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2′-Chloro-2′,3′-dideoxy-3′-fluoro-D-ribonucleosides: Synthesis, Stereospecificity, Some Chemical Transformations, and Conformational Analysis

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The synthesis of methyl 5-*O*-benzoyl-2-chloro-2,3-dideoxy-3-fluoro-*β*-D-ribofuranoside (**5**) and its use as a glycosylating agent for persilylated thymine, N^6-benzoyladenine, and N^4-benzoylcytosine are described (Scheme 1). The 2′-chloro-2′,3′-dideoxy-3′-fluoro-D-ribonucleosides **10**−**12** synthesized were transformed to 2′,3′-dideoxy-3′-fluoro-α- and -*β*-D-*erythro*-pentofuranoside nucleosides of thymine (**13a**,**b**), adenine (**14a**,**b**), and cytidine (**15a**,**b**) by treatment with tributyltin hydride in the presence of α,α′-azobisisobutyronitrile (Scheme 2). Treatment of 2′-chloro-2′,3′-dideoxy-3′-fluoro-D-ribonucleosides with 1 M MeONa/MeOH under reflux for 1−5 h afforded 2′,3′-didehydro-2′,3′-dideoxy-2′-chloro-D-pentofuranosyl nucleosides as the principal products (47−81%) of the reaction, along with recovered starting nucleoside (11−33%) (Scheme 3). Easy HF elimination was also observed in the case of the 2′-azido-2′,3′-dideoxy-3′-fluoro-*β*-D-ribofuranosides of thymine (**17**) and adenine (**20**) (Scheme 3). The role of conformational peculiarities of 2′-chloro-2′,3′-dideoxy-3′-fluoro-D-ribonucleosides as well as of **17** and **20** in the observed exclusive elimination of HF is discussed. The conformational analysis of a rather broad palette of 2,3-dideoxy-3-fluoro-2-(X-substituted)-D-ribofuranosides was performed with the aid of the PSEUROT (version 6.3) program, using (i) the recently reparametrized Karplus-type relation (Chattopadhyaya and co-workers. *J. Org. Chem.* **1998**, *63*, 4967) and (ii) empirical bond angle correction terms suggested by us. The predictive power of the Brunck and Weinhold model (*J. Am. Chem. Soc.* **1979**, *101*, 1700) of the *gauche* effect between atoms and groups as a conformational driving force acting upon the pentofuranose ring is explored. Their model invokes maximum antiperiplanar $\sigma \leftrightarrow \sigma^*$ stabilization when the donating bond is the least polar one and the acceptor orbital is at the most polarized bond and is found at least as satisfactory, and in various specific cases more so than, as rationalizations on the basis of the preference of the *gauche* vs the *trans* conformation of two vicinal electronegative substituents (Wolfe. *Acc. Chem. Res.* **1972**, *5*, 102).

Introduction

A number of 2′,3′-dideoxy-3′-fluoro-*β*-D-*erythro*-pentofuranosyl nucleosides display high antiviral activity (for reviews, see, e.g., refs 1−3; see also refs 4−9). Potent anti-HIV activity has been reported for 1-(2,3-dideoxy-3-fluoro-*β*-D-*erythro*-pentofuranosyl)thymine (FLT, **13b**)[5−7] and 1-(2,3-dideoxy-3-fluoro-*β*-D-*erythro*-pentofuranosyl)-5-chlorouracil;[6,7] the former was found to be the most potent anti-HIV-1 nucleoside analogue, whereas the latter emerged as the most selective inhibitor of HIV-1 replication.

Since the first synthesis of FLT from thymidine,[10] much attention has been devoted to the preparation of 2′,3′-dideoxy-3′-fluoro-*β*-D-*erythro*-pentofuranosyl nucleosides (earlier works are reviewed in ref 11). Two approaches are used for the preparation of these analogues,

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viz., (i) transformation of natural 2′-deoxyribonucleosides or less serviceable ribonucleosides to the desired dideoxyfluoro derivatives[11−15] and (ii) coupling of heterocyclic bases with suitable furanose derivatives containing the C3-fluorine atom or the C3-*xylo*-hydroxyl group, which may be replaced by a fluorine atom[6,11,16−21] (for a recent review, see ref 22). The most important advantage of the first approach lies in the presence of the requisite β-configuration at the anomeric center. Nonetheless, the preparation of FLT from thymidine through the intermediary O^2,3′-anhydro derivative is probably the only expedient example.[23]

The main limitation of the second approach is the poor stereoselectivity of the glycosidic bond formation employing suitable derivatives of 2,3-dideoxy-3-fluoro-D-*erythro*-pentofuranose as glycosylating agents. On the other hand, the use of the universal glycosylating agents makes possible the preparation of a rather broad spectrum of nucleosides having both natural and modified heterocyclic bases. The transglycosylation reaction employing the 5′-*O*-acylated FLT as glycosyl donor and purine bases as glycosyl acceptors[24] combines both of the above approaches.

The use of pentofuranosyl sugars containing at the C2-atom an α-arranged iodine,[25,26] phenylsulfenyl,[27,28] phenylselenenyl,[21,29] or *m*-trifluoromethylbenzoyl group[30,31] as the transient anomeric control group, which can be removed after the glycosidic bond formation, led to an essential improvement of the β-stereoselectivity of the convergent methods. The elegant stereocontrolled syntheses of pyrimidine 2′,3′-dideoxy-β-D-nucleosides including AZT and FLT based on the intramolecular glycosylation concept have recently been described.[32−34]

As a continuation of our efforts in the synthesis of 2,3-dideoxy-3-fluoro-D-*erythro*-pentofuranosides,[12,18,20,24] we describe a new approach for the preparation of these compounds by coupling methyl 5-*O*-benzoyl-2-chloro-2,3-dideoxy-3-fluoro-β-D-ribofuranoside (**5**) with persilylated thymine, N^6-benzoyladenine, and N^4-benzoylcytosine followed by the radical-mediated hydrodehalogenation of the prepared nucleosides and subsequent deprotection. We also demonstrate that the dehalogenation of 2′-chloro-2′,3′-dideoxy-3′-fluoro-D-ribonucleosides with 1 M MeONa/MeOH under reflux for 1−5 h afforded 2′,3′-didehydro-2′,3′-dideoxy-2′-chloro-D-pentofuranosyl nucleosides as the principal products. Similar easy elimination of HF was also observed in the case of 2′-azido-2′,3′-dideoxy-3′-fluoro-β-D-ribofuranosides of thymine (**17**) and adenine (**20**). The role of conformational peculiarities of 2′-chloro-2′,3′-dideoxy-3′-fluoro-D-ribonucleosides as well as **17** and **20** in the observed exclusive elimination of HF is discussed.

The conformational behavior of the various pentofuranoses is discussed in terms of the anomeric effect (AE) and an alternative model of the *gauche* effect (GE).

Results and Discussion

Chemical Transformations. The key glycosylating riboside **5** was prepared from methyl 3-deoxy-5-*O*-benzyl-3-fluoro-2-*O*-tosyl-β-D-arabinofuranoside (**1**)[35] in three steps using two different sequences of the same chemical reactions (Scheme 1). Two-step substitution of the benzoyl group for the benzyl group followed by replacement of the tosyloxy group by a chlorine atom gave the riboside **5** in 51% combined yield. The reversed sequence of the chemical transformations resulted in a somewhat lower yield (45%) of the desired **5**. The reaction of the riboside **5** with persilylated thymine in the presence of trimethylsilyl triflate [(TMS)Tfl] (1.0:2.0:3.0, mol) in refluxing acetonitrile for 5 h followed by chromatography afforded a mixture of the α- and β-anomers **7a**,**b** (the ratio of α to β was 1:2 according to ^{1}H NMR) in 49% yield and a mixture of the methyl glycosides **5** and **6** in 19% yield. This result revealed a close resemblance with the previously described coupling of methyl 2-azido-5-*O*-benzoyl-2,3-dideoxy-3-fluoro-β-D-ribofuranoside with persilylated thymine under similar conditions.[35] Treatment of **7a**,**b** with methanolic ammonia and subsequent chromatography on silica gel afforded 1-(2-chloro-2,3-dideoxy-3-fluoro-β-D-ribofuranosyl)thymine (**10b**) and its α-anomer **10a** in 55% and 28% yield, respectively.

Along the same line, the condensation of silylated N^6-benzoyladenine with methyl glycoside **5** in the presence of excess $SnCl_4$ (2.0:1.0:5.0, mol) in a refluxing acetoni-

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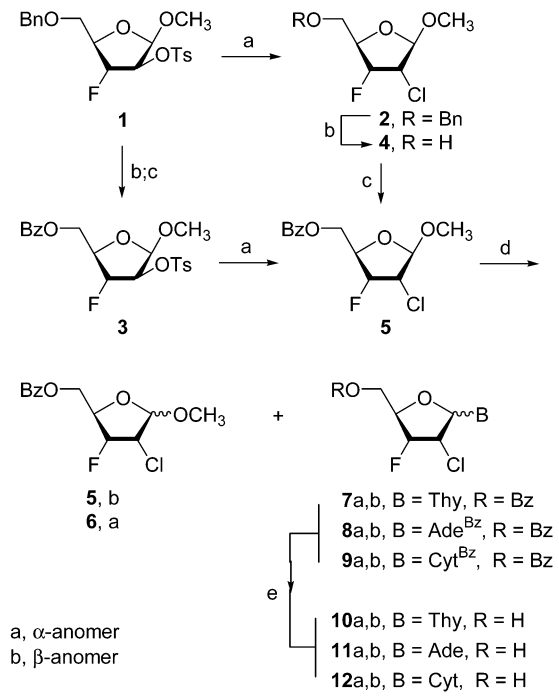
SCHEME 1[a]

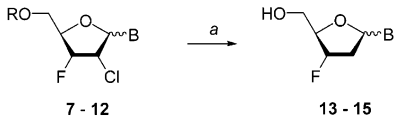


[a] Reagents and conditions: (a) LiCl, DMSO, 200 °C (bath temperature), 2 h (**2**, 55%; **5**, 72%); (b) H_2, 5% Pd/C, EtOH, rt, 18 h; (c) BzCl, pyridine, rt,18 h (b + c, sum 71%); (d) persilylated base, (1) **5**/thymine/(TMS)Tfl, 1.0:2.0:3.0, mol; CH_3CN, reflux, 5 h (**5** + **6**, 19%; **7a,b**, 49%); (2) **5**/N^{6Bz}-adenine/$SnCl_4$, 1.0:2.0:5.0, mol; CH_3CN/1,2-dichloroethane (2:1, vol), reflux, 5 h (**5** + **6**, 7.5%; **8a**, 9%, **8b**, 66%); (3) **5**/N^{4Bz}-cytosine/$SnCl_4$, 1.0:2.0:3.0, mol; CH_3CN, reflux, 5 h (**5** + **6**, 18%; **9a**, 8%; **9b**, 56%); (e) NH_3/MeOH, rt, 24 h (**10a**, 28%; **10b**, 55%; **11a**, 78%; **11b**, 83%; **12a**, 80%; **12b**, 78%).

trile/1,2-dichloroethane (2:1, v/v) mixture for 5 h followed by column chromatography gave 1-(5-*O*-benzoyl-2-chloro-2,3-dideoxy-3-fluoro-*β*-D-ribofuranosyl)-N^6-benzoyladenine (**8b**; 66%) and its α-anomer **8a** (9%) as well as a mixture of the methyl glycosides **5** and **6** (7.5%). An excess of $SnCl_4$ was employed to minimize the formation of the N^7-adenine nucleoside(s).[35−37] No evidence for the presence of the N^7-isomer(s) was detectable by means of TLC. It is noteworthy that the reaction of the furanoside **5** with silylated N^6-benzoyladenine proceeded with better stereoselectivity (a ca. 1:7 α:*β* ratio) of the glycosidic bond formation compared to the similar reaction of methyl 2-azido-5-*O*-benzoyl-2,3-dideoxy-3-fluoro-*β*-D-ribofuranoside (a ca. 1:3 α:*β* ratio).

The reaction of silylated N^4-benzoylcytosine with the furanoside **5** in the presence of excess $SnCl_4$ (2.0:1.0:3.0, mol) in refluxing acetonitrile for 5 h gave, after standard workup and column chromatography, 1-(5-*O*-benzoyl-2-chloro-2,3-dideoxy-3-fluoro-*β*-D-ribofuranosyl)-N^4-benzoylcytosine (**9b**; 56%), its α-anomer **9a** (8%), and a mixture of the methyl glycosides **5** and **6** (18%). Thus, this reaction gave better results in terms of both the yields of the nucleosides (ca. 64%, combined) and the α:*β* ratio (1:7) vs the similar reaction of methyl 2-azido-5-*O*-benzoyl-2,3-dideoxy-3-fluoro-*β*-D-ribofuranoside (ca. 50% combined, α:*β* ratio 1:4). Treatment of protected individual nucleosides **8a**,**b** and **9a**,**b** with saturated methanolic ammonia afforded in good yield the free nucleosides **11a**,**b** and **12a**,**b**, respectively.

SCHEME 2



Run	Starting nucleoside(s)				Reaction conditions[a] (time of reflux, h)	Product(s) of reaction (yield, %)
	No.	anomer	R	Base		
1	**7**a,b	α/β (~1:2)	Bz	Thy	A (2); C	**13**b (55%) **13**a (27%)
2	**8**a	α	Bz	Ade^{Bz}	A (6); C	**14**a (82%)
3	**8**b	β	Bz	Ade^{Bz}	A (6); C	**14**b (79%)
4	**9**b	β	Bz	Cyt^{Bz}	A (16); C	**15**b (31%)
5	**10**b	β	H	Thy	A (2); B (15)	**13**b (90%)
6	**11**b	β	H	Ade	B (15)	**14**b (84%)
7	**12**a	α	H	Cyt	B (15)	**15**a (77%)
8	**12**b	β	H	Cyt	B (15)	**15**b (86%)

[a] (A) Nucleoside(s)/Bu_3SnH/AIBN (1.0:6.0:0.33, mol), dioxane. (B) Nucleoside/Bu_3SnH/AIBN (1.0:5.0:0.33, mol), dioxane/MeOH (1:1, vol). (C) NH_3/MeOH, rt, 24−48 h.

The radical-mediated hydrodehalogenation of a mixture of **7a**,**b** with tributyltin hydride in anhydrous dioxane in the presence of α,α′-azobisisobutyronitrile (AIBN) and subsequent debenzoylation and chromatography gave FLT (**13b**) and its α-anomer **13a** (αFLT) in 55% and 27% yield, respectively (Scheme 2). Similar transformation of deprotected *β*-anomer **10b** afforded FLT in 90% yield. Adenine nucleosides **8a** and **8b** were easily converted in excellent yields into the corresponding α- and *β*-fluorides **14a** (αFLA) and **14b** (FLA), whereas the dehydrohalogenation of cytosine nucleoside **9b** gave a complex reaction mixture, from which nucleoside **15b** (FLC) was isolated in 31% yield after debenzoylation and chromatography. In contrast to this, treatment of deprotected cytosine nucleosides **12a** and **12b** with tributyltin hydride in 1:1 dioxane−methanol gave the corresponding α- and *β*-fluorides **15a** (αFLC) and **15b** (FLC) in high yield, although the reaction requires more prolonged heating. In a similar way, nucleosides **10b** and **11b** were converted into FLT and FLA, respectively.

In extension of this work, we studied the dehydrohalogenation of nucleosides **8a**,**b**, **10b**, and **11b** under the action of 1 M MeONa in methanol (Scheme 3). Treatment of nucleoside **10b** with 1 M MeONa/MeOH under reflux for 5 h followed by silica gel column chromatography gave the chloroolefin **16** (yield 46%) and unchanged starting compound (17%).[39] The preferred elimination of HF instead of HCl is unexpected on the basis of the greater strength of the C−F bond (105.5 kcal/mol) compared to

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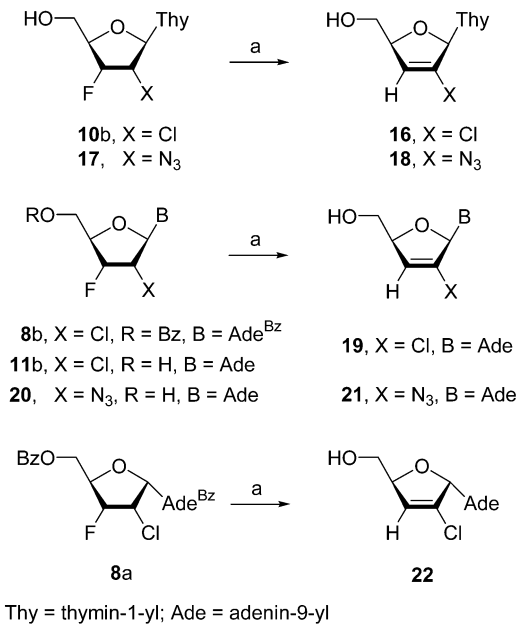
SCHEME 3[a]



[a] Reagents and conditions: (a) 1 M MeONa in MeOH, reflux for (i) 5 h (**16**, 46%; **18**, 47%), (ii) 4 h (**19**, 82% from **8b** and 77% from **11b**; **21**, 69%), and (iii) 1 h (**22**, 86%).

that of the C−Cl bond (78.5 kcal/mol[38]). A similar trend is displayed by 1-(2-azido-2,3-dideoxy-3-fluoro-β-D-ribofuranosyl)thymine (**17**):[35] treatment of **17** with 1 M MeONa/MeOH under reflux for 5 h furnished, after standard workup and subsequent chromatography, the vinyl azide **18**[40] as the main product, along with the unconsumed starting compound **17** in 47% and 33% isolated yield, respectively.

Adenine nucleosides **8a**,**b**, **11b**, and **20**[35] displayed a similar course of HF elimination on treatment with 1 M MeONa/MeOH under reflux, affording the corresponding vinyl chlorides **19** and **22** and the vinyl azide **21** (Scheme 3). It is noteworthy that the rate of conversion of the α-nucleoside **8a** to the α-vinyl chloride **22** was much higher than that of the analogous reaction with the β-anomers **8b** and **11b**.

A likely explanation of the HF vs HCl elimination is suggested by the conformational peculiarities of the starting nucleosides (vide supra). As can be seen from Table 1, the strong predominance of the south (S) type conformer of the furanose ring is a common characteristic of these nucleosides. It should be stressed that the phase angle (*P*) of the pseudorotational equilibrium is in a narrow domain (150° ≤ *P* ≤ 162°) characteristic of the ^{2}E furanose puckering. In this conformation of the D-ribofuranose ring a fluorine atom and the C2′ proton are *trans*-oriented (antiperiplanar, ap) whereas a chlorine atom and the C1′ and C3′ protons are *gauche*-arranged (synclinal, sc) in both the β- and α-nucleosides studied. These considerations imply that the HF elimination leading to the olefins proceeds via a concerted *trans* elimination by the attack of the MeO^- anion at the C2′ proton as a driving force.

In contrast to the above-discussed HF elimination, methyl 3-deoxy-3-fluoro-2-*O*-mesyl-β-D-ribofuranoside was transformed to the vinyl 3-fluoride on treatment with *t*-BuOK.[41] Similarly, 2′-deoxy-2′-fluoro-3′-*O*-mesyl-β-D-ribofuranosyl nucleosides were converted to vinyl 2-fluorides under the action of *t*-BuOK[41] or NaOH in ethanol.[42] The stereochemistry of these fluoromesylates was not investigated to the best of our knowledge. Marquez and co-workers suggested, however, the formation of the vinyl fluorides via *trans* elimination, implying a major population of the S-type conformation of the furanose ring of the starting N^6-benzoyl-2′-deoxy-5′-*O*-dimethoxytrityl-2′-fluoro-3′-*O*-mesyladenosine.[42]

NMR Spectroscopic Studies. The structure of the synthesized compounds is corroborated by ^{1}H (Tables S1 and S2 in the Supporting Information) and ^{13}C (Tables S3 and S4 in the Supporting Information) NMR data and by UV spectroscopy (see the Experimental Section). The most informative features of the NMR spectra of the α-anomers are (i) the 0.26−0.60 and 0.25−0.39 ppm shifts of the respective H1′ and H4′ resonance signals to a lower field on going from the β-anomers to α-anomers and (ii) the long-range couplings between the fluorine atom and C6 of the thymine base of **10a** ($^5J_{6,F}$ = 7.85 Hz) and C8 of the adenine base of **11a** ($^5J_{8,F}$ = 11.63 Hz) in the ^{13}C NMR spectra. The latter couplings are generally indicative of a spatial proximity of the nuclei involved[20,43,44] and are not observed in the corresponding β-anomers **10b** and **11b**.

The ^{1}H NMR data of the fluorides **13**−**15** are in accord with those measured for the same compounds prepared by alternative procedures.[12,18,24] The structures of the olefins **16**, **18**, **19**, **21**, and **22** were confirmed by ^{1}H and ^{13}C NMR spectroscopy and are in agreement with the reported data for closely related compounds.[39,40,45]

A qualitative inspection of the absolute values of $^3J_{FC1'}$ and $^3J_{FC5'}$ (Table S4) of the nucleosides **10a**,**b**, **11a**,**b**, **12b**, **17**, and **20** point clearly to a high preference for the S-type pentofuranose ring conformation. In this conformation, the F−C3′−C4′−C5′ and F−C3′−C2′−C1′ fragments are in antiperiplanar (ca. 170°) and gauche (ca. 90°) arrangements, respectively, which is consistent[46] with the corresponding $^3J_{CF}$ values within the range 9.1−11.6 Hz and of <2.0 Hz (Table S4). It is striking that the β → α change of the anomeric configuration does not seem to give rise to an essential displacement of the predominant population of the S-type puckered conformers (see below). By contrast, sugars **2**−**6** show a conformational diversity as can be seen from both the $^3J_{HH}$ and $^3J_{FH}$ couplings (Table S2).

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TABLE 1. Pseudorotational Parameters of Some 2′,3′-Dideoxy-3′-fluoro-2′-(X-substituted)-D-ribonucleosides

compd	base	C2′−X	P_N (deg)	ψ_N (deg)	P_S (deg)	ψ_S (deg)	rms (Hz)	ΔG_{eff}[a](2′−3′) (Hz)	ΔG_{eff}[a](3′−4′) (Hz)	ΔJ (Hz)	% S	$\Delta G_{S/N}$ (kJ·mol^{-1})
						β-Series						
10b[b]	T	Cl	18[e]	36[e]	155.5	36.9	0.01	−6.7	6.7	0.0	97	−9.1
10b[c]	T	Cl	18[e]	36[e]	157.0	36.4	0.02	−7.1	6.3	0.0	95	−7.7
11b[b]	A	Cl	18[e]	36[e]	161.8	35.4	0.01	−6.7	7.6	0.0	95	−7.7
11b[c]	A	Cl	18[e]	36[e]	164.4	35.1	0.01	−5.6	7.1	0.0	94	−7.2
12b[c]	C	Cl	18[e]	36[e]	165.0	35.0	0.02	−9.1	6.3	0.0	95	−7.7
13b[c]	T	H	−20	32[e]	160.6	32.2	0.4	4.7	7.1	0.6	94	−7.2
14b[b]	A	H	0	32[e]	171.9	31.6	0.2	4.1	8.2	0.3	98	−9.1
FLG[b]	G	H	0	32[e]	167.9	32.0	0.2	4.1	8.2	0.3	96	−8.3
17[b]	T	N_3	18[e]	33[e]	152.3	32.4	0.01	−5.8	6.0	0.0	99	−9.1
17[c]	T	N_3	18[e]	40[e]	154.6	36.7	0.01	−5.6	6.3	0.0	94	−7.2
20[c]	A	N_3	18[e]	38[e]	155.7	36.8	0.03		6.3	0.1	95	−7.7
23[b]	A	NH_2	18[e]	36[e]	150.1	39.3	0.01	−2.2	6.0	0.0	97	−9.1
24[c]	T	NH_2	18[e]	36[e]	159.5	36.7	0.01	−2.6	8.4	0.0	95	−7.7
25[b]	C	NH_2	18[e]	36[e]	159.3	36.7	0.01	−3.0	6.9	0.0	95	−7.7
26[d,f]	A	OH	18[e]	33[e]	175.3	32.0	0.1	−2.6	3.9	0.0	98	−9.1
27[c,g]	A	F	13.2	37.6	165.4	37.0[e]	0.0	−8.2	7.4	0.0	80	−3.6
						α-Series						
10a[c]	T	Cl	58.3	33[e]	185.7	31.6	0.1	−3.5	3.7	0.1	82	−4.0
11a[c]	A	Cl	0.3	33[e]	168.1	30.8	0.1	−3.5	3.7	0.3	94	−7.2
12a[c]	C	Cl	−7.8	33[e]	189.6	40.1	0.1	−3.5	3.7	0.2	58	−0.9
13a[c]	T	H	36[e]	36[e]	167.3	29.2	0.1	7.3	4.1	0.1	97	−9.1
14a[b]	A	H	0[e]	36[e]	173.3	27.6	0.2	6.0	5.4	0.3	95	−7.7
αFLG[b]	G	H	0[e]	36[e]	180.3	26.7	0.1	6.0	5.4	0.3	96	−8.3

[a] $\Delta G_{eff} = -3.72[(\alpha_{FCC} + \alpha_{HCC})/2 - 110]$ along a given C−C bond (see the text). [b] DMSO. [c] CD_3OD. [d] $CDCl_3$. [e] Kept fixed during the final minimization. [f] 5′-*O*-Benzyl derivative.[63] [g] See ref 64.

Conformational Analysis

Analysis of Pseudorotation Parameters. The conformational analysis of the furanose rings of selected sugars and nucleosides described was performed with the aid of the PSEUROT (version 6.3) program, which calculates the best fits of three $^3J_{HH}$ and two $^3J_{HF}$ experimental coupling constants [$^3J_{H1'H2'}$, $^3J_{H2'H3'}$, and $^3J_{H3'H4'}$, and $^3J_{H2'F3'}$ and $^3J_{H4'F3'}$] to the five conformational parameters (phase angles *P* and puckering amplitudes ψ_m for both the north (N) and the south (S) type conformers and the corresponding molar ratio).[47] In the PSEUROT program a minimization of the differences between the experimental and calculated couplings is accomplished by a nonlinear Newton−Raphson minimization; the quality of the fit is expressed by the root-mean-square (rms) difference. This procedure presupposes the existence of a two-state N/S equilibrium. When only three vicinal $^3J_{HH}$ coupling constants along the ring bonds exist, as is the case in the present series, two of the five conformational parameters must be kept fixed to preset values during the minimization. This fixing is usually not much of a problem whenever the equilibrium is strongly one-sided (major form ≥85%) but may lead to more-or-less wide ranges of possible conformational parameters otherwise. These ranges can be narrowed by increasing the ratio of the number of data points vs the number of optimized parameters. To achieve this end, two different strategies can be employed: (i) measurement of the NMR spectra over a wide range of temperatures; (ii) the inclusion of other coupling information in the calculation.

Chattopadhyaya and co-workers have recently developed a new Karplus-type relation between vicinal proton−fluorine coupling constants and the corresponding H−C−C−F torsion angles including correction terms for substituent electronegativity and for the H−C−C (α_{HCC}) and F−C−C (α_{FCC}) bond angle changes from the tetrahedral values.[48] The latest release (version 6.3) of the PSEUROT program incorporates the published Karplus parameters for $^3J_{HF}$ and allows simultaneous analysis of $^3J_{HH}$ and $^3J_{HF}$ experimental coupling constants, which greatly facilitates the conformational analysis of pentofuranose rings because of the increase in the number of experimental data points over the puckering parameters *P* and ψ_m.[47,48] We propose to write the bond angle correction term as

$$\Delta^3 J_{HF} = \Delta G_{eff} \cos^2 \Phi_{HF} \qquad (1)$$

where $\Delta G_{eff} = G[(\alpha_{FCC} + \alpha_{HCC})/2 - 110]$ ($G = -3.72$ Hz) and Φ_{HF} is the H−C−C−F torsion angle under consideration.

In the original work[48] the bond angles α were determined from 3-21G ab initio calculations and the parameter *G* was optimized, together with the remaining Karplus parameters *A*−*F*, to fit both J_{HH} and J_{HF} simultaneously. Lacking ab initio data spanning pseudorotational space for the compounds in the present collection, we chose to invert the procedure and fitted ΔG_{eff} to minimize ΔJ_{HF} along each bond (Tables 1 and 2). Note that this approach involves, first of all, the determination of the best pseudorotation parameters or range of best parameters on the basis of $^3J_{HH}$ only and then fixing the conformers found to manually fit ΔG_{eff} along the coupling paths in question. Another main criterion used here was that ΔG_{eff} in a series of similar compounds should be fairly constant in sign and magnitude. A rough correlation with the electronegativity of

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TABLE 2. Pseudorotational Parameters of Some Methyl 2,3-Dideoxy-3-fluoro-2-(X-substituted)-D-ribofuranosides

compd	5-*O*-R	C2′−X	P_N (deg)	ψ_N (deg)	P_S (deg)	ψ_S (deg)	rms (Hz)	ΔG_{eff}[a](2′−3′) (Hz)	ΔG_{eff}[a](3′−4′) (Hz)	ΔJ (Hz)	% S	$\Delta G_{S/N}$ (kJ·mol^{-1})
						β-Series[b]						
2	Bn	Cl	−13.8	42.1	166.0	39[c]	0.0	−8.2	3.5	0.0	41	0.9
4	H	Cl	−7.5	31.9	179.5	39[c]	0.0	−8.2	3.5	0.0	40	1.1
5	Bz	Cl	−22.5	38.4	167.2	38[c]	0.0	−6.7	6.3	0.0	10	5.7
28[d]	Bn	F	0.1	34.9	171[c]	36.3	0.1	−10.8	2.1	0.2	15	4.5
29[d]	H	F	10.4	32.4	153[c]	32.4	0.1	−10.8	2.1	0.2	18	4.0
30[d]	Bn	H	−59.8	42[c]	225.5	40.1	0.1	0.4	10.2	0.2	69	−2.1
31[d]	H	H	−67.3	42[c]	218.8	43.5	0.2	0.4	10.2	0.4	64	−1.5
						α-Series[b]						
6I	Bz	Cl	−55.5	33.5	142.4	36.9	0.0	6.7	2.1	0.2	63[e]	−1.4
6II	Bz	Cl	−61.1	37.5	137.3	36.5	0.0	2.1	2.1	0.0	76[e]	−3.0
32[f]	Bz	OH	−47.0	28[c]	145.2	28.0	0.0	0.2	−0.7	0.0	96	−8.3

[a] $\Delta G_{eff} = -3.72[(\alpha_{FCC} + \alpha_{HCC})/2 - 110]$ along a given C−C bond (see the text). [b] All ^{1}H NMR spectra have been measured in $CDCl_3$. [c] Kept fixed during the final minimization. [d] See ref 64. [e] These examples serve to illustrate the unusual uncertainty in the conformational populations of **6**. Actually, all populations between about 60% S and 90% S are compatible with the data. [f] See ref 63.

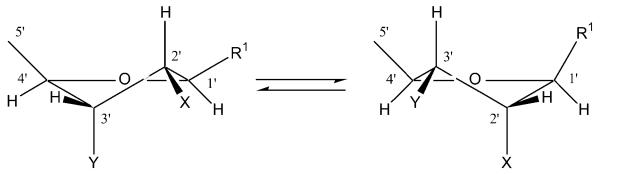

FIGURE 1. Schematic presentation of the north (N; C2′-*exo*/C3′-*endo*) ⇌ south (S; C2′-*endo*/C3′-*exo*) pseudorotational equilibrium in β-D-nucleosides (R1 = base) and -pentofuranose sugars (R1 = OR, where R = H, Me, etc).

neighboring substituents is expected and found (Tables 1 and 2). The nature of the solvent also seems to play a role.

The necessary *A* and *B* parameters, which relate the *endo*cyclic to the *exo*cyclic torsion angles between coupling nuclei,[47] were taken from the literature[48] and averaged for similar structures. To account for the facts that the magnitude of $^3J_{HF}$ is roughly 5 times larger than the magnitude of $^3J_{HH}$ and that the Karplus parameters for the HF coupling were obtained on a relatively small set of experimental *J* values, scale factors were introduced (1.0 for $^3J_{HH}$ and 0.1 for $^3J_{HF}$).

Stereoelectronic Factors. Besides steric interactions, the north (N) (C2′-*exo*/C3′-*endo*)/south (S) (C2′-*endo*/C3′-*exo*) pseudorotational equilibrium in nucleosides, nucleotides, and pentafuranose sugars (Figure 1) is driven by competing stereoelectronic factors known as the anomeric effect (AE) and *gauche* effect (GE).

A broad definition of the AE is embodied in the statement that, in a fragment C−X−C−Y where ligand X carries one or two lone pairs of electrons and Y represents an electronegative ligand, the *gauche* conformers along the central X−C bond are preferred over the *trans* form (antiperiplanar, ap).[49] In nucleosides and related sugars this means that an electronegative ligand L at C1′ is driven to adopt the pseudoaxial position (*gauche* C4′−O4′−C1′−L). Of course, steric forces counteract this drive. Preference for a pseudoaxial position at C1′ means a drive toward the N form in the β-D-series and toward the S form in the α-D-series. Interestingly, it was demonstrated experimentally that the strength of this drive can be manipulated by protonation or deprotonation of the nucleobase.[50,51] Following convention, the associated enthalpy and free-energy changes are termed positive when the drive favors the N-type conformers and negative when it favors the S-type conformers.

In the discussion of the AE presented here the so-called Altona−Havinga model[49] will be used, which entails n → σ* stabilization, where n represents an available lone pair of electrons and σ* is a suitably positioned antibonding orbital. It is important to note that quantum-chemical calculations of *gauche* and *trans* conformers in XCH_2OH indicate a linear correlation between the strength of the AE and the electronegativity of X ($\chi_{CH_3} < \chi_{NH_2} < \chi_{OH} < \chi_F$).[52] In practice, the matters are often more complicated by competition among various stereoelectronic factors at the same anomeric center,[53] and the anomeric strength of a given aglycon varies with the chemical nature of nearby substituents.

The term "GE" was coined by Wolfe,[54a] who showed that a vicinal fragment such as X−C−C−Y prefers to adopt a *gauche* conformation along the central C−C bond in cases where X and Y represent highly electronegative ligands (or electron pairs) although dipole−dipole repulsions and steric factors work in favor of the antiperiplanar form. In work with the aid of the earliest version of the PSEUROT program Haasnoot et al.[54b] suggested that the conformational behavior of a series of nucleic acid constituents could be rationalized on the basis of the GE concept. The possible origin(s) of the GE merits some discussion here because different views may lead to different conclusions.

The first view focuses on the *gauche* situation itself

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and accepts either an attraction between the *gauche*-oriented electronegative ligands X and Y,[54a] which from this point on will be denoted as the standard view as it is most widely used, or a relative destabilization of antiperiplanar X−C−C−Y because of bond bending.[55] For example, it is often stated[54c,d] that in β-D-ribonucleosides the GE of O4′−C1′−C2′−O2′ favors a pseudoaxial O2′ ligand, i.e., drives the ribonucleoside toward the N form, whereas this drive is counteracted by the GE of N−C1′−C2′−O2′, which will drive both the nucleobase and O2′ to adopt pseudoequatorial positions, i.e., the S form. In a similar vein, the GE of O4′−C4′−C3′−O3′ in β-D-ribonucleosides drives them toward the S form with the O3′ ligand in a pseudoaxial position. Finally, in this view the fragment X2′−C2′−C3′−Y3′ remains *gauche* in either the N or S form and the GEs of both forms effectively cancel each other. However, a closer look at the geometries involved in the first three of the above examples, which involve interactions between an exocyclic and an endocyclic ligand, shows that in the Newman projections the relevant bonds are approximately perpendicular to one another (90° ± 12°). This means that any orbital−orbital interaction will tend to be minimal.

A radically different view on the GE, proposed by Brunck and Weinhold,[57a] is embodied in the statement that this effect arises from a relative stabilization of a situation where the most electronegative ligand is approximately antiperiplanar to the least electronegative ligand. In analogy with the antiparallel $n_X \leftrightarrow \sigma^*_{C-Y}$ lone pair−antibonding donor−acceptor orbital mixing explanation of the AE,[56] Brunck and Weinhold suggest maximum antiperiplanar $\sigma \leftrightarrow \sigma^*$ stabilization where the donating bond is the least polar one (usually but not necessarily C−H) and the acceptor orbital is at the most polar bond.[57a] A recent quantum-chemical study[57b] supports this model. According to the second view the term "*gauche* effect" is confusing[57a] and could be more aptly named the antiperiplanar effect (AP). To avoid misunderstandings, the accepted name is best retained. However, for the sake of clarity it is desirable at this point to introduce a modified notation, which does not refer to the *gauche* orientation of the polar bonds but instead draws attention to the AP situations (favorable and unfavorable), which are available to the fragment considered. Note that lone electron pairs are not counted as ligands here. As our examples pertain to the furanose rings shown in Tables 1 and 2, the standard notation is often also given to clarify the differences between the two views discussed. It is better to keep in mind that along each C−C bond in a nonplanar ring and for a given conformer there is one AP interaction between a vicinal pseudodiaxial (aa) exocyclic ligand pair against two AP interactions between each pseudoequatorial exocyclic ligand and a ring atom. In the case of a two-conformer equilibrium, one has to examine six APs per bond. As the central bond is always C−C there is no need to refer explicitly to the so-called L-polar bonds[57a] at each end of the L−C−C−L′ fragment, and it suffices to concentrate on the electronegativity of the ligands themselves. Moreover, we assume that APs between like ligands, for example, AP[OR−OR], do not contribute to the conformational energy. At this point three types of APs can be distinguished: (i) neutral APs, which presumably do not influence the drive toward one conformer or another, for example, AP[H3′−H4′] in the N-type ribosides; (ii) constant APs, which are in the first approximation only dependent on the electronegativity difference between the two ligands at either end of the intervening bonds, for example, AP[O4′−H3′] favoring the S form and AP[O4′−H2′] favoring the N form of ribose rings; in practice, these APs are not constant but modulated by other substituents present; (iii) potentially variable APs, the driving force of which is expected to increase with the electronegativity difference between the ligands L and L′ at each end of the central bond. Moreover, the relatively small differences between the various AP torsion angles in ribosides (usually ranging from 140° to 160°) are neglected. The following dissection is based on hypothetical β- and α-D-2,3-dideoxy-X2,Y3-ribosides; the aglycon is indicated by R1. For obvious reasons the neutral APs such as AP[H−H] and AP[C−H] need no discussion.

Let us first look along the C3′−C4′ and C2′−C3′ bonds of ribosides, concentrating on the APs involving Y3′. In the N form one has two variable APs: (i) AP[O4′−Y3′], the energy of which will vary from highly stabilizing in the case of Y3′ = H to zero for Y3′ = OR and possibly even destabilizing upon a further increase of the electronegativity χ of Y3′; (ii) AP[Y3′−C1′], which, however, balances (cancels) the variable AP[Y3′−C5′] of the S form. In the S form, one has additionally the variable and stabilizing AP[Y3′−H2′] and the constant and stabilizing AP[O4′−H3′]. The well-known GE of O4′−C4′−C3′−Y3′ thus represents the sum of six APs; however, the variability of this GE with χ_Y rests solely upon the balance between AP[O4′−Y3′] and AP[Y3′−H2′], and the net effect will be an increasing stabilization of the S form relative to the N form upon increasing $\chi_{Y3'}$. In fact, it was experimentally demonstrated[58] that in a series of 3′-substituted 2′,3′-dideoxythymidines the enthalpy $\Delta H°_{GE}$ linearly correlates with $\chi_{Y3'}$ on Mullay's scale.[59] It was also shown[60] that in the abasic sugar skeleton the GE of O4′−C4′−C3′−O3′ and the GE of O4′−C1′−C2′−O2′ are of equal magnitude and of opposite sign. In terms of APs this magnitude is equal to two AP[O−H] interactions if one neglects the small difference between AP[O2′−H1′] and AP[O3′−C5′]. Other work[61] has revealed that the nominal strength of the GE of O4′−C4′−C3′−O3′ in β-D-2′-deoxynucleosides appears to depend on the nature of the nucleobase.

Along the C2′−C3′ bond the overall GE of X2′−C2′−C3′−Y3′ may slightly differ according to the viewpoint taken. The first view predicts that, as the geometry remains *gauche* in either the N or S form, there will not be any detectable drive toward one side or another regardless of the electronegativities of X2′ and Y3′.

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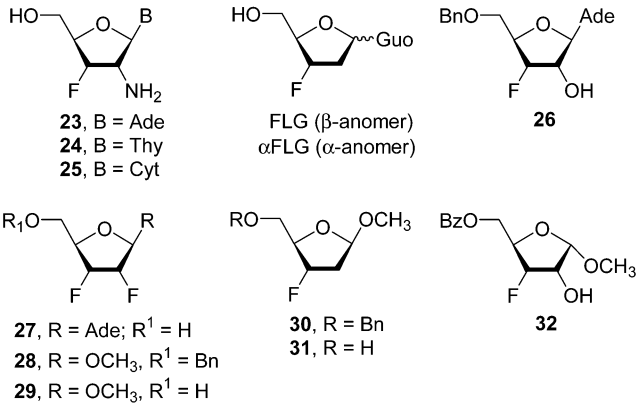
According to the second view, one distinguishes on one hand two variable APs that favor the N form, the pseudodiaxial AP[X2′−H3′] and the endocyclic AP[Y3′−C1′], vs two APs that favor the S form, the pseudodiaxial AP[Y3′−H2′] and the endocyclic AP[X2′−C4′]. On first sight, one expects virtually complete mutual cancellation of these APs and thus a net drive of zero because in the normal N and S pseudorotational ranges the respective AP torsion angles are approximately constant, amounting to roughly ±155°. A small differential effect could occur when the electronegativity of C1′ is modified inductively by a change of aglycon.

Along the C1′−C2′ bond two GEs are customarily recognized, the GE of O4′−C1′−C2′−X2′ and the GE of R1′−C1′−C2′−X2′, the former driving toward the N form in cooperation with the anomeric effect in the β-D-anomers and counteracted by the AE in the α-D-anomers and the latter driving toward the S form in β-D-anomers but balancing in the α-D-anomers. In terms of APs, matters look more complicated. Considering the β-D-ribonucleosides first (R1′ = B), one recognizes that the N form, besides the favorable anomeric effect, is characterized by a strongly favorable but constant AP[O4′−H2′] and by a highly variable pseudodiaxial AP[B−X2′]. Unfortunately, the electronegativity χ_B of any nucleobase on Mullay's scale is unknown, but it is safe to assume $\chi_C < \chi_B < \chi_O$. In the case of 2′-deoxynucleosides (X2′ = H2′) the AP[B−H2′] reinforces the AE drive toward the N form, but for X2′ = Cl, O, or F little can be said for the moment. In the S form, one has the variable AP[O4′−X2′] and a base-dependent variable AP[B−C3′]; in the β-D-2′-deoxy case the former AP balances AP[O4′−H2′]. In β-D-ribonucleosides AP[O4′−O2′] is zero. It follows that the net effect of base changes on AP energies along the C1′−C2′ bond is probably relatively small compared to the AE. In the N form of α-D-ribonucleosides one again encounters the constant N-driving AP[O4′−H2′], counteracted by the S-driving AP[O4′-H3′], as well as the strongly variable AP[X2′−H1′], the N drive of which runs from zero for X2′ = H to a maximum value for X2′ = F. The S form is mainly characterized by the variable AP[X2′−O4′], which runs from highly stabilizing for X2′ = H (balancing AP[O4′−H2′] in the N form) to zero for X2′ = O, and by the variable AP[B−H2′] augmenting the AE. Of course, the AE is now S-driving. In methylated sugars (R1′ = OMe), more specific predictions can be made, and these will be treated in the next section.

PSEUROT Calculations. The conformational data on 2′,3′-dideoxy-3′-fluoro-2′-(X-substituted)-β,α-D-ribonucleosides are collected in Table 1 and those on some similarly substituted methyl glycosides in Table 2. To gain more detailed insight into the role of a *ribo* substituent at C2′, the PSEUROT analyses of 9-(2,3-dideoxy-3-fluoro-β-D-*erythro*-pentofuranosyl)guanine (FLG) and its α-anomer (αFLG),[24] 2′-amino-2′,3′-dideoxy-3′-fluoro-β-D-ribonucleosides of adenine (**23**), thymine (**24**), and cytosine (**25**),[62] as well as 5′-*O*-benzyl-3′-deoxy-3′-fluoroadenosine (**26**)[63]

SCHEME 4



and 2′,3′-dideoxy-2′,3′-difluoroadenosine (**27**),[64] are included in Table 1 (Scheme 4). Note that the pseudorotational parameters for 9-(2-amino-2,3-dideoxy-3-fluoro-β-D-ribofuranosyl)guanine are identical with those of cytosine nucleoside **25** and are, therefore, not included in Table 1. The carbohydrate precursors in the synthesis of **27**, viz., methyl 2,3-dideoxy-2,3-difluoro-5-*O*-benzyl-β-D-ribofuranoside (**28**) and its 5-*O*-debenzoylated derivative **29**,[64] are included in Table 2. Moreover, methyl 2,3-dideoxy-3-fluoro-5-*O*-benzyl-β-D-*erythro*-pentofuranoside (**30**) and its derivative **31**[64] are also included in Table 2.

Due to the fact that only free-energy differences are available from the present work the following analysis is necessarily of a qualitative nature. The 3′-deoxy-3′-fluoro-β-D-ribonucleoside series (substituent X2′ = H, Cl, N_3, NH_2, OH, and F) shows remarkable constant behavior. Except for X2′ = F, all compounds display a strong preference (≥94%) for the S-type sugar conformer regardless of the nature of the nucleobase and regardless of the electronegativity of the X2′ substituent. This means that the pseudoaxial F3′ ligand of the S-form completely dominates the situation. Disregarding the APs that mutually cancel in the S vs N form, for example, AP[O4′−H3′] vs AP[O4′−H2′], the strong S drive must be due to AP[F3′−H2′], far outweighing the anomeric effect of the nucleobase. Only for X2′ = F2′ this dominance is partly broken (80% S). In the first approximation one could expect that AP[F2′−H3′] in the N form would perfectly match AP[F3′−H2′] in the S form. Nevertheless, the strongly N-driving AE of the base does not gain the upper hand. A closer look reveals that the S vs N AP situation is not symmetrical because the former has AP[F3′−C5′], which is expected to be strongly S-driving compared to the relatively neutral AP[F2′−B] in the N form. In addition, it is likely that the anomeric effect of the base diminishes with increasing electronegativity of X2′, judging by the conclusion that the anomeric effect of Ade in the β-D-ribonucleoside is smaller than the AE in its 2′-deoxy counterpart.[51] In terms of the standard view the rationalization would involve the balancing of all GEs except for a strongly S-driving GE(F2′−C2′−C1′−B) counteracting the N-driving AE.

In the α-D-nucleoside series (Table 1), only two different X2′ substituents are at hand, H and Cl. For X2′ = H

(62) Mikhailopulo, I. A.; Sivets, G. G.; Pricota, T. I.; Poopeiko, N. E.; Balzarini, J.; De Clercq, E. *Nucleosides Nucleotides* **1991**, *10*, 1743−1757.

(63) Mikhailopulo, I. A.; Sivets, G. G. *Helv. Chim. Acta* **1999**, *82*, 2052−2065.

(64) The synthesis and characterization are described in the Supporting Information.

(**13a**, **14a**, αFLG) either view would predict (in different words) a strong predominance of the S form, and this is found (≥95% S). Matters are different for X2′ = Cl (**10a**, **11a**, **12a**). In going from Ade (**11a**, 94% S) to Thy (**10a**, 82%S) to Cyt (**12a**, 58%S) a remarkable base-dependent progression in the S/N population ratio is seen. It is extremely difficult to rationalize this behavior in terms of the standard GE model. This model would predict (i) a strong S-driving force from GE(O4′−C4′−C3′−F3′) counteracted by the much weaker N-driving O4′−C1′−C2′−Cl2′ and (ii) mutual cancellation of the *cis* GEs of B−C1′−C2′−Cl2′. The S-driving GE is augmented by the additional S drive from the AE. In all, the standard view predicts a highly predominant S population that is (almost) independent of the nature of the nucleobase. The AP model offers a satisfying rationalization: (i) The strongly S-driving AP[F3′−H2′] is counteracted by two N-driving APs induced by chlorine, AP[Cl2′−H3′] and AP[Cl2′−H1′]. Since the relative electronegativity $\Delta\chi = \chi_X - \chi_H$ of Cl (0.99) is about half that of F (1.9) on the Mullay scale,[59b] the opposing drives of the two halogens will mutually cancel. (ii) There remains a weaker S-driving AP[F3′−C5′]. (iii) The S-driving AP[B−H2′] is probably weak, and the situation is dominated by the S-driving AE of the base, thus qualitatively explaining the base dependency of the population ratio. This behavior runs counter to expectations based on the strength of the AE displayed by 2′-deoxy-α-D-nucleosides (α-D-dNs) wherein the S form is relatively more stabilized by the nucleobase in the sequence thymine-1-yl < adenin-9-yl < cytosin-1-yl.[50] Perhaps unfortunately, the conformational behavior and thermodynamics of a series of α-D-rNs, to the best of our knowledge, seem not to have been investigated, and extrapolation from α-D-dNs to α-D-rNs need not be necessarily correct.

Compared to the F3′-substituted β-D-nucleosides discussed above, a more outspoken behavioral differentiation is displayed by the methyl 2,3-dideoxy-3-fluoro-2-(X-substituted)-β-D-ribofuranosides (X = H, Cl, and F; Table 2), where we find a progressive shift toward the N form when the electronegativity of X increases: 31−36% N for X = H (**30**, **31**), 59−60% N for X = Cl (**2**, **4**, **5**), and 82−85% N for X = F (**28**, **29**). This trend appears to run counter to predictions based on the conventional GE approach. For example, when X = F, GE(F2′−C2′−C1′−O4′) in the N form should balance GE(F3′−C3′−C4′−O4′) in the S form, but there remains the strongly S-driving GE(F2′−C2′−C1′−OMe), which counteracts the N-driving AE(OMe). The data can be rationalized by assuming that AE(OMe) ≫ GE(F2′−C2′−C1′−OMe), but this assumption does not fit the predominance of the S form when X = H, where obviously GE(F3′−C3′−C4′−O4′) ≫ AE(OMe). The experimental trend is well compatible with our proposed AP description in conjunction with the anomeric effect. First, one recognizes that two important APs, AP[X2′−OMe] in the N form and AP[X2′−O4′] in the S form, balance for each given X substituent. Second, in the special case that X = F the effects of all strongly driving APs cancel, and only three weaker ones remain: AP[F3′−O4′] in the N form vs AP[OMe−C3′] plus AP-[F3′−C5′] in the S form. A partial cancellation occurs, the AE(OMe) assumes the predominant role, and the N form is favored (ΔG = +4.0 to +4.5 kJ·mol^{-1}). In the case that X = H the net result of various cancellations is that the S-driving AP[F3′−H2′], aided by AP[OMe−C3′], dominates over the N-driving AE(OMe) (ΔG = −1.5 to −2 kJ·mol^{-1}). With a 2′-substituent of moderate electronegativity (X = Cl) it is no surprise to find a ΔG value between the two extremes (+0.9 to +1.1 kJ·mol^{-1}).

The strong AE(OMe), due to the high electronegativity of OMe combined with its relatively small steric size compared to that of a nucleobase, also helps to explain the peculiar pseudorotational behavior of the first member of this series (X = H): $P_N \approx -60°$ and $P_S \approx 225°$. By contrast, normal 2′-deoxy-β-D-ribonucleosides prefer to occupy the ranges $P_N = 0°-18°$ and $P_S = 144°-180°$. It is generally agreed that for maximum n → σ* interaction the orbital of the lone pair donor should be aligned with the antibonding orbital of the acceptor bond. The question now pertains to the best description of the hybridization of the lone pairs of an ether oxygen atom. In the course of time two different models were proposed: the sp^3 model and the sp^2 (π-like) model. Although in descriptions of the anomeric effect the sp^3 model was originally favored,[56] it now appears preferable[65] to use the π-like model wherein the p lone pair is positioned perpendicular to the C1′−O4′−C4′ plane. Consideration of the Newman projections along the C1′−O4′ bond shows that in β-D-ribosides a pseudorotation of P_N toward negative values ($P_N = -36°$ to $-54°$) brings about a perfect antiparallel alignment between the p-type lone pair of O4′ and the C1′−O1′ bond (181°−187°, respectively). Even more interesting is the observation that pseudorotation of P_S beyond 180° (high S, $P_S = 216°-234°$) improves the same alignment (162°−173°), suggesting that the high-S form of β-D-ribofuranosides is also stabilized by a certain amount of anomeric interaction. By contrast, the geometrical situation in α-D-ribosides is completely different. The observed pseudorotation of the N form toward negative P_N appears to be related to an increasingly improving alignment of AP[OMe−C4′] (157° for $P_N = -54°$); in the S form one predicts the maximum favorable anomeric alignment of 180° to occur near $P_S = 144°$, and this corresponds with the results of the present PSEUROT analyses.

Finally, the conformational populations of the methyl α-D-ribofuranosides merit a brief discussion. Remarkably, for X2′ = Cl (**6**) the PSEUROT calculations yield an unusually wide range of satisfactory (low rms) solutions of the least-squares problem. Representative examples are shown in Table 2 (**6I** and **6II**). It is interesting to see that different values of ΔG_{eff} hardly affect the resulting geometrical parameters but yield different populations. For both X2′ = Cl (**6**) and X2′ = OH (**32**) the AP[F3′−H2′] cooperates with the AE(OMe) to drive the sugar ring to adopt the S form. For X2′ = OH the N-driving AP-[O2′−H1″] balances the S-driving AP[OMe−H2′]. No such balancing is expected for X2′ = Cl, and one predicts a strong predominance of the S-type conformer.

Conclusions

We have shown that the α-arranged chlorine substituent at the C2 carbon of methyl pentofuranosides can be used as the anomeric control factor in the glycosylation

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reaction. Subsequent efficient removal of the chlorine atom under the action of Bu_3SnH/AIBN afforded 2′-deoxynucleosides. Employing methyl 5-*O*-benzoyl-2-chloro-2,3-dideoxy-3-fluoro-β-D-ribofuranoside (**5**) as the universal glycosylating agent, the 2′,3′-dideoxy-3′-fluoro-β-D-erythro-pentofuranosyl nucleosides of thymine (FLT), cytosine (FLC), and adenine (FLA) were synthesized along with the corresponding α-anomers αFLT, αFLC, and αFLA as byproducts. Dehalogenation of 2′-chloro-2′,3′-dideoxy-3′-fluoro-β-D-ribofuranosides of thymine (**10b**) and adenine (**11b**) with 1 M MeONa/MeOH resulted in exclusive HF elimination, giving rise to the respective vinyl chlorides **16** and **19** as the principal products. Similar easy HF elimination was also observed in the cases of the blocked anomeric adenine α- and β-nucleosides **8a**,**b** and of 2′-azido-2′,3′-dideoxy-3′-fluoro-β-D-ribofuranosides of thymine (**17**) and adenine (**20**). It is suggested that this behavior is governed by the antiparallel configuration of the C3′−F and the C2′−H bonds in the predominant S conformation of the pentofuranose ring in the above compounds.

The conformational behavior of the 3′-fluorinated furanoside rings was explored on the basis of $^3J_{HH}$ and $^3J_{HF}$ with the aid of the PSEUROT6.3 program.[47] The predictive power of the standard model of the GE[54a] was compared to that of an alternative model proposed by Brunck and Weinhold,[57a] which invokes maximum AP $\sigma \leftrightarrow \sigma^*$ stabilization when the donating bond is the least polar one and the acceptor orbital is at the most polarized bond. The 2′,3′-dideoxy-3′-fluoro-2′-(X-substituted)-β-D-ribonucleosides (X2′ = H, Cl, N_3, NH_2, and OH) display a strong preference for the S conformation (≥94% S), independent of the nature of the nucleobase. When X2′ = F (**27**), this preference drops to 80% S. Both models tested appear to explain these data well, at least qualitatively. Matters are different in the corresponding α-D-nucleoside series **10a**, **11a**, and **12a** (X2′ = Cl), which displays a remarkable base-dependent progression in the population of the N form in going from Ade to Thy to Cyt. Here the AP model offers a satisfying rationalization, whereas the standard view would predict a strong predominance of the S form in all compounds. Similarly, the conformational behavior of the corresponding substituted methyl α- and β-D-ribofuranosides is more compatible with predictions from the AP model than it is with those from the standard GE model. However, further research is needed before a final verdict concerning the relative merits of the two competing views can be passed.

Experimental Section

General Procedures. Melting points are uncorrected. The UV spectra were recorded in ethanol, except where otherwise indicated. The ^1H and ^{13}C NMR spectra were measured at 200.13 and 50.325 MHz, respectively, at 23 °C with tetramethylsilane as an internal standard. Standard Silufol UV_{254} and silica gel $60F_{254}$ plates were used for thin-layer chromatography (TLC) of sugars and nucleosides, respectively; solvent systems used were hexane−diethyl ether (1:1) (A), $CHCl_3$–MeOH (9:1) (B), and $CHCl_3$–MeOH (4:1) (C). Column chromatography was performed on a silica gel L 40/100 μm column. Freshly distilled anhydrous DMSO was used throughout this work. Except otherwise indicated, the reactions were carried out at room temperature. The solutions of compounds in organic solvents were dried with anhydrous Na_2SO_4 for 4 h.

Methyl 5-*O*-Benzyl-2-chloro-2,3-dideoxy-3-fluoro-β-D-ribofuranoside (2). To a stirred solution of **1**[35] (0.41 g, 1.0 mmol) in DMSO (15 mL) was added LiCl (0.43 g, 10 mmol), and the mixture was stirred for 2 h at 200 °C (bath temperature). After being cooled to ambient temperature, the mixture was partitioned between $CHCl_3$ (50 mL) and H_2O (30 mL). The organic layer was separated, washed with H_2O (4 × 30 mL), dried, and evaporated. The residue was chromatographed on a silica gel column (3 × 30 cm) using a linear gradient of Et_2O in hexane (10% → 50%, v/v; 1.0 L) to yield compound **2** (0.15 g; 55%) as a syrup, R_f 0.72 (A), and the starting material **1** (50 mg; 12%).

Methyl 5-*O*-Benzoyl-2-chloro-2,3-dideoxy-3-fluoro-β-D-ribofuranoside (5). Method A. From 2. To a solution of **2** (0.5 g, 1.8 mmol) in EtOH (50 mL) was added 5% Pd/C (0.5 g), and the mixture was stirred in a H_2 atmosphere for 18 h. The catalyst was filtered off and washed with EtOH (3 × 20 mL). The combined filtrates were evaporated, and the residue was coevaporated with toluene (2 × 20 mL) to afford the oily residue of **4** [0.3 g, 1.6 mmol; 89%; R_f 0.26 (A)]. The residue was dissolved in anhydrous pyridine (10 mL), BzCl (0.2 mL, 0.25 g, 1.76 mmol) was added, and the mixture was stirred for 18 h. The mixture was diluted with $CHCl_3$(50 mL), washed with H_2O (30 mL), aqueous $NaHCO_3$ (30 mL), H_2O (30 mL), 1 N H_2SO_4 (30 mL), and H_2O (30 mL), dried, evaporated, and chromatographed as described above to give compound **5** (0.42 g; 92%) as a syrup: R_f 0.65 (A).

Method B. From 3. Tosylate **3** was prepared from **1** in 71% yield.[35] To a solution of **3** (2.05 g, 4.83 mmol) in DMSO (60 mL) was added LiCl (2.04 g, 48.2 mmol), and the mixture was stirred for 2 h at 200 °C (bath temperature). The workup and purification, performed as described above for **2**, yielded **5** (1.0 g; 72%) and the starting tosylate **3** (0.33 g; 16%).

1-(2-Chloro-2,3-dideoxy-3-fluoro-β-D-ribofuranosyl)-thymine (10b) and Its α-Anomer (10a). A solution of **5** (0.42 g, 1.45 mmol), the bis(trimethylsilyl) derivative of thymine [obtained from 0.37 g (2.9 mmol) of thymine and (TMS)Tfl (0.79 mL, 0.97 g, 4.35 mmol)] in anhydrous CH_3CN (30 mL) was refluxed for 5 h and then cooled to room temperature. The reaction mixture was diluted with $CHCl_3$ (100 mL) and washed with aqueous $NaHCO_3$ (100 mL). The water layer was washed with $CHCl_3$ (2 × 50 mL). The organic extracts were combined, washed with H_2O (50 mL), dried, and evaporated. The residue was chromatographed on a silica gel column (3 × 30 cm) using a linear gradient of EtOAc in hexane (10% → 90%, v/v; 2.0 L) to yield a mixture of the starting material **5** and its α-anomer **6** (80 mg; 19%) and a mixture of the nucleosides **7a**,**b** (0.27 g; 49%). Rechromatography of a mixture of glycosides **5** and **6** gave the individual β-anomer **5** (30 mg) and the α-anomer **6** [35 mg; R_f 0.62 (A)]. The mixture of **7a**,**b** (0.24 g, 0.62 mmol) in methanol, saturated with ammonia at 0 °C (25 mL), was stirred for 24 h and evaporated. The residue was chromatographed on a silica gel column (3 × 30 cm) using a linear gradient of MeOH in $CHCl_3$ (0% → 10%, v/v; 1.5 L) to yield in order of elution **10b** (95 mg; 55%) and its α-anomer **10a** (48 mg; 28%). Data for **10b**: R_f 0.36 (B); mp 222−223 °C (from EtOAc−hexane); UV λ_{max} 263 nm (ε 9700). Anal. Calcd for $C_{10}H_{12}ClFN_2O_4$ (278.66): C, 43.10; H, 4.34. Found: C, 43,22; H, 4.62. Data for **10a**: R_f 0.30 (B); mp 206−209 °C (from EtOAc−hexane); UV λ_{max} 265 nm (ε 9800). Anal. Found: C, 43.18; H, 4.54.

2′-Chloro-2′,3′-dideoxy-3′-fluoroadenosine (11b) and Its α-Anomer (11a). A solution of **5** (0.4 g, 1.38 mmol), the bis(trimethylsilyl) derivative of N^6-benzoyladenine [obtained from 0.66 g (2.76 mmol) of N^6-benzoyladenine], and $SnCl_4$ (0.8 mL, 1.8 g, 6.9 mmol) in an anhydrous acetonitrile/1,2-dichloroethane mixture (45 mL; 2:1, v/v) was refluxed for 5 h. After standard workup and chromatography on a silica gel column (3 × 30 cm) using a linear gradient of EtOAc in hexane (10% → 90%, v/v; 2.0 L), a mixture of **5** and **6** (30 mg; 7.5%) and individual **8b** (0.45 g; 66%) and its α-anomer **8a** (60 mg; 9%) were isolated. Standard deprotection of **8b** (0.25 g, 0.5 mmol) followed by column chromatography [silica gel column, 2 × 32 cm; a linear gradient of MeOH in $CHCl_3$ (0% → 10%, v/v;

1.5 L)] and crystallization from EtOH yielded **11b** (0.12 g; 83%): R_f 0.3 (B); mp 236 °C; UV λ_{max} 260 nm (ϵ 14700). Anal. Calcd for $C_{10}H_{11}ClFN_5O_2$ (287.68): C, 41.75; H, 3.85. Found: C, 41.48, H, 4.07. In a similar way, starting from **8a** (60 mg, 0.12 mmol), deblocked nucleoside **11a** was obtained (27 mg; 78%): R_f 0.2 (B); mp 105−106 °C (from EtOH); UV λ_{max} 260 nm (ϵ 14300). Anal. Found: C, 41.37; H, 4.02.

2′-Chloro-2′,3′-dideoxy-3′-fluorocytidine (12b) and Its α-Anomer (12a). A solution of **5** (0.51 g, 1.76 mmol), the bis-(trimethylsilyl) derivative of N^4-benzoylcytosine [obtained from 0.76 g (3.52 mmol) of N^4-benzoylcytosine], and $SnCl_4$ (0.67 mL, 1.37 g, 5.28 mmol) in anhydrous CH_3CN (50 mL) was refluxed for 5 h. After standard workup and chromatography on a silica gel column (3 × 30 cm) using a linear gradient of EtOAc in hexane (10% → 90%, v/v; 2.0 L), a mixture of **5** and **6** (90 mg; 18%) and individual **9b** (0.47 g; 56%) and its α-anomer **9a** (70 mg; 8%) were isolated in order of elution. Standard deprotection of **9b** (0.24 g, 0.51 mmol) followed by column chromatography [silica gel column, 2 × 32 cm; a linear gradient of MeOH in $CHCl_3$ (0% → 20%, v/v; 1.5 L)] and crystallization from EtOH yielded **12b** (0.105 g; 78%): R_f 0.48 (C); mp 111−112 °C; UV (pH 7.0) λ_{max} 243 nm (ϵ 8800), 265 nm (shoulder); (pH 2.0) λ_{max} 280 nm (ϵ 13500). Anal. Calcd for $C_9H_{11}ClFN_3O_3$ (263.65): C, 41.00; H, 4.21. Found: C, 41.23; H, 4.58. In a similar way, starting from **9a** (70 mg, 0.15 mmol), deblocked nucleoside **12a** was obtained (31 mg; 80%): R_f 0.45 (C); mp 223−225 °C (from EtOH); UV (pH 7.0) λ_{max} 241 nm (ϵ 8400), 273 nm (8700); (pH 2.0) λ_{max} 282 nm (ϵ 14300). Anal. Found: C, 41.27; H, 4.60.

3′-Deoxy-3′-fluorothymidine (13b) and Its α-Anomer (13a). Method A. To a solution of a mixture of nucleosides **7a**,**b** (76 mg, 0.2 mmol) in anhydrous dioxane (10 mL) were added Bu_3SnH (0.31 mL, 0.35 g; 1.2 mmol) and AIBN (10 mg, 0.06 mmol), and the reaction mixture was refluxed for 2 h and evaporated. The residue was treated with methanol, saturated with ammonia at 0 °C (25 mL) for 24 h, and evaporated. The residue was portioned between MeOH (30 mL) and pentane (10 mL). The methanol layer was separated and evaporated, and the residue was chromatographed on a silica gel column (2 × 32 cm) using a linear gradient of MeOH in $CHCl_3$ (0% → 10%, v/v; 1.5 L) to afford nucleoside **13b** [27 mg; 55%; R_f 0.3 (B)] and its α-anomer **13a** [13 mg; 27%; R_f 0.25 (B)]. Both compounds **13b** and **13a** were identical in all respects (mp and UV and ^{1}H and ^{13}C NMR spectroscopy) with the corresponding authentic samples.[12,18]

Method B. To a solution of deblocked nucleoside **10b** (56 mg, 0.2 mmol) in anhydrous dioxane (10 mL) were added Bu_3SnH (0.26 mL, 0.29 g; 1.0 mmol) and AIBN (10 mg, 0.06 mmol), and the reaction mixture was refluxed for 2 h and evaporated. The residue was triturated with pentane, and the precipitate was filtered off, washed with pentane, and purified by silica gel column chromatography as described above to afford the β-fluoride **13b** (44 mg; 90%).

Method C. To a solution of **10b** (28 mg, 0.1 mmol) in a mixture of dioxane/MeOH (5 mL, 1:1; v/v) were added Bu_3SnH (0.13 mL, 0.145 g; 0.5 mmol) and AIBN (5 mg, 0.03 mmol), and the reaction mixture was refluxed for 15 h. After workup and chromatography as described in method A or B, the β-fluoride **13b** (22 mg; 90%) was obtained.

2′,3′-Dideoxy-3′-fluoroadenosine (14b) and Its α-Anomer (14a). A. To a solution of **8b** (0.3 g, 0.6 mmol) in anhydrous dioxane (30 mL) were added Bu_3SnH (0.95 mL, 1.05 g, 3.6 mmol) and AIBN (30 mg, 0.18 mmol), and the reaction mixture was refluxed for 6 h and evaporated. The residue was treated with methanol, saturated with ammonia at 0 °C (25 mL) for 48 h, and evaporated. The residue was triturated with pentane, and the precipitate was filtered off, washed with pentane, and purified by silica gel column chromatography as described above to afford the β-fluoride **14b** [120 mg; 79%; R_f 0.25 (B)]. In a similar way, starting from **8a** (60 mg, 0.12 mmol), the α-fluoride **14a** [25 mg; 82%; R_f 0.15 (B)] was obtained. Compounds **14b** and **14a** were identical in all respects (mp and UV and ^{1}H and ^{13}C NMR spectroscopy) with the corresponding authentic samples.[24]

Method B. To a solution of **11b** (15 mg, 0.052 mmol) in a dioxane/MeOH mixture (3 mL, 1:1, v/v) were added Bu_3SnH (0.07 mL, 76 mg, 0.26 mmol) and AIBN (3 mg, 0.018 mmol), and the reaction mixture was refluxed for 15 h. After standard workup and chromatography, the β-fluoride **14b** (11 mg; 84%) was obtained.

2′,3′-Dideoxy-3′-fluorocytidine (15b) and Its α-Anomer (15a). Method A. To a solution of **9b** (0.1 g, 0.21 mmol) in anhydrous dioxane (10 mL) were added Bu_3SnH (0.34 mL, 0.39 g, 1.26 mmol) and AIBN (10 mg, 0.06 mmol), and the reaction mixture was refluxed for 16 h and evaporated. The residue was treated with methanol, saturated with ammonia at 0 °C (10 mL) for 48 h, and evaporated. The residue was triturated with pentane, and the precipitate was filtered off, washed with pentane, and purified by silica gel column chromatography as described above for **12b** to afford the β-fluoride **15b** [15 mg; 31%; R_f 0.42 (C)].

Method B. To a solution of **12b** (16 mg, 0.061 mmol) in an anhydrous dioxane/MeOH mixture (3.0 mL; 1:1, v/v) were added Bu_3SnH (0.06 mL, 88 mg, 0.3 mmol) and AIBN (3 mg, 0.018 mmol), and the reaction mixture was refluxed for 15 h. After standard workup and chromatography, the β-fluoride **15b** (12 mg; 86%) was obtained. Similarly, starting from **12a** (15 mg, 0.057 mmol), the α-fluoride **15a** [10 mg; 77%; R_f 0.41 (C)] was obtained. Compounds **15b** and **15a** were identical in all respects (mp and UV and ^{1}H and ^{13}C NMR spectroscopy) with the corresponding authentic samples.[12]

1-(2-Chloro-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (16). To a solution of **10b** (60 mg, 0.22 mmol) in CH_3OH (5 mL) was added 0.45 mL of a 1 M solution of CH_3ONa in CH_3OH, and the reaction mixture was refluxed for 5 h. After cooling, the reaction mixture was neutralized with 1 N CH_3COOH in CH_3OH and evaporated, and the residue was chromatographed on a silica gel column (2 × 32 cm) using a linear gradient of MeOH in $CHCl_3$ (0% → 10%, v/v; 1.5 L) to give in order of elution unconsumed starting nucleoside **10b** (10 mg; 17%) and olefin **16** (26 mg; 46%): R_f 0.28 (B); mp 192−195 °C (from EtOAc−hexane); UV λ_{max} 263 nm (ϵ 9500). Anal. Calcd for $C_{10}H_{11}ClN_2O_4$ (258.66): C, 46.44; H, 4.28; Cl, 13.71. Found: C, 46.71; H, 4.10; Cl, 14.07.

1-(2-Azido-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-thymine (18). To a solution of **17**[35] (175 mg, 0.61 mmol) in CH_3OH (15 mL) was added 1.2 mL of 1 M CH_3ONa in CH_3OH, and the reaction mixture was refluxed for 5 h. After standard workup and chromatography, unconsumed starting nucleoside **17** (58 mg; 33%) and **18** (76 mg; 47%) were isolated. Data for **18**: R_f 0.29 (B); mp 143−145 °C (from EtOAc−hexane); UV λ_{max} 263 nm (ϵ 9400); IR (KBr) $\nu(N_3)$ 2120 cm^{-1}. Anal. Calcd for $C_{10}H_{11}N_5O_4$ (265.22): C, 45.29; H, 4.18. Found: C, 45.61; H, 3.96. The ^{1}H and ^{13}C NMR spectra are in accord with those measured for the same compound previously synthesized by an alternative procedure[40] and obtained as an amorphous powder.

9-(2-Chloro-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)adenine (19) and Its α-Anomer (22). Method A. To a solution of **8b** (80 mg, 0.16 mmol) in CH_3OH (10 mL) was added 0.24 mL of 1 M CH_3ONa in CH_3OH, and the reaction mixture was refluxed for 4 h. Standard workup and chromatography gave debenzoylated nucleoside **11b** (5 mg; 11%) and **19** (35 mg; 82%): R_f 0.24 (B); mp 240 °C dec (from EtOH); UV λ_{max} 260 nm (ϵ 14800). Anal. Calcd for $C_{10}H_{10}ClN_5O_2$ (267.67): C, 44.87; H, 3.76; Cl, 13.25. Found: C, 45.20; H, 3.48; Cl, 13.58.

Method B. Similarly, starting from **11b** (50 mg, 0.17 mmol), unconsumed nucleoside **11b** (7 mg; 12%) and **19** (36 mg; 77%) were isolated.

Method C. In a similar way, treatment of **8a** (75 mg, 0.15 mmol) under reflux for 1 h gave, after standard workup and chromatography, compound **22** (35 mg; 86%): R_f 0.13 (B); mp 173−175 °C (from EtOH); UV λ_{max} 260 nm (ϵ 14300). Anal. Found: C, 44.91; H, 3.97; Cl, 13.05.

9-(2-Azido-2,3-dideoxy-*β*-D-*glycero*-pent-2-enofuranosyl)adenine (21) was obtained, as described above for compound **19**, starting from 50 mg (0.17 mmol) of **20**[35] to give 32 mg (69%) as a slightly yellow amorphous powder: R_f 0.25 (B); UV λ_{max} 259 nm (ϵ 14500); IR (KBr) $\nu(N_3)$ 2120 cm^{-1}. Anal. Calcd for $C_{10}H_{10}N_8O_2$ (274.24): C, 43.80; H, 3.67. Found: C, 44.07; H, 3.41.

Supporting Information Available: Synthesis and characterization of **27**−**31** and ^1H and ^{13}C NMR data (chemical shifts and coupling constants) of a series of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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