77.8 (C(4')); 68.2 (C(5')); 68.0 (C(5')); 64.7 (C(3')); 27.4, 19.8 (*t*-Bu).

**Synthesis of Nucleosides 29–35 (General Procedure E; GPE).** To a soln. of **26–28** (1 equiv.) in MeOH was added the aldehyde (1.2 equiv.; see Scheme 4), and the resulting mixture was stirred at r.t. for 10 min. Then,  $\text{NaBH}_3\text{CN}$  (2 equiv.) was added in small portions, and the mixture was stirred at r.t. for another 10 min. After evaporation to dryness, the residue was dissolved in  $\text{CH}_2\text{Cl}_2$ , and the resulting soln. was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated. The crude products were purified by FC ( $\text{SiO}_2$ ).

**[5'-O-[(tert-Butyl)diphenylsilyl]-3'-[butyl(hydroxyamino)-2',3'-dideoxy-2'-fluoro- $\alpha,\beta$ -D-arabinofuranosyl]thymine ( $\alpha,\beta$ -29):** GPE, with  $\alpha,\beta$ -26 and butanal: 84% (two steps; anomeric mixture). White solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 10.48 (*m*, NH); 7.50 (*m*, 10 arom. H, H–C(6)); 6.20 (*m*, H–C(1')); 5.50 (*m*, H–C(2')); 4.48 (*m*, H–C(4') ( $\alpha$ )); 4.00 (*m*, H–C(4') ( $\beta$ ), H–C(3'), 2 H–C(5')); 2.82 (*m*,  $\text{CH}_2\text{N}$ ); 0.90–0.79 (*m*, Me–C(5), *t*-Bu, Me, 2  $\text{CH}_2$ ).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ): 164.8 (C(4)); 151.3, 151.0 (C(2)); 138.0, 136.9 (C(6)); 136.1, 136.0, 133.6, 133.3, 130.4, 130.3, 128.3, 128.2 (2 Ph); 111.2, 110.3 (C(5)); 94.6, 90.8 (C(2')); 85.1, 84.8, 82.9, 82.8 (C(1')); 79.2 (C(4')); 72.5, 72.1 (C(5')); 65.7, 63.8 (C(3')), 61.0, 59.0 ( $\text{NCH}_2$ ); 29.4, 27.4 (2  $\text{CH}_2$ ); 20.9, 19.9 (*t*-Bu); 14.5, 12.7 (2 Me).

**1-[5'-O-[(tert-Butyl)diphenylsilyl]-2',3'-dideoxy-2'-fluoro-3'-[hydroxy(2-methylpropyl)amino]- $\alpha,\beta$ -D-arabinofuranosyl]thymine ( $\alpha,\beta$ -30):** GPE, with  $\alpha,\beta$ -26 and 2-methylpropanal: 87% (two steps; anomeric mixture). White solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 10.01 (br. *s*, NH); 7.75–7.29 (*m*, 10 arom. H–C(6)); 6.94, 6.40 (2 br. *s*, OH); 6.12 (*m*, H–C(1')); 5.42 (*m*, H–C(2')); 4.49 (*m*, H–C(4') ( $\alpha$ )); 4.23 (*m*, H–C(4') ( $\beta$ )); 3.78 (*m*, H–C(3')),

2 H–C(5')); 2.55 (*d*, *J* = 7.0, CH<sub>2</sub>N); 1.90 (*m*, 2.2 H, Me–C(5), CH); 1.75 (*s*, 1.8 H; Me–C(5)); 1.10 (*s*, *t*-Bu); 0.94 (*d*, *J* = 6.6, 2 Me). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 164.8, 164.6 (C(4)); 151.0 (C(2)); 137.9, 136.9 (C(6)); 136.1, 135.9, 133.6, 133.4, 130.4, 130.3, 128.3 (2 Ph); 110.7, 110.4 (C(5)); 98.9, 95.2, 95.0, 91.4 (C(2')); 91.3, 90.7, 85.3, 84.9 (C(1')); 83.8, 79.2 (C(4')); 73.5, 73.3, 73.0, 72.8 (C(5')); 67.5, 66.9 (C(3')); 65.4, 64.0 (NCH<sub>2</sub>); 27.4, 26.7, 26.5, 19.9 (3 Me); 21.4, 21.3, 13.0, 12.8 (*t*-Bu).

1-[5'-O-[(tert-Butyl)diphenylsilyl]-3'-[(cyclohexylmethyl)(hydroxy)amino]-2',3'-dideoxy-2'-fluoro- $\alpha,\beta$ -D-arabinofuranosyl]thymine ( $\alpha$ -**31**): GPE, with  $\alpha$ -**26** and cyclohexanecarboxaldehyde: 68% (two steps; anomeric mixture). White solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 10.00 (*m*, NH); 7.53 (*m*, 10 arom. H, H–C(6)); 6.93 (*br. s*, OH ( $\alpha$ )); 6.41 (*br. s*, OH ( $\beta$ )); 6.14 (*m*, H–C(1')); 5.49 (*m*, H–C(2')); 4.48 (*m*, H–C(4') ( $\alpha$ )); 4.26 (*m*, H–C(4') ( $\beta$ )); 3.81 (*m*, H–C(3'), 2 H–C(5')); 2.58 (*d*, *J* = 6.6, NCH<sub>2</sub>); 1.92–0.78 (*m*, Me–C(5), 5 CH<sub>2</sub>, CH); 1.11 (*s*, *t*-Bu). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 164.9, 164.7 (C(4)); 151.3 (C(2)); 137.9, 137.3 (C(6)); 136.0, 135.9, 133.7, 133.5, 130.2, 130.1, 128.1 (2 Ph); 110.6, 110.3 (C(5)); 98.9, 95.4, 95.3, 91.5 (C(2')); 90.5, 85.2, 84.9 (C(1')); 84.0, 79.1 (C(4')); 73.8, 73.6, 72.8 (C(5')); 66.2, 65.9 (C(3')); 65.7, 64.1 (NCH<sub>2</sub>); 36.1, 32.2, 27.6, 26.4 (5 CH<sub>2</sub>); 19.9, 12.8 (*t*-Bu).

1-[5'-O-[(tert-Butyl)diphenylsilyl]-3'-[butyl(hydroxy)amino]-2',3'-dideoxy-2'-fluoro- $\beta$ -D-arabinofuranosyl]uracil ( $\beta$ -**32**): GPE, with  $\beta$ -**27** and butanal: 93% (two steps). White solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 10.58 (*br. s*, NH); 7.69 (*m*, 4 arom. H, H–C(6)); 7.40 (*m*, 6 arom. H); 7.11 (*br. s*, OH); 6.20 (*dd*, *J* = 3.4, 18.5, H–C(1')); 5.56 (*d*, *J* = 8.2, H–C(5)); 5.50 (*dd*, *J* = 3.2, 52.7, H–C(2')); 4.28 (*m*, H–C(4')); 3.92 (*m*, H–C(3'), 2 H–C(5')); 2.81 (*m*, NCH<sub>2</sub>); 1.67–0.88 (*m*, *t*-Bu, Me, 2 CH<sub>2</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 164.4 (C(4)); 150.9 (C(2)); 142.3 (C(6)); 136.1, 136.0, 133.6, 133.3, 130.4, 128.3 (2 Ph); 101.9 (C(5)); 94.6, 90.9 (C(2')); 85.4, 85.0 (C(1')); 79.4 (C(4')); 72.5 (C(5')); 72.0 (C(5')); 64.2 (C(3')); 58.9 (CH<sub>2</sub>N); 29.6 (2 CH<sub>2</sub>); 20.9, 14.6 (*t*-Bu); 19.9 (Me).

1-[5'-O-[(tert-Butyl)diphenylsilyl]-2',3'-dideoxy-2'-fluoro-3'-[hydroxy(2-methylpropyl)amino]- $\beta$ -D-arabinofuranosyl]uracil ( $\beta$ -**33**): GPE, with  $\beta$ -**27** and 2-methylpropanal: 92% (two steps). White solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 10.16 (*br. s*, NH); 7.69 (*m*, 4 arom. H, H–C(6)); 7.41 (*m*, 6 arom. H); 6.51 (*br. s*, OH); 6.19 (*dd*, *J* = 3.2, 18.7, H–C(1')); 5.58 (*d*, *J* = 8.1, H–C(5)); 5.45 (*m*, H–C(2')); 4.27 (*m*, H–C(4')); 4.04 (*dd*, *J* = 3.0, 11.6, 1 H–C(5')); 3.88 (*dd*, *J* = 3.0, 11.0, 1 H–C(5')); 3.69 (*dd*, *J* = 5.0, 26.4, H–C(3')); 2.55 (*d*, *J* = 7.0, CH<sub>2</sub>N); 1.91 (*m*, CH); 1.11 (*s*, *t*-Bu); 0.94 (*dd*, *J* = 1.8, 6.6, 2 Me). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 164.2 (C(4)); 150.8 (C(2)); 142.1 (C(6)); 136.1, 136.0, 133.5, 133.3, 130.5, 130.4, 128.3 (2 Ph); 102.0 (C(5)); 94.9, 91.2 (C(2')); 85.5, 85.1 (C(1')); 79.3 (C(4')); 73.2, 72.7 (C(5')); 66.9 (C(3')); 64.3 (NCH); 27.5, 26.7 (2 Me); 21.3, 19.9 (*t*-Bu).

1-[5'-O-[(tert-Butyl)diphenylsilyl]-3'-[(cyclohexylmethyl)(hydroxy)amino]-2',3'-dideoxy-2'-fluoro- $\beta$ -D-arabinofuranosyl]uracil ( $\beta$ -**34**): GPE, with  $\beta$ -**27** and cyclohexanecarboxaldehyde: 88% (two steps). White solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 9.89 (*br. s*, NH); 7.53 (*m*, 10 arom. H, H–C(6)); 6.25 (*br. s*, OH); 6.17 (*dd*, *J* = 3.7, 18.8, H–C(1')); 5.56 (*d*, *J* = 8.3, H–C(5)); 5.42 (*m*, H–C(2')); 4.22 (*m*, H–C(4')); 4.02 (*dd*, *J* = 3.0, 11.1, 1 H–C(5')); 3.87 (*dd*, *J* = 3.3, 11.3, 1 H–C(5')); 3.69 (*dd*, *J* = 4.4, 27.1, H–C(3')); 2.59 (*d*, *J* = 6.7, CH<sub>2</sub>N); 1.85–0.79 (*m*, CH, 5 CH<sub>2</sub>); 1.09 (*s*, *t*-Bu). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 164.1 (C(4)); 150.9 (C(2)); 142.1 (C(6)); 136.1, 136.0, 133.5, 133.3, 130.4, 128.3 (2 Ph); 102.0 (C(5)); 94.8, 91.0 (C(2')); 85.4, 85.1 (C(1')); 79.3 (C(4')); 73.0, 72.5 (C(5')); 65.8 (C(3')); 64.2 (CH<sub>2</sub>N); 36.1 (CH); 32.2, 27.5 (5 CH<sub>2</sub>), 27.3, 26.6, 19.9 (*t*-Bu).

1-[5'-O-[(tert-Butyl)diphenylsilyl]-2',3'-dideoxy-2'-fluoro-3'-[hydroxy(2-methylpropyl)amino]- $\beta$ -D-arabinofuranosyl]-5-fluorouracil ( $\beta$ -**35**): GPE, with  $\beta$ -**28** and 2-methylpropanal: 65% (2 steps). White solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 10.34 (*br. s*, NH); 7.71 (*m*, 4 arom. H, H–C(6)); 7.43 (*m*, 6 arom. H); 6.30 (*br. s*, OH); 6.13 (*d*, *J* = 18.0, H–C(1')); 5.45 (*dd*, *J* = 2.4, 52.1, H–C(2')); 4.28 (*m*, H–C(4')); 4.02 (*dd*, *J* = 3.6, 11.4, 1 H–C(5')); 3.84 (*dd*, *J* = 3.3, 11.4, 1 H–C(5')); 3.64 (*dd*, *J* = 5.0, 27.0, H–C(3')); 2.50 (*d*, *J* = 6.7, CH<sub>2</sub>N); 1.89 (*m*, CH); 1.11 (*s*, *t*-Bu); 0.92 (*dd*, *J* = 2.5, 6.6, 2 Me). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 157.9, 157.4 (C(4)); 149.5 (C(2)); 142.9, 138.2 (C(5)); 136.1, 136.0, 133.3, 130.5, 128.3, 126.6 (2 Ph); 126.0 (C(6)); 95.1, 91.4 (C(2')); 85.7, 85.4 (C(1')); 79.4 (C(4')); 73.2, 72.7 (C(5')); 66.7 (C(3')); 64.2 (CH<sub>2</sub>N); 27.4 (CH); 26.6, 19.8 (*t*-Bu); 21.2 (2 Me).

1-[5'-O-[(tert-Butyl)diphenylsilyl]-2',3'-dideoxy-2'-fluoro-3'-[hydroxy(2-methylpropyl)amino]- $\alpha$ -D-arabinofuranosyl]-5-fluorouracil ( $\alpha$ -**35**): GPE, with  $\alpha$ -**28** and 2-methylpropanal: 83% (2 steps). White solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 10.46 (*br. s*, NH); 7.55 (*m*, 10 arom. H, H–C(6)); 6.62 (*br. s*, OH); 6.00 (*d*, *J* = 14.6, H–C(1')); 5.62 (*d*, *J* = 49.1, H–C(2')); 4.49 (*m*, H–C(4')); 3.84 (*m*, 2 H–C(5')); 3.64 (*m*, H–C(3')); 2.51 (*d*, *J* = 6.4, CH<sub>2</sub>N); 1.95 (*m*, CH); 1.10 (*s*, *t*-Bu); 0.90 (*dd*, *J* = 2.3, 6.6, 2 Me). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 158.5, 158.1 (C(4)); 149.2 (C(2)); 142.5, 137.8 (C(5)); 136.1, 133.4, 130.4, 128.3, 126.5 (2 Ph); 125.8 (C(6)); 99.5, 95.9 (C(2')); 92.6, 91.8 (C(1')); 84.9 (C(4')); 74.1, 73.6 (C(5')); 67.5 (C(3')); 65.1 (CH<sub>2</sub>N); 27.4 (CH), 26.4, 19.8 (*t*-Bu); 21.3 (2 Me).

**Synthesis of Nucleosides 36–42 (General Procedure F; GPF).** To a soln. of compounds **29–35**, resp., in anh. THF was added a soln. of TBAF (1.2 equiv.) in THF. The mixture was stirred for 1 h at r.t., then directly (without evaporation) subjected to FC (SiO<sub>2</sub>).

*1-[3'-[Butyl(hydroxy)amino]-2',3'-dideoxy-2'-fluoro- $\alpha,\beta$ -D-arabinofuranosyl]thymine ( $\alpha,\beta$ -36):* GPF, with  $\alpha,\beta$ -29: 82% (anomeric mixture). White solid.  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ ): 7.71 (s, H-C(6) ( $\beta$ )); 7.54 (s, H-C(6) ( $\alpha$ )); 6.12 (dd,  $J = 2.8, 16.1$ , H-C(1') ( $\alpha$ )); 6.05 (dd,  $J = 3.9, 18.7$ , H-C(1') ( $\beta$ )); 5.56 (dt,  $J = 2.9, 51.6$ , H-C(2') ( $\alpha$ )); 5.45 (ddd,  $J = 1.7, 3.7, 53.0$ , H-C(2') ( $\beta$ )); 4.56 (m, H-C(4') ( $\alpha$ )); 4.19 (m, H-C(4') ( $\beta$ )); 3.75 (m, H-C(3'), 2 H-C(5')); 2.89 (m,  $\text{CH}_2\text{N}$ ); 1.87 (s, Me-C(5)); 1.45 (m, 2  $\text{CH}_2$ ); 0.96 (t,  $J = 7.2$ , Me).  $^{13}\text{C-NMR}$  ( $\text{CD}_3\text{OD}$ ): 166.5, 166.4 (C(4)); 152.7, 152.6 (C(2)); 139.5, 138.5 (C(6)); 111.9, 110.8 (C(5)); 95.9, 95.1, 92.4 (C(2')); 91.7, 91.4, 86.3, 86.0 (C(1')); 84.9, 80.8 (C(4')); 74.6, 74.2, 73.7, 73.2 (C(5')); 64.2, 63.1 ((C(3'))); 59.7 ( $\text{CH}_2\text{N}$ ), 30.6, 30.2, 21.6 (2  $\text{CH}_2$ ); 14.7, 12.9, 12.7 (2 Me). Anal. calc. for  $\text{C}_{14}\text{H}_{22}\text{FN}_3\text{O}_5 \cdot 0.3 \text{ H}_2\text{O}$ : C 49.93, H 6.77, N 12.48; found: C 50.16, H 6.75, N 12.65.

*1-[2',3'-Dideoxy-2'-fluoro-3'-[hydroxy(2-methylpropyl)amino]- $\alpha,\beta$ -D-arabinofuranosyl]thymine ( $\alpha,\beta$ -37):* GPF, with  $\alpha,\beta$ -30: 95% (anomeric mixture). White solid.  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ ): 7.72 (s, H-C(6) ( $\beta$ )); 7.54 (s, H-C(6) ( $\alpha$ )); 6.13 (dd,  $J = 2.3, 13.7$ , H-C(1') ( $\alpha$ )); 6.04 (dd,  $J = 3.9, 18.7$ , H-C(1') ( $\beta$ )); 5.45 (dt,  $J = 2.5, 51.3$ , H-C(2') ( $\alpha$ )); 5.32 (ddd,  $J = 1.8, 3.8, 53.4$ , H-C(2') ( $\beta$ )); 4.52 (m, H-C(4') ( $\alpha$ )); 4.17 (m, H-C(4') ( $\beta$ )); 3.97–3.29 (m, H-C(3'), 2 H-C(5')); 2.72–2.38 (m,  $\text{CH}_2\text{N}$ ); 1.89 (m, Me-C(5), CH); 0.92 (m, 2 Me).  $^{13}\text{C-NMR}$  ( $\text{CD}_3\text{OD}$ ): 166.7, 166.5 (C(4)); 152.6, 152.3 (C(2)); 139.5, 138.3 (C(6)); 111.5, 110.7 (C(5)); 100.2, 96.6, 95.4, 92.3 (C(2')); 91.6, 86.3, 86.0, 85.7 (C(1')); 81.2, 81.1 (C(4')); 75.1, 74.7, 74.2, 73.8 (C(5')); 68.2, 68.0 (C(3')); 64.3, 63.2 ( $\text{CH}_2\text{N}$ ); 27.7, 27.6 (CH); 21.5 (Me); 21.4 ( $\text{Me}_2\text{CH}$ ). Anal. calc. for  $\text{C}_{14}\text{H}_{22}\text{FN}_3\text{O}_5 \cdot 0.8 \text{ H}_2\text{O}$ : C 48.63, H 6.88, N 12.15; found: C 48.58, H 6.62, N 12.37.

*1-[3'-[(Cyclohexylmethyl)(hydroxy)amino]-2',3'-dideoxy-2'-fluoro- $\alpha,\beta$ -D-arabinofuranosyl]thymine ( $\alpha,\beta$ -38):* GPF, with  $\alpha,\beta$ -31: 96% (anomeric mixture). White solid.  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ ): 7.72 (s, H-C(6) ( $\beta$ )); 7.54 (s, H-C(6) ( $\alpha$ )); 6.09 (m, H-C(1') ( $\alpha$ )); 5.42 (m, H-C(2') ( $\beta$ )); 4.51 (m, H-C(4') ( $\alpha$ )); 4.14 (m, H-C(4') ( $\beta$ )); 3.97–3.29 (m, H-C(3'), 2 H-C(5')); 2.73–2.40 (m,  $\text{CH}_2\text{N}$ ); 2.00–0.78 (m, Me-C(5), CH, 5  $\text{CH}_2$ ).  $^{13}\text{C-NMR}$  ( $\text{CD}_3\text{OD}$ ): 166.5, 164.7 (C(4)); 152.3 (C(2)); 139.5, 138.3 (C(6)); 111.4, 110.7 (C(5)); 100.4, 96.4, 95.4, 92.4 (C(2')); 91.6, 86.3, 86.0 (C(1')); 81.1 (C(4')); 74.2, 73.8 (C(5')); 66.8, 64.4 (C(3')); 63.2 ( $\text{CH}_2\text{N}$ ); 37.2, 37.1 (CH); 33.0, 32.9, 28.3, 27.6 (5  $\text{CH}_2$ ); 13.0, 12.8 (Me). Anal. calc. for  $\text{C}_{17}\text{H}_{26}\text{FN}_3\text{O}_5 \cdot 0.1 \text{ H}_2\text{O}$ : C 54.71, H 7.08, N 11.26; found: C 54.97, H 7.13, N 11.19.

*1-[3'-[Butyl(hydroxy)amino]-2',3'-dideoxy-2'-fluoro- $\beta$ -D-arabinofuranosyl]uracil ( $\beta$ -39):* GPF, with  $\beta$ -32: 93%. White solid.  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ ): 7.86 (dd,  $J = 2.0, 8.1$ , H-C(6)); 6.06 (dd,  $J = 3.7, 18.7$ , H-C(1')); 5.69 (d,  $J = 8.1$ , H-C(5)); 5.43 (ddd,  $J = 1.5, 3.7, 53.1$ , H-C(2')); 4.19 (m, H-C(4')); 3.90 (dd,  $J = 2.9, 12.4$ , 1 H-C(5')); 3.75 (dd,  $J = 4.72, 12.4$ , 1 H-C(5')); 3.52 (ddd,  $J = 1.5, 6.1, 27.5$ , H-C(3')); 2.79 (m,  $\text{CH}_2\text{N}$ ); 1.48 (m, 2  $\text{CH}_2$ ); 0.95 (t,  $J = 7.1$ , Me).  $^{13}\text{C-NMR}$  ( $\text{CD}_3\text{OD}$ ): 166.3 (C(4)); 152.2 (C(2)); 143.9, 143.8 (C(6)); 102.1 (C(5)); 95.4, 91.6 (C(2')); 86.6, 86.3 (C(1')); 81.3, 81.2 (C(4')); 74.0, 73.5 (C(5')); 63.3 (C(3')); 59.6 ( $\text{CH}_2\text{N}$ ); 31.1, 21.7 (2  $\text{CH}_2$ ); 14.8 (Me). Anal. calc. for  $\text{C}_{15}\text{H}_{20}\text{FN}_3\text{O}_5 \cdot 0.5 \text{ H}_2\text{O}$ : C 47.85, H 6.49, N 12.88; found: C 48.00, H 6.62, N 12.97.

*1-[2',3'-Dideoxy-2'-fluoro-3'-[hydroxy(2-methylpropyl)amino]- $\beta$ -D-arabinofuranosyl]uracil ( $\beta$ -40):* GPF, with  $\beta$ -33: 94%. White solid.  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ ): 7.86 (dd,  $J = 2.0, 8.1$ , H-C(6)); 6.06 (dd,  $J = 3.7, 18.6$ , H-C(1')); 5.69 (d,  $J = 8.1$ , H-C(5)); 5.43 (ddd,  $J = 1.6, 3.8, 53.2$ , H-C(2')); 4.18 (m, H-C(4')); 3.83 (ddd,  $J = 2.8, 12.2, 29.4$ , 2 H-C(5')); 3.48 (ddd,  $J = 1.5, 6.1, 27.4$ , H-C(3')); 2.67 (dd,  $J = 6.2, 12.1$ , 1 H of  $\text{CH}_2\text{N}$ ); 2.46 (dd,  $J = 7.6, 12.2$ , 1 H of  $\text{CH}_2\text{N}$ ); 1.90 (m, CH); 0.95 (m, 2 Me).  $^{13}\text{C-NMR}$  ( $\text{CD}_3\text{OD}$ ): 166.3 (C(4)); 152.2 (C(2)); 143.8 (C(6)); 102.1 (C(5)); 95.4, 91.7 (C(2')); 86.6, 86.3 (C(1')); 81.3 (C(4')); 74.3, 73.9 (C(5')); 67.9 (C(3')); 63.4 ( $\text{CH}_2\text{N}$ ); 27.7 (CH); 21.5, 21.4 (2 Me). Anal. calc. for  $\text{C}_{15}\text{H}_{20}\text{FN}_3\text{O}_5 \cdot 0.2 \text{ H}_2\text{O}$ : C 48.65, H 6.41, N 13.09; found: C 48.61, H 6.65, N 12.93.

*1-[3'-[(Cyclohexylmethyl)(hydroxy)amino]-2',3'-dideoxy-2'-fluoro- $\beta$ -D-arabinofuranosyl]uracil ( $\beta$ -41):* GPF, with  $\beta$ -34: 85%. White solid.  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ ): 7.86 (dd,  $J = 2.0, 8.1$ , H-C(6)); 6.05 (dd,  $J = 3.8, 18.6$ , H-C(1')); 5.68 (d,  $J = 8.1$ , H-C(5)); 5.41 (ddd,  $J = 1.6, 3.8, 53.2$ , H-C(2')); 4.17 (m, H-C(4')); 3.90 (dd,  $J = 3.2, 12.4$ , H-C(5')); 3.74 (dd,  $J = 4.6, 12.2$ , 1 H-C(5')); 3.46 (ddd,  $J = 1.7, 6.3, 27.4$ , H-C(3')); 2.68 (dd,  $J = 5.6, 12.1$ , 1 H of  $\text{CH}_2\text{N}$ ); 2.51 (dd,  $J = 7.4, 12.5$ , 1 H of  $\text{CH}_2\text{N}$ ); 1.98–0.81 (m, CH, 5  $\text{CH}_2$ ).  $^{13}\text{C-NMR}$  ( $\text{CD}_3\text{OD}$ ): 166.3 (C(4)); 152.2 (C(2)); 143.8 (C(6)); 102.0 (C(5)); 95.4, 91.7 (C(2')); 86.6, 86.3 (C(1')); 81.4, 81.3 (C(4')); 74.4, 73.9 (C(5')); 66.7 (C(3')); 63.4 ( $\text{CH}_2\text{N}$ ); 37.2 (CH); 33.0, 28.3, 27.6 (5  $\text{CH}_2$ ). Anal. calc. for  $\text{C}_{16}\text{H}_{24}\text{FN}_3\text{O}_5$ : C 53.77, H 6.77, N 11.76; found: C 53.57, H 6.75, N 12.06.

*1-[2',3'-Dideoxy-2'-fluoro-3'-[hydroxy(2-methylpropyl)amino]- $\beta$ -D-arabinofuranosyl]-5-fluorouracil ( $\beta$ -42):* GPF, with  $\beta$ -35: 76%. White solid.  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ ): 8.08 (dd,  $J = 1.8, 6.8$ , H-C(6)); 6.04 (ddd,  $J = 1.7, 3.9, 18.0$ , H-C(1')); 5.44 (ddd,  $J = 1.7, 3.7, 53.1$ , H-C(2')); 4.18 (m, H-C(4')); 3.92 (dd,  $J = 3.6, 12.6$ , 1 H-C(5')); 3.75 (dd,  $J = 4.4, 12.4$ , 1 H-C(5')); 3.51 (ddd,  $J = 1.7, 6.2, 27.4$ , H-C(3')); 2.67 (dd,  $J = 6.2, 12.8$ , 1 H of  $\text{CH}_2\text{N}$ ); 2.46 (dd,  $J = 7.7, 12.4$ , 1 H of  $\text{CH}_2\text{N}$ ); 1.89 (m, CH); 0.97, 0.94 (2d,  $J = 2.2$  each, 2 Me).  $^{13}\text{C-NMR}$  ( $\text{CD}_3\text{OD}$ ): 159.8 (C(4)); 150.8 (C(2)); 143.8, 139.2 (C(5)); 128.1, 127.4 (C(6)); 95.4, 91.6 (C(2')); 86.6, 86.3

(C(1'))); 81.5, 81.4 (C(4'))); 74.0, 73.6 (C(5'))); 67.9 (C(3'))); 63.1 (CH<sub>2</sub>N); 27.7 (CH), 21.4, 21.3 (2 Me). Anal. calc. for C<sub>13</sub>H<sub>19</sub>F<sub>2</sub>N<sub>3</sub>O<sub>5</sub> · 0.5 H<sub>2</sub>O: C 45.48, H 5.87, N 12.24; found: C 45.60, H 5.55, N 12.17.

*1-[2',3'-Dideoxy-2'-fluoro-3'-[hydroxy(2-methylpropyl)amino]-α-D-arabinofuranosyl]-5-fluorouracil* (**α-42**). GPF, with **α-35**: 70%. White solid. <sup>1</sup>H-NMR (CD<sub>3</sub>OD): 7.89 (*d*, *J* = 6.7, H–C(6)); 6.09 (*d*, *J* = 15.6, H–C(1')); 5.45 (*dt*, *J* = 1.9, 50.5, H–C(2'))); 4.54 (*m*, H–C(4'))); 3.74 (*m*, 2 H–C(5'))); 3.44 (*ddd*, *J* = 2.0, 4.6, 24.6, H–C(3'))); 2.57 (*dd*, *J* = 6.2, 12.5, 1 H of CH<sub>2</sub>N); 2.46 (*dd*, *J* = 7.5, 12.4, 1 H of CH<sub>2</sub>N); 1.93 (*m*, CH); 0.93 (*dd*, *J* = 4.6, 6.6, 2 Me). <sup>13</sup>C-NMR (CD<sub>3</sub>OD): 160.0, 159.5 (C(4)); 151.0 (C(2)); 144.2, 139.5 (C(5)); 127.0, 126.3 (C(6)); 100.5, 96.9 (C(2'))); 93.0, 92.2 (C(1'))); 86.3, 86.2 (C(4'))); 75.2, 74.7 (C(5'))); 68.1 (C(3'))); 64.2 (CH<sub>2</sub>N); 27.6 (CH); 21.4, 21.3 (2 Me). Anal. calc. for C<sub>13</sub>H<sub>19</sub>F<sub>2</sub>N<sub>3</sub>O<sub>5</sub> · 0.4 H<sub>2</sub>O: C 45.59, H 5.83, N 12.27; found: C 45.85, H 5.59, N 12.58.

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