Experimental Evidence for Intramolecular Attractive Nonbonded C–F···H–C Interactions in 2′,3′-Dideoxy-4′-(fluoromethyl)nucleosides – Through-Space J_{CF} and J_{HF} NMR Coupling Constants, Correlation with Empirical Parameters of Solvent Polarity and Single-Crystal X-ray Structures

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A collection of 5′-*O*-benzyl-2′,3′-dideoxy-4′-(fluoromethyl)-nucleosides carrying both purinic and pyrimidinic nucleobases (uracil, 5-Br-uracil, 5-O_2N-uracil, 6-Cl-purine and inosine) were synthesized in both the α and the β form. Through-space-transmitted $^6J_{CF}$ NMR coupling constants between F and C-6 (pyrimidinic base) or C-8 (purinic base) were observed for all of the α anomers of the compounds examined, whilst the corresponding $^7J_{HF}$ coupling constants were resolved only for the 5-substituted uracil derivatives. The absolute values of all the through-space couplings were found to decrease monotonically with increasing solvent polarity ($CDCl_3$, MeOD, [D_6]acetone, [D_6]DMSO). This trend suggests that the through-space interaction is mediated by an intramolecular (sp^3)C–F···H–C(sp^2) hydrogen bond. The possibility of any relevant solvent-induced conformational change influencing the F/base mutual spatial relationship in the molecules investigated was ruled out by heteronuclear steady-state ^{1}H{^{19}F}-NOE experiments. A linear correlation was observed between $^6J_{CF}$ and $^7J_{HF}$ coupling constants and the Kamlet–Taft's hydrogen bond basicity parameter β. The crystal structures of the α and β anomers of the 5-nitrouracil nucleoside show evidence that the H-6 of the nucleobase forms hydrogen-bond-like interactions involving the *O*-benzyl oxygen atom in the β anomer, and that in the case of the α anomer this is replaced by the F atom of the fluoromethyl group.

Considerable efforts have been made in the last few years to develop new nucleoside analogues likely to exhibit improved activity, or decreased toxicity, with respect to 3′-azido-3′-deoxythimidine (AZT), the first anti-HIV drug.[1] In this context, we have developed a synthetic strategy for obtaining new fluoro-substituted nucleoside analogues by exploiting the sulphoxide-mediated route to optically active fluoro-substituted compounds.[2,3] The structure-activity correlation for nucleoside analogues is difficult to establish due to the number of alternative metabolic pathways available for activation and the number of different routes for biological activity;[4] thus, many studies have been devoted to establishing the conformational preferences of nucleosides, either active or inactive against HIV.[5] The role of fluorine substitution in bioorganic substrates is often discussed in terms of the ability of fluorine to act as a hydrogen or hydroxy mimic.[6] Furthermore, the ability of carbon-bound fluorine (C−F) to establish hydrogen bonds with H−D groups (D = donor) is often invoked, but still not unequivocally accepted, as factor playing a role in the binding of fluoro compounds to receptors. The terms of this controversial debate can be summarized as follows: (i) although some crystallographic studies revealed short C−F···H−D (D = donor = O, N) contacts, consistent with inter- or intramolecular hydrogen bonds,[7] an extensive Cambridge Structural Database search showed that the statistical occurrence of C−F···H−D contacts with F···H distances below the sum of their van der Waals radii is very low with respect to the more classical D−H···A interactions (D = donor, O or N, typically; A = acceptor atom, e.g. carbonyl oxygen atom etc.).[8] In a recent NMR and X-ray study on the protonation of fluoro cryptands,[9] the authors were unable to decide for or against intramolecular $CF\cdots HN^+$ hydrogen bond, concluding that "should a $CF\cdots HN^+$ hydrogen bonding interaction exist, it is certainly going to be very weak in nature". (ii) Conversely, other scientists, mainly crystallographers, introduced a broader concept of hydrogen bond including, along with the traditional "strong" O···H−O and O···H−N interactions, "weak" and unusual interactions, like O···H−C.[10] Although the large difference in energy range between the two sets of nonbonded interactions (2−20 kJ mol^{-1} for the "weak" hydrogen bonds compared to the 20−40 kJ mol^{-1} generally accepted for the "strong" ones), it was demonstrated that O···H−C interactions possess the directional features distinguishing hydrogen bonds and that, even if characterized by contacts longer than the sum of O and C van der Waals radii, they play a role in driving crystal packing, especially when stronger O···H−O or O···H−N interactions are not available. More importantly, the relevance of these interactions is enhanced by increasing the C−H acidity and by the presence of cooperative effects.[11−13]

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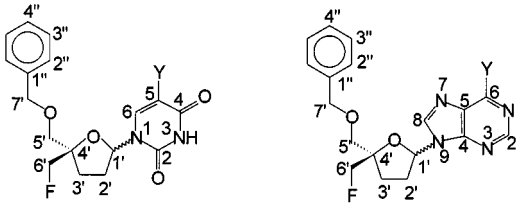
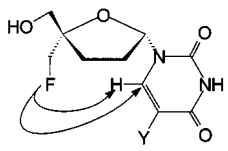
In a previous solution NMR study on a collection of 2′,3′-dideoxy-4′-(fluoroalkyl)nucleosides[14] (fluoroalkyl = R_F = CH_2F, CHF_2 and CF_3; bases: thymine and 5-F-uracil; see Scheme 1 for atom numbering of pyrimidinic bases), we showed the existence of through-space scalar coupling between the F of the remote R_F moiety and the H-6/C-6 of the nucleobase in the α anomer of all the compounds examined, the only exception being the CF_3 derivatives (Scheme 2).



1 : Y = H
2 : Y = Br
3 : Y = NO_2
4 : Y = Cl
5 : Y = OH

Scheme 1. Molecular formulae and structures of compounds **1**−**5**



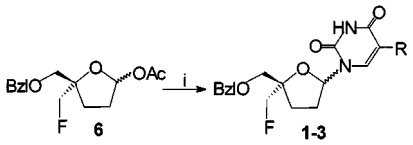
Scheme 2. Through-space $^7J_{HF}$ and $^6J_{CF}$ couplings constants

All the observed through-space couplings were found to exhibit a strong solvent effect, and without exception this led to a decrease in the absolute value of *J* with increasing hydrogen bond acceptor capabilities of the solvent. Accordingly, we proposed that through-space heteronuclear *J* coupling constants could be exploited in the investigation of nonbonded C−F···H−C interactions which, in turn, can be regarded as the analogues of the putative O···H−C hydrogen bonds mentioned above. In the present work we report on the synthesis, NMR and X-ray investigations carried out on a selection of 5′-O-benzyl-2′,3′-dideoxy-4′-(fluoromethyl)nucleosides carrying both purinic and pyrimidinic nucleobases with the purpose of obtaining more general and quantitative insight into the nonbonded C(sp^3)−F···H−C(sp^2) interaction which gives rise to the through-space transmission of spin-spin coupling.

Results and Discussion

Synthesis

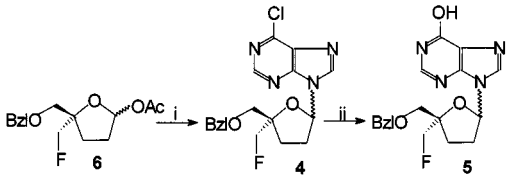
The molecular structure and atom numbering of the nucleosides **1**−**5** are displayed in Scheme 1. The 5-*O*-benzyl-protected nucleoside analogues **1**−**4** were obtained as a mixture of β and α anomers in good yields (≥ 80% in every case) at room temp. and in a few minutes, by the addition of a solution of acetylated lactol **6**, dissolved in dichloromethane or 1,2-dichloroethane, to the silylated bases and subsequently pouring trimethylsilyl triflate into the resulting slurry as a catalyst (Schemes 3 and 4).



1, R = H
2, R = Br
3, R = NO_2

Scheme 3. Reagents and conditions: (i) 2,4-bis(trimethylsilyloxy)-uracil (R = H), 5-bromo-2,4-bis(trimethylsilyloxy)uracil (R = Br), 5-nitro-2,4-bis(trimethylsilyloxy)uracil (R = NO_2); $(CH_2Cl)_2$; TMSOTf; room temp.

The inosyl derivative **5** was synthesized by dissolving the 6-chloropurin-9-yl intermediate **4** in methanol and adding dropwise an aqueous solution of sodium hydroxide. The mixture was refluxed for 2 h; the final compound **5** was obtained in a yield of 70% (Scheme 4).



Scheme 4. Reagents and conditions: (i) 6-chloro-9-(trimethylsilyl)-purine (Y = Cl); CH_2Cl_2; TMSOTf; room temp.; (ii) NaOH, CH_3OH, H_2O; Δ*T*

^{1}H- and ^{13}C-NMR Study

The notation $^7J_{HF}$ and $^6J_{CF}$ will be used throughout this paper to indicate the through-space couplings between F and the nuclei (H or C) on the purinic or pyrimidinic base, although this notation refers to a hypothetical through-bonds pathway. The majority of the compounds investigated was analysed as a 1:1 mixture of the α and β anomers. The reported NMR data (^{1}H- and ^{13}C-chemical shifts, heteronuclear H−F and C−F coupling constants) are related to both the α and β anomers of compounds **1**−**5**, although only α nucleosides exhibit the F atom and the nucleobase in a *syn* relationship, which is mandatory for the occurrence of any through-space interaction between the remote F and a suitable H/C nucleus on the base. The values of the normally observed through-bonds heteronuclear coupling constants (namely $^2J_{HF}$, $^1J_{CF}$, $^2J_{CF}$, $^3J_{CF}$) in the β isomers, and their variation as a function of the solvent polarity, were used as a reference for the qualitative estimation of solvent effects on couplings. As through-space F···H interactions cannot take place for the β nucleosides in our model compounds (for obvious geometrical reasons) the solvent effects on the coupling constants of the latter represent a non-specific and constant contribution that will be taken into account when discussing the possible solute-solvent inter-

Table 1. Heteronuclear H−F coupling constants (Hz) of compounds **1−5** (α and β anomers) in different solvents;[a] see Scheme 1 for atom numbering

compd.	J(F−H)	$CDCl_3$		MeOD		[D_6]acetone		[D_6]DMSO	
		α anomer	β anomer	α anomer	β anomer	α anomer	β anomer	α anomer	β anomer
1	^2J(F−H-6′a)	45.1	47.2	48.0	47.5	47.9	47.5	47.4	47.4
	^2J(F−H-6′b)	47.1	47.2	47.1	47.3	47.4	47.5	47.4	47.4
	^4J(F−H-5′a)	1.7	1.3	[b]	1.5	1.8	1.6	1.8	1.4
	^4J(F−H-5′b)	2.3	1.7	[b]	1.7	2.1	1.6	2.2	1.1
	^7J(F−H-6)	1.8	–	1.4	–	1.1	–	–	–
2	^2J(F−H-6′a)	48.3	47.1	48.1	47.4	48.1	47.4	47.8	47.4
	^2J(F−H-6′b)	47.0	47.1	47.1	47.4	47.3	47.4	47.0	47.4
	^4J(F−H-5′a)	1.6	1.0	[b]	1.3	[b]	1.5	1.8	1.4
	^4J(F−H-5′b)	2.1	1.6	[b]	1.6	[b]	1.6	1.8	1.4
	^7J(F−H-6)	2.7	–	2.2	–	2.0	–	1.4	–
3	^2J(F−H-6′a)	48.4	46.9	47.9	47.4	48.3	47.5	[b]	[b]
	^2J(F−H-6′b)	47.3	46.9	47.3	47.2	46.6	47.1	[b]	[b]
	^4J(F−H-5′a)	[b]	0.8	[b]	1.0	[b]	1.1	[b]	1.3
	^4J(F−H-5′b)	[b]	1.6	[b]	1.8	[b]	1.6	[b]	1.8
	^7J(F−H-6)	3.1	–	2.6	–	2.4	–	2.2	–
4	^2J(F−H-6′a)	47.8	47.5	47.8	[b]	47.8	47.5	47.3	47.3
	^2J(F−H-6′b)	46.8	47.1	47.4	[b]	47.4	47.5	47.3	47.3
	^4J(F−H-5′a)	[b]	1.8	[b]	1.6	2.2	2.0	[b]	1.8
	^4J(F−H-5′b)	[b]	1.9	[b]	1.9	2.1	1.8	[b]	1.9
	LW(H-8)[c]	1.53	0.98	[b]	[b]	2.21	1.47	1.51	1.54
5	^2J(F−H-6′a)	47.8	47.3	47.8	47.5	47.7	47.7	47.3	[d]
	^2J(F−H-6′b)	47.3	46.9	47.4	47.2	47.7	47.7	47.6	[d]
	^4J(F−H-5′a)	[b]	2.8	[b]	1.9	[b]	2.1	1.8	[d]
	^4J(F−H-5′b)	[b]	1.8	[b]	1.9	[b]	1.8	1.9	[d]
	LW(H-8)[c]	1.5	1.6	1.35	1.32	1.41	1.0	1.76	[d]

[a] The diastereotopic pairs H-6′ and H-5′ were not assigned stereospecifically. In all the cases the more deshielded proton was labelled as "a". – [b] Not determined due to peak overlap. – [c] As ^7J(F−H-8) was not resolved, we report here the value (Hz) of the linewith at half height. – [d] Data not available in this solvent.

ference with the through-space transmission of HF and CF spin information in the α anomers.

The NMR experiments were carried out in $CDCl_3$, [D_6]-acetone, MeOD and [D_6]DMSO. The choice of the NMR solvents was based upon their polarity and hydrogen bond profile. $CDCl_3$ can be considered, as a first approximation, as apolar and without any specific hydrogen bond properties, acetone and DMSO are hydrogen bond acceptors, whilst MeOD is amphiprotic, e.g. both hydrogen bond donor and acceptor.[15]

Table 1 gives a selection of ^{1}H-NMR data for the compounds **1**−**5** in the solvents mentioned above. Only those signals that are affected by heteronuclear F−H spin-spin couplings are considered. The α anomer of compounds **1**, **2** and **3** show a large through-space F−H coupling constant, whilst the corresponding values for **4** and **5** could not be obtained due to the intrinsic large width of the signal related to H-8.

^{13}C-NMR data for compounds **1**−**5** in all of the solvents are summarized in Tables 2 and 3. As expected, C-6 of compounds **1α**, **2α** and **3α**, and C-8 of **4α** and **5α** show a quite large $^6J_{CF}$ value between the fluorine nucleus and C-6/8. The absence of a C−F coupling constant on C-1′ supports the hypothesis of a through-space pathway for the transmission of the spin information between these nuclei. As an example, we show in Figures 1 and 2 an expansion of the ^{1}H- and ^{13}C-NMR spectrum of compound **1**, showing the difference between the anomers α and β and the decrease in through *J*-space with increasing solvent polarity.

Tables 1, 2 and 3 show that a clear and monotonic trend for the variation of HF and CF coupling constants with the nature of the solvent can only be found in the case of the through-space coupling constants $^7J_{HF}$ and $^6J_{CF}$, and that solvent-induced values of ΔJ on the latter are much larger than those found, if any, for the other heteronuclear through-bond-transmitted coupling constants. For compound **2**, for example, the relative changes in $^7J_{HF}$ and $^6J_{CF}$ (defined as $\Delta J/J_{max}$) are 48 and 41%, respectively. For comparison, the same quantities for the one-bond J_{CF} of **2α** and **2β** are 1.8 and 2.8%, respectively, and 10% for $^3J_{C\text{-}3'-F}$ of **2β**. The apparent anomalies in the data for MeOD will be discussed later. When dealing with the solvent dependence of the NMR coupling constants, it is generally assumed that any variation in *J* can be ascribed to two main factors:[16] (i) electronic changes due to mutual solute-solvent interaction; (ii) solvent-induced conformational transitions, such as internal rotation and ring interconversions. The necessity of a clear distinction between these two different sources of solvent dependence restricted the investigation to purely rigid molecular structures, such as unsaturated and aromatic compounds,[17,18] or model compounds with few rotational barriers.[19,20] The compounds considered in the present study are highly flexible and, therefore, do not belong to either class of molecules mentioned above. The issue of the large solvent dependency of the long-range couplings in **1**−**5** must be correctly addressed at this stage. We carried out a set of heteronuclear steady-state ^{1}H{^{19}F}-NOE experiments in order to investigate possible

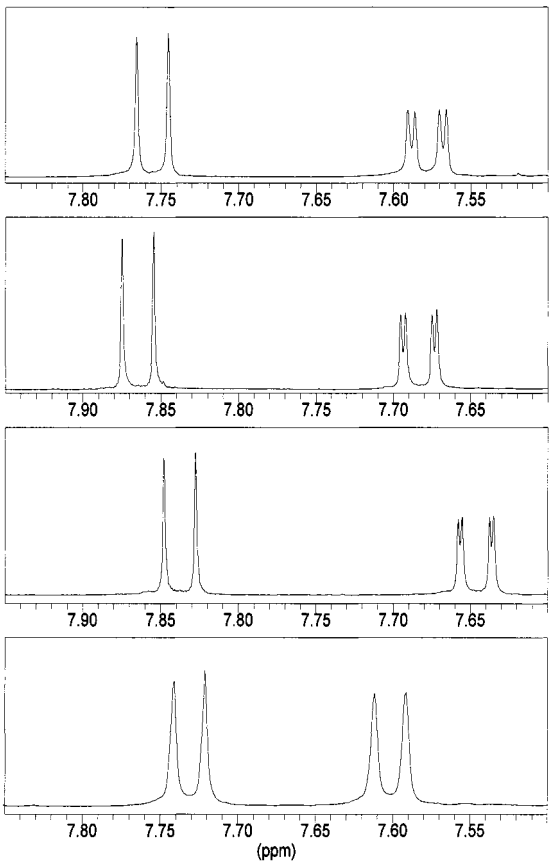


Figure 1. Expansion of ^{1}H-NMR spectrum of compound **1** in different solvents showing the signals assigned to H-6; anomer β: doublet; anomer α: doublet of doublets due to through-space J_{HF}; from top to bottom: $CDCl_3$, [D_4]methanol, [D_6]acetone and [D_6]DMSO

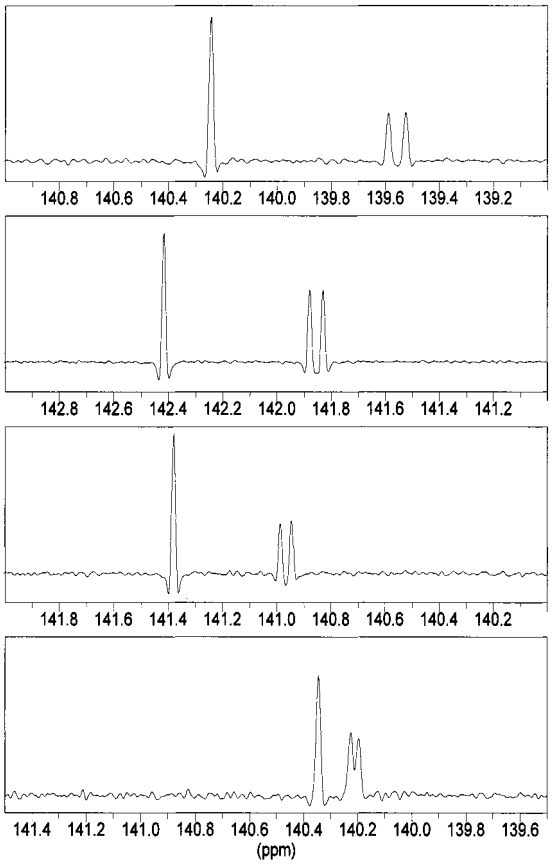


Figure 2. Expansion of ^{13}C{^{1}H}-NMR spectrum of compound **1** in different solvents showing the signals assigned to C-6; anomer β: singlet; anomer α: doublet due to through-space J_{CF}; from top to bottom: $CDCl_3$, [D_4]methanol, [D_6]acetone and [D_6]DMSO; the spectra are resolution-enhanced by gaussian multiplication prior to Fourier transform

changes, caused by the solvent, in the mutual position of the R_F moiety with respect to the nucleobase. The results, expressed as % enhancement of H-6/8, are summarized in Table 4. It is well known that steady-state NOE does not allow the quantitative measurement of internuclear distances,[21] hence the data in Table 4 emphasize that positive, detectable and significant NOEs between F and H-6/8 in the α anomers of all the investigated compounds can be measured, independent of solvent polarity. Indeed, no dramatic change in the conformational preferences of the nucleosides (at least as far as R_F and the base are concerned) can be observed experimentally. This rules out any possible significant contribution of solvent-induced conformational transitions to the large solvent effect detected in both the through-space $^7J_{HF}$ and $^6J_{CF}$. The latter, which monotonically decreases with solvent as shown in Tables 1, 2 and 3, can thus be consistently correlated with the increasing hydrogen bond acceptor properties of the medium.

The physical basis for the through-space transmission of spin-spin couplings has been extensively reviewed.[22] The main factor affecting the through-space route is the overlapping of F lone pairs with the σ*(CH) molecular orbital. Theoretical and experimental studies on 2-fluoro-*N*-methylbenzamide[23] showed that the intramolecular C−F···H−N hydrogen bond is an efficient pathway for the transmission of spin information from F to the amide moiety. The authors corroborated this view by reporting on a marked decrease of through-space $^4J_{NF}$ and $^6J_{HF}$ with increasing solvent polarity, as a result of the decreased persistence of intramolecular hydrogen bond. More recently, through-space HF coupling constants in urolobin difluoroboron complexes were reported, giving direct evidence of F···H−N hydrogen bond.[24] The data reported in Tables 1, 2 and 3 fit well with the model of through-space couplings mediated via an intramolecular hydrogen bond. Solvents like acetone and DMSO diminish but do not destroy the intramolecular C−F···H−C interaction, by participating via a solute/solvent hydrogen bond. The efficiency of the H-relayed transmission of spin-spin couplings is hence lowered, affording lower values of $^7J_{HF}$ and $^6J_{CF}$ accordingly. We also attempted to make this qualitative view more quantitative by searching for a linear correlation between the through-space *J* and some empirical solvent hydrogen bond donor indicator. The NMR parameters of compound **3** were therefore measured in three more solvents, [D_3]acetonitrile, [D_8]tetrahydrofuran and [D_9]hexamethylphosphoric triamide (HMPT), in order to provide a minimum number of data points for a linear correlation with a good confidence level, and the observed values of $^7J_{HF}$ and $^6J_{CF}$ plotted against

Table 2. Selection of $^{13}C\{^1H\}$-NMR data (chemical shift δ in ppm from internal TMS and heteronulcear J_{CF} in Hz) of compounds **1**−**3** (α and β anomer) in different solvents; see Scheme 1 for atom numbering; chemical shifts are reported with two decimal figures only when required for peak assignment

compd.	C atom	$CDCl_3$				MeOD				[D_6]acetone				[D_6]DMSO			
		α anomer		β anomer		α anomer		β anomer		α anomer		β anomer		α anomer		β anomer	
		δ	*J*	δ	*J*	δ	*J*	δ	*J*	δ	*J*	δ	*J*	δ	*J*	δ	*J*
1	C6	139.5	6.5	140.2	−	141.8	5.0	142.4	−	141.4	4.2	141.8	−	140.2	3.0	140.3	−
	C6′	85.6	174.1	85.0	177.7	86.2	173.0	86.3	174.6	86.6	172.4	86.6	174.5	84.5	171.5	84.7	172.6
	C4′	85.7	17.1	85.6	18.2	87.3	17.2	87.3	17.7	86.9	17.1	86.8	17.6	84.8	17.1	84.9	17.4
	C5′	72.1	6.6	71.9	4.8	73.1	6.1	72.8	5.5	73.4	6.0	73.2	5.4	71.4	5.5	71.1	5.3
	C3′	28.1	4.2	27.7	3.4	28.7	4.3	28.5	3.8	29.2	4.3	29.0	4.0	27.5	4.2	27.2	4.2
2	C6	139.3	7.6	140.1	−	141.3	6.8	141.9	−	141.2	5.8	141.7	−	139.9	4.5	140.0	−
	C6′	85.4	174.1	84.9	177.2	86.2	172.8	86.2	174.4	85.1	171.0	86.6	174.2	84.5	171.0	84.7	172.3
	C4′	86.3	17.3	86.1	18.4	87.8	16.8	87.7	17.6	87.7	16.6	87.5	17.4	85.3	16.8	85.4	17.1
	C5′	71.9	6.6	71.3	5.2	73.0	6.3	72.4	5.5	73.5	6.0	72.9	5.5	71.5	5.5	70.8	5.3
	C3′	27.7	4.2	27.4	3.5	28.3	4.5	28.2	3.7	28.9	4.2	28.7	3.9	27.1	4.2	26.8	3.9
3	C6	144.3	9.1	145.3	−	146.0	7.3	146.9	−	145.9	6.7	146.6	−	144.5	5.9	145.1	−
	C6′	84.82	174.6	84.77	177.8	85.7	172.8	85.9	174.8	86.2	172.5	86.4	174.0	84.21	171.7	84.29	172.5
	C4′	88.2	17.0	88.0	18.2	89.4	16.7	89.3	17.7	89.4	16.7	89.2	17.9	87.1	16.7	87.0	17.6
	C5′	71.6	6.4	70.5	5.6	72.7	6.3	71.8	5.8	73.2	6.2	72.2	5.3	71.1	5.9	70.1	5.3
	C3′	27.03	4.1	26.96	3.5	27.6	4.4	27.7	3.5	28.2	<0.5	28.1	<0.5	26.3	4.4	26.1	3.8

Table 3. Selection of $^{13}C\{^1H\}$-NMR data (chemical shift δ in ppm from internal TMS and heteronulcear J_{CF} in Hz) of compounds **4**−**5** (α and β anomer) in different solvents; see Scheme 1 for atom numbering; chemical shifts are reported with two decimal figures only when required for peak assignment

compd.	C atom	$CDCl_3$				MeOD				[D_6]acetone				[D_6]DMSO			
		α anomer		β anomer		α anomer		β anomer		α anomer		β anomer		α anomer		β anomer	
		δ	*J*	δ	*J*	δ	*J*	δ	*J*	δ	*J*	δ	*J*	δ	*J*	δ	*J*
4	C8	143.6	5.7	144.0	−	146.4	4.2	146.8	−	146.3	3.2	146.5	−	145.69	1.8	145.75	−
	C4′	87.0	17.4	86.9	17.9	88.5	17.4	88.4	17.1	88.3	17.2	88.2	17.2	86.27	17.1	86.29	17.1
	C6′	84.9	175.3	85.3	176.1	85.7	174.0	86.2	174.0	86.1	172.6	86.5	172.6	84.2	172.1	84.7	172.1
	C5′	71.9	5.9	71.5	5.3	72.9	5.5	72.3	5.3	73.2	5.6	72.9	5.3	71.3	5.0	70.8	5.3
	C3′	27.9	4.3	28.1	3.5	28.7	4.2	28.9	4.2	29.2	4.6	29.4	4.0	27.6	4.2	27.7	4.2
5	C8	138.4	4.5	138.6	−	139.9	4.1	140.3	−	139.3	3.2	139.5	−	138.3	[a]	[b]	[b]
	C4′	86.56	17.8	86.52	17.8	88.0	17.4	88.0	17.4	87.9	17.5	87.8	17.8	85.3	17.4	[b]	[b]
	C6′	84.9	175.2	85.3	175.5	85.8	173.7	86.2	174.2	86.3	173.6	86.7	173.6	84.2	172.4	[b]	[b]
	C5′	71.9	5.7	71.6	5.4	73.0	5.6	72.5	5.5	73.5	5.4	73.3	5.4	71.3	4.8	[b]	[b]
	C3′	28.1	4.1	28.3	3.5	28.8	4.3	29.1	3.7	29.6	4.5	29.7	4.1	27.7	4.1	[b]	[b]

[a] Broad singlet. − [b] Data not available in this solvent.

Table 4. $^1H\{^{19}F\}$ NOE (%) observed on the signal of H-6 (compounds **1**, **2** and **3**, anomer α only) and H-8 (compounds **4** and **5**, anomer α only) in different solvents; see Scheme 1 for atom numbering

compd.	$CDCl_3$	MeOD	[D_6]acetone	[D_6]DMSO
1	2.8	3.4	2.0	1.0
2	4.1	3.5	3.3	2.2
3	4.2	5.7	5.1	3.6
4	0.8	0.6	1.1	0.5
5	0.9	0.8	0.6	1.0

the Kamlet−Taft′s solvatochromic parameter β, taken as empirical hydrogen bond acceptor scale.[25−27] The graph is reported in Figure 3 and it is based on the data summarized in Table 5.[28]

This linear relationship provides further quantitative evidence that the through-space CF and HF coupling constants are mediated by intramolecular C−F···H−C hydrogen bond. The quantitative correlation obtained on the model compound **3** may shed some light on the solvent effect experienced by all the compounds examined, including **4** and **5**, whose $^7J_{HF}$ are not resolved. Moreover, the inductive electronic effect (+I or −I) of the Y substituent on the nucleobase is likely to affect the electron-withdrawing character of C-6/8, hence affecting the hydrogen bond donor capabilities of H-6/8. This would represent a further proof, albeit indirect, of the attractive interaction between F and H-6/8. Indeed, the Hammett′s constants for inductive substituent effect σ_I show a reasonable linear correlation with the values of SCC (Substituent Coupling Constant) in $CDCl_3$.[29] The regression indicates that the electron-withdrawing properties of the functional groups on the nucleobase do affect the entity of the observed couplings, in good agreement with the model of F···H interaction proposed hitherto. The NMR data we have reported and discussed so far and the regression analyses permit us to conclude that the intramolecular hydrogen bond mechanism provides a relevant contribution to the through-space HF and CF

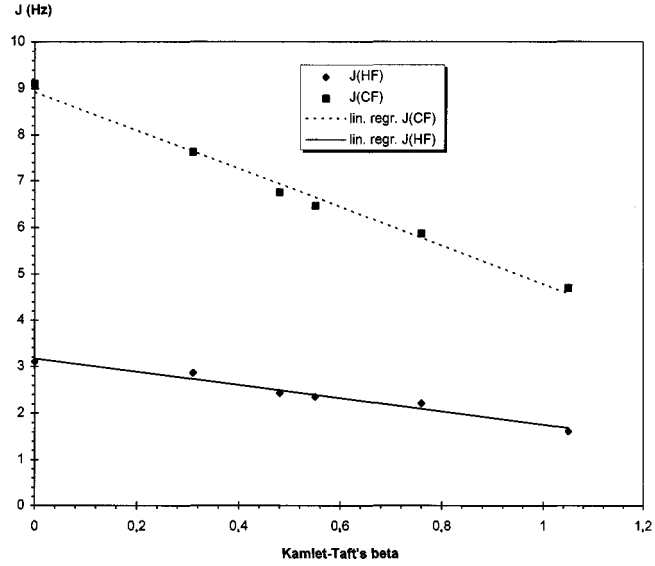


Figure 3. Plot of experimental through-space spin-spin coupling constants of compound **3** vs. Kamlet−Taft's parameter β

Table 5. $^{7}J_{(F-H-6)}$ and $^{6}J_{(F-C-6)}$ of compound **3** in the extended set of solvents and empirical solvent parameters for linear correlation

solvent[a]	Kamlet−Taft's β[b]	rel. permitt.[c]	$^{7}J_{HF}$[d]	$^{6}J_{CF}$[d]
chloroform	0.00	4.81	3.10	9.10
acetonitrile	0.31	35.94	2.86	7.33
acetone	0.48	20.56	2.43	6.75
THF	0,55	7.58	2.35	6.46
methanol	(0.62)	33.66	2.62	7.33
DMSO	0,76	46.45	2.21	5.87
HMPT	1.05	29.6	1.61	4.70

[a] Literature data are referred to nondeuterated solvents. − [b] Values taken from ref.[15], p. 378. The value referred to methanol is in parentheses in the original reference and is reported by the author as "relatively less certain". − [c] Values taken from ref.[15], pp. 408−411. − [d] Coupling constants in Hz. Sine bell multiplication of the FID were applied prior to Fourier transform.

Table 6. Values of substituent coupling constant (SCC, see text for definition) of 5-Y-uracil nucleosides and corresponding values of Hammett's σ_I[a]

substituent Y	Hammett's σ_I	SCC(HF)	SCC(CF)
H[b]	0.00	0.0	0.0
Me[c]	−0.04	−0.3	−0.1
F[c]	0.50	1.0	1.3
Br[b]	0.44	0.9	1.0
NO_2[b]	0.65	1.3	2.4

[a] Values taken from ref.[31] − [b] Values taken from ref.[14] − [c] This work.

spin-spin coupling, although other sources of transmission of spin information may also be operating. On the other hand, the present study demonstrated the existence of a significant interaction in solution between F and H in the title class of compounds which is likely to be described as $(sp^3)C-F\cdots H-C(sp^2)$ hydrogen bond.

Table 7. Significant torsion angles [°] in the solid-state conformation of **3α** and **3β**

	3α	**3β**
C6−N1−C1′−O1′	2.1(10)	47.1(8)
C1′−O1′−C4′−C6′	−105.1(10)	−105.0(6)
C1′−O1′−C4′−C5′	132.2(8)	135.9(5)
O1′−C4′−C5′−O5′	−174.0(8)	−56.9(7)
C7′−O5′−C5′−C4′	173.4(11)	178.0(5)
C5′−O5′−C7′−C1″	−168.2(13)	−66.6(7)
O5′−C7′−C1″−C2″	−103.2(16)	−36.1(9)
O1′−C4′−C6′−F6′	−50.7(13)	
O1′−C4′−C6′−F6′A		51.3(8)
O1′−C4′−C6′−F6′B		−73.4(9)

X-ray Crystallography

Views of the molecular conformations of **3α** and **3β** are presented in Figure 4. Bond lengths and angles are normal, considering the associated standard errors, and do not require comments. Rather our focus will be on the comparison between the conformations, the hydrogen bonding and the packing patterns of the two isomers.

The furanoside is an envelope with apical C3′ in **3α** and a twist boat in **3β**. In both cases deviations from planarity are modest: C3′ is 0.156 Å away from the ring atoms′ mean least-squares plane in the α anomer, while deviations of ring atoms from the plane are less than 0.09 Å for the β isomer. The differences mentioned for the furanoside should hardly affect the overall conformation of the two molecules, given the flexibility of five-membered rings. The benzyl ether side chain bound to C5′ is fully extended in **3α** while the C5′−O5′−C7′−C1″ and the O1′−C4′−C5′−O5′ torsion angles are *gauche* in the more compact β isomer (see Figure 4 and Table 7) bringing the O5′ atom in proximity to the base residue. Other related (substantial) differences involve the C6−N1−C1′−O1′ torsion angle linking the base to the sugar residue: It is 2° in **3α** and 47°, i.e. nearly *gauche*, in **3β**. As a consequence, the hydrogen atom on C1′ is found close to the O2 atom while the hydrogen atom on C6, in both moieties at ca. 2.3 Å to O5A of the nitro group, interacts with the furanoside O1′ atom, at distances of 2.26 and 2.54 Å in the α and β anomer, respectively. The intramolecular environment of H6 is completed by another relatively short interaction involving the appropriately located O5′ in **3β** and F6′ in **3α**. Further geometrical details of the "cage" around the H6 atom are given in Table 8. The conformational arrangement of both molecules suggest an attractive nature of all the mentioned interactions involving H6. More specifically, in the β anomer, the H6···O5′ distance (2.36Å) and the C6−H6···O5′ angle (162°) are values close to the optimized geometry for this kind of hydrogen bond. In the α-anomer the eclipsing of C6 with O1′ leads to the optimization of the interaction of H6 with O1′ rather than with F6′, which however does not display disorder, contrary to what we find in the β anomer, where the fluorine atom is distributed with a 0.5 occupancy factor over two positions. The relative conformational freedom of the fluoromethyl group leads in the present instances to *gauche* ar-

rangements to the O1′ atom: In the case of the α anomer the rotational isomeric state giving the best compromise geometry [H6···F6′ 2.81 Å, for C6−H6···F6′ = 141°] results, with deviations from the exact *gauche* conformation of the F6′−C6′−C4′−O1′ angle bringing F6′ closer to H6. All these features support the idea of a weakly attractive nature of the H6···F6′ interaction, and this is also consistent with the observed distance, which is somewhat larger than the sum of the van der Waals radii. What has been noted for O···H−C bonds[10] should be even more true for F···H−C bonds: The energy of these primarily electrostatic interactions should decrease much more slowly with distance than for van der Waals interactions. Therefore, even if the distances H···F are long and cannot be expected to be the main factor in determining conformational preferences or crystal packing, they should be considered carefully. In Table 9 the more relevant intermolecular hydrogen bonds and a number of rather short contacts involving the fluorine, nitrogen and oxygen atoms are listed for both crystals. Interestingly, both are characterized by the hydrogen bond involving H3 and the O4 atom with closely similar geometrical features, and by an interaction involving the O5B of the nitro group to a hydrogen atom. In addition a number of O···H−C and F···H−C interactions are apparent with geometrical features similar to those identified intramolecularly for the α and β anomers, confirming suggestions that these interactions are also likely to play a significant cooperative role in the process of crystal formation and stabilization.

Table 8. Intramolecular distances [Å] and angles [°] in **3α** and **3β**; notation: A = acceptor, D = donor

	3α			**3β**		
	H···A	D···A	D−H···A	H···A	D···A	D−H···A
C6−H6···O1′	2.26	2.65	104	2.54	2.77	95
C6−H6···O5A	2.34	2.67	100	2.33	2.66	101
C6−H6···F6′	2.81	3.58	141			
C6−H6···O5′				2.36	3.26	162
C1′−H1′···O2	2.63	2.71	84	2.35	2.76	104
C2′−H2′···O2	2.78	2.97	92			

Conclusions

The α anomers of the class of compounds discussed in the present paper represent an example of systems preorganized in a conformation such that F and the nucleobase are in an ideal relationship for an attractive interaction (hydrogen bond) to take place. Only in preorganized environments, as already observed for fluorocarbons[30], do intrinsically weak interactions like C−F···H−C become relevant. The linear correlations of through-space *J* couplings with the hydrogen bond basicity parameter β and the effect of the Y substituent support the conclusion that through-space couplings reflect not only the geometrical vicinity of the interacting nuclei, but the existence of an attractive interaction between them as well. This opens up the possibility to exploit these NMR parameters, easily accessible from routine spectra, for the investigation of unusual types of

Table 9. Intermolecular distances [Å] in **3α** and **3β**; notation: A = acceptor, D = donor

	3α			**3β**		
	H···A	D···A	D−H···A	H···A	D···A	D−H···A
N3−H3···O4	2.00	2.83	161	2.06	2.88	160
N3−H3···O5B	2.69	3.26	125	2.61	3.14	121
C1′−H1′···O2	2.70	3.22	114			
C1′−H1′···O4	2.63	3.39	135			
C2′−H2′···F6′B				2.68	3.47	138
C2′−H2′···O5A	2.64	3.56	157			
C2′−H2′···O5B	2.86	3.55	128			
C2′−H2′···O2				2.65	3.56	156
C3′−H3′···F6′	2.78	3.52	134			
C3′−H3′···O5B	2.71	3.48	137			
C5′−H5′···N5	2.80	3.50	129			
C5′−H5′···O2				2.83	3.55	132
C5′−H5′···O5B	2.87	3.43	118			
C6′−H6′···O5B				2.57	3.51	161
C5″−H5″···F6′A				2.72	3.16	110
C5″−H5″···O5B				2.69	3.60	169
O5B···O4		3.03			3.19	
N1···O2		2.95				
C2···O2		3.06				
N5···O4					3.17	
F6′B···O2					2.87	
F6′A···O5B					3.16	

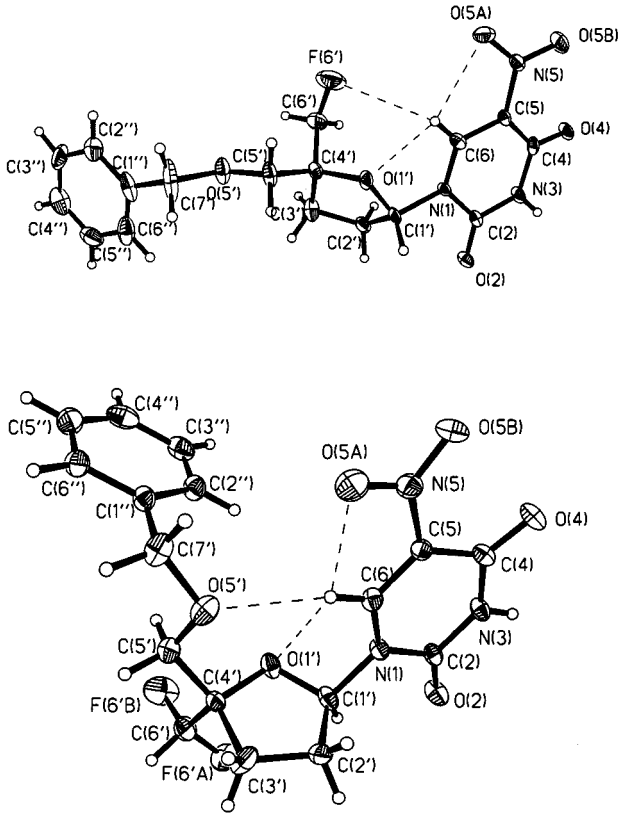


Figure 4. ORTEP view of **3α** and **3β** showing the atomic labelling scheme

fluorine-involving hydrogen bonds. The results of the X-ray investigation on both anomers of compound **3** indicate that, in the presence of appropriate cooperative effects, the hydrogen bond acceptor profile is not dramatically upset upon replacement of O with F. It is clear that the energy involved

in C−F···H−C hydrogen bonds is low since it involves distances larger than the sum of van der Waals radii.

Experimental Section

^{1}H and ^{13}C NMR: Bruker ARX 400 spectrometer (400/100 MHz). − Heteronuclear ^{1}H{^{19}F} NOE: Bruker AC 250 (250 MHz operating frequency on proton) equipped with a supplementary BM1 broadband modulator operating at 235 MHz. Chemical shifts are given in ppm (δ) relative to internal tetramethylsilane (TMS). All the samples have been accurately degassed by carefully bubbling N_2. The coupling constants were determined on the resolution enhanced spectra (typically LB = −2.5; GB = 0.28). − MS: Shimadzu MALDI II equipped with a pulsed N_2 laser (λ = 337 nm), α-cyanohydroxycinnamic acid was used as matrix for all the compounds, time-delayed extraction was optimized for *m/z* of the protonated (or cationized) molecule for all compounds. − X-ray crystallography: See Table 10. − Flash chromatographies: Silica gel 60 (60−200 μm, Merck). − All reactions were monitored by TLC: Analytical Merck silica gel 60F_{254} TLC plates. − Combustion microanalyses: Redox SNC, Cologno Monzese (Milano). − All the reactions run in organic solvents were carried out in flame-dried flasks under nitrogen. Dichloromethane and 1,2-dichloroethane were distilled from calcium hydride prior to use. Commercially available reagent-grade reagents were employed without purification. The synthesis of 1-*O*-acetyl-5-*O*-benzyl-2,3-dideoxy-4-*C*-(fluoromethyl)-β/α-D-*glycero*-pentafuranose (**6**) has already been described.[3]

Table 10. Crystal data, collection and refinement parameters for **3α** and **3β**

	3α	**3β**
crystal data		
formula	$C_{17}H_{18}FN_3O_6$	$C_{17}H_{18}FN_3O_6$
M [g mol^{-1}]	379.34	379.34
a [Å]	5.9830(10)	5.9620(10)
b [Å]	8.222(2)	14.342(2)
c [Å]	35.411(6)	20.051(3)
V [Å^3]	1741.9(6)	1714.5(5)
$\rho_{calcd.}$ [g cm^{-1}]	1.446	1.470
Z	4	4
crystal system	orthorhombic	orthorhombic
space group	$P2_12_12_1$	$P2_12_12_1$
F(000)	792	792
μ (Cu-$K_α$) [mm^{-1}]	1.006	1.022
data collection		
radiation	(λ = 1.54178 (Cu-$K_α$), graphite monochromator	(λ = 1.54178 (Cu-$K_α$), graphite monochromator
diffractometer	Siemens P4	Siemens P4
crystal size [mm]	0.8 × 0.4 × 0.02	0.4 × 0.08 × 0.06
temperature [°C]	25	25
data collection mode	θ−2 θ scan	θ−2 θ scan
scan range (2 θ) [°]	5.00/133.90	7.58/136.00
measured reflections	2439	2581
unique reflections	2034	2125
observed reflections	1299	1316
$I \geq$	2 σ(*I*)	2 σ(*I*)
absorption correction	ψ scan	ψ scan
min./max. transmission	0.238/0.367	0.239/0.366
structure solution and refinement		
structure solution program	SIR92[32]	SIR92[32]
refinement method	full-matrix least squares on F^2	full-matrix least squares on F^2
refined parameters	245	256
*R*1	0.0794	0.0579
*wR*2	0.2173	0.1379
goodness-of-fit	1.016	1.019
Δρ (max/min) [e Å^{-3}]	0.211/−0.249	0.291/−0.197
structure refinement program	SHELXL97[33]	SHELXL97[33]

General Procedure for the Glycosylation Reaction: The purinic/pyrimidinic base (2.5 mmol) was suspended in hexamethyldisilazane (HMDS, 35.4 mmol) and refluxed in the presence of catalytic amounts (0.2 mmol) of ammonium sulfate for 4 h under nitrogen. Volatiles were distilled off under reduced pressure and the resulting residue dried under reduced pressure for 1 h at room temp. A solution of acetylated lactol **6** (1.0 mmol) in CH_2Cl_2 or $(ClCH_2)_2$ (25 mL) was added to the silylated base followed by the addition of trimethylsilyl triflate (TMSOTf, 2.0 mmol) to the resulting slurry. The clear solution was stirred at room temp. for 15 min, diluted with $CHCl_3$ and washed with satd. $NaHCO_3$ solution. The aqueous portions were extracted with $CHCl_3$ and the combined organic layers were dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure to give a crude product that was purified by flash chromatography.

1-[5-*O*-Benzyl-2,3-dideoxy-4-*C*-(fluoromethyl)-β/α-D-*glycero*-pentafuranosyl]uracil (1): Starting from **6** and 2,4-bis(trimethylsilyloxy)-uracil in $(ClCH_2)_2$, a 1:1 β/α mixture (^{1}H-NMR ratio) of monofluorobenzyl-protected uridine analogues **1** was obtained (85% yield) and purified, but not resolved, by flash chromatography (*n*-hexane/ethyl acetate, 7:3) to give the product mixture as a white solid, R_f = 0.35. − M. p. 82°C (DMSO/CH_3COCH_3, 1:1). − $[α]_D^{20}$ = −2.19 (*c* = 0.7, CH_3COCH_3). − NMR of α anomer: ^{1}H NMR ($CDCl_3$): δ = 1.93−2.53 (m, 8 H, H-2′ and H-3′ α/β), 3.40 (dd, *J* = 9.9 and 2.3 Hz, 1 H, H-5′b), 3.44 (dd, *J* = 9.9 and 1.7 Hz, 1 H, H-5′a), 4.50 (dd, *J* = 47.0 and 10.1 Hz, 1 H, H-6′b), 4.61 (dd, *J* = 45.1 and 10.1 Hz, 1 H, H-6′a), 4.54−4.60 (m, 4 H, H-7′ α/β), 5.74 (d, *J* = 8.1 Hz, 1 H, H-5), 6.23−6.16 (m, 2 H, H-1′ α/β), 7.27−7.41 (m, 10 H, H_{arom} α/β), 7.58 (dd, *J* = 8.1 and 1.8 Hz, 1 H, H-6), 9.06 (s, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 28.1 (d, *J* = 4.2 Hz, C-3′), 32.1 (s, C-2′), 72.1 (d, *J* = 6.6 Hz, C-5′), 73.7 (s, C-7′), 85.7 (d, *J* = 17.1 Hz, C-4′), 85.60 (d, *J* = 174.1 Hz, C-6′), 86.2 (s, C-1′), 102.6 (s, C-5), 127.9, 128.00, and 128.5 (s, C_{arom}), 137.4 (s, C-1″), 139.5 (d, *J* = 6.5 Hz, C-6), 150.4 (s, C-2), 163.1 (s, C-4). − NMR of β anomer: ^{1}H NMR ($CDCl_3$): δ = 1.93−2.53 (m, 8 H, H-2′ and H-3′ α/β), 3.60 (dd, *J* = 10.0 and 1.7 Hz, 1 H, H-5′b), 3.73 (dd, *J* = 10.0 and 1.3 Hz, 1 H, H-5′a), 4.30 (AB part of ABX, *J* = 47.2 and 10.0 Hz, 2 H, H-6′), 4.54−4.60 (m, 4 H, H-7′ α/β), 5.44 (dd, *J* = 8.1 and 1.0 Hz, 1 H, H-5), 6.23−6.16 (m, 2 H, H-1′ α/β), 7.27−7.41 (m, 10 H, H_{arom} α/β), 7.75 (d, *J* = 8.1 Hz, 1 H, H-6), 9.01 (s, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 27.7 (d, *J* = 3.4 Hz, C-3′), 32.7 (s, C-2′), 71.9 (d, *J* = 4.8 Hz, C-5′), 73.9 (s, C-7′), 85.6 (d, *J* = 18.2 Hz, C-4′), 85.0 (d, *J* = 177.7 Hz, C-6′), 86.33 (s, C-1′), 105.1 (s, C-5), 127.94, 128.3, and 128.7 (s, C_{arom}), 137.2 (s, C-1″), 140.2 (s, C-6), 150.35 (s, C-2), 163.20 (s, C-4). − MS (MALDI): *m/z* = 357.0 [M + Na]$^+$. − IR (neat): $\tilde{ν}$ = 3388.23 cm^{-1}, 2960.06, 1691.03, 1486.92, 1452.84, 1377.54, 1283.29, 1222.20, 1053.25, 817.31, 766.11. − $C_{17}H_{19}FN_2O_4$ (334): calcd. C 61.07, H 5.73, N 8.38; found C 61.10, H 5.72, N 8.35.

1-[5-*O*-Benzyl-2,3-dideoxy-4-*C*-(fluoromethyl)-β/α-D-*glycero*-pentafuranosyl]-5-bromouracil (2): Starting from **6** and 5-bromo-2,4-bis-(trimethylsilyloxy)uracil in $(ClCH_2)_2$, a 1:1 β/α mixture (^{1}H-NMR ratio) of monofluorobenzyl-protected uridine analogues **2** was obtained (82% yield) and purified, but not resolved, by flash chromatography (*n*-hexane/ethyl acetate, 3:2) to give the product mixture as an oil, R_f = 0.35. − $[α]_D^{20}$ = −4.73 (*c* = 0.9, CH_3COCH_3). − NMR of α anomer: ^{1}H NMR ($CDCl_3$): δ = 1.87−2.58 (m, 8 H, H-2′ and H-3′ α/β), 3.40 (dd, *J* = 9.9 and 2.3 Hz, 1 H, H-5′b), 3.44 (dd, *J* = 9.9 and 1.7 Hz, 1 H, H-5′a), 4.516 (d, *J* = 12.2 Hz, 1 H, H-7′b), 4.518 (dd, *J* = 47.0 and 10.1 Hz, 1 H, H-6′b), 4.57 (d, 1 H, *J* = 12.2 Hz, H-7′a), 4.66 (dd, *J* = 48.3 and 10.1 Hz, 1 H, H-6′a), 6.14 (dd, 1 H, *J* = 5.8 and 6.9 Hz, H-1′), 7.27−7.41 (m, 10 H, H_{arom} α/β), 7.92 (d, *J* = 2.7 Hz, 1 H, H-6), 9.52 (br. s, 1

H, NH). – ^{13}C NMR ($CDCl_3$): δ = 27.7 (d, *J* = 4.2 Hz, C-3′), 32.3 (s, C-2′), 71.9 (d, *J* = 6.6 Hz, C-5′), 73.7 (s, C-7′), 85.4 (d, *J* = 174.1 Hz, C-6′), 86.3 (d, *J* = 17.3 Hz, C-4′), 86.7 (s, C-1′), 96.8 (s, C-5), 127.7, 127.9, and 128.5 (s, C_{arom}), 137.3 (s, C-1″), 139.3 (d, *J* = 7.5 Hz, C-6), 149.8 (s, C-2), 159.0 (s, C-4). – NMR of β anomer: ^{1}H NMR ($CDCl_3$): δ = 1.87–2.58 (m, 8 H, H-2′ and H-3′ α/β), 3.53 (dd, *J* = 10.1 and 1.6 Hz, 1 H, H-5′b), 3.71 (dd, *J* = 10.1 and 1.0 Hz, 1 H, H-5′a), 4.26 (dd, *J* = 47.1 and 9.8 Hz, 1 H, H-6′b), 4.29 (dd, *J* = 47.1 and 9.8 Hz, 1 H, H-6′a), 4.61 (d, 1 H, *J* = 12.1 Hz, H-7′b), 4.70 (d, *J* = 12.1 Hz, 1 H, H-6′a), 6.17 (dd, 1 H, *J* = 5.9 and 6.2 Hz, H-1′), 7.27–7.41 (m, 10 H, H_{arom} α/β), 8.32 (s, 1 H, H-6), 9.50 (br. s, 1 H, NH). – ^{13}C NMR ($CDCl_3$): δ = 27.4 (d, *J* = 3.5 Hz, C-3′), 32.6 (s, C-2′), 71.3 (d, *J* = 5.5 Hz, C-5′), 73.8 (s, C-7′), 84.9 (d, *J* = 177.2 Hz, C-6′), 86.1 (d, *J* = 18.4 Hz, C-4′), 86.8 (s, C-1′), 96.6 (s, C-5), 127.8, 128.1 and 128.6 (s, C_{arom}), 137.0 (s, C-1″), 140.1 (s, C-6), 149.77 (s, C-2), 159.1 (s, C-4). – MS (MALDI): *m/z* = 436.6 $[M + Na]^+$, 452.5 $[M + K]^+$. – IR (neat): $\tilde{\nu}$ = 3431.40 cm^{-1}, 2959.01, 1695.72, 1453.08, 1271.46, 1054.69, 1028.07, 1008.09, 757.98. – $C_{17}H_{18}BrFN_2O_4$ (412): calcd. C 49.41, H 4.39, N 6.78; found C 49.40, H 4.42, N 6.75.

1-[5-*O*-Benzyl-2,3-dideoxy-4-*C*-(fluoromethyl)-β/α-D-*glycero*-pentafuranosyl]-5-nitrouracil (3): Starting from **6** and 5-nitro-2,4-bis(trimethylsilyloxy)uracil in $(ClCH_2)_2$, a 1:1 β/α mixture (^{1}H-NMR ratio) of monofluorobenzyl-protected nitrouridine analogues **3** was obtained (85% yield) and purified, but not resolved, by flash chromatography (chloroform/methanol, 95:5) to give the product mixture as a white solid, R_f = 0.35. – NMR of α anomer: ^{1}H NMR ($CDCl_3$): δ = 1.98–2.74 (m, 8 H, H-2′ and H-3′ α/β), 3.45 (m, 2 H, H-5′), 4.53 (dd, *J* = 47.3 and 10.4 Hz, 1 H, H-6′b), 4.54 (d, *J* = 12.0 Hz, 1 H, H-7′b), 4.58 (d, *J* = 12.0 Hz, 1 H, H-7′a), 4.73 (dd, *J* = 48.4 and 10.4 Hz, 1 H, H-6′a), 6.10 (dd, 1 H, *J* = 6.2 and 4.3 Hz, H-1′), 7.27–7.40 (m, 10 H, H_{arom} α/β), 8.41 (br. s, 1 H, NH), 9.17 (d, *J* = 3.1 Hz, 1 H, H-6). – ^{13}C NMR ($CDCl_3$): δ = 27.0 (d, *J* = 4.4 Hz, C-3′), 33.2 (d, *J* = 1.1 Hz, C-2′), 71.6 (d, *J* = 6.4 Hz, C-5′), 73.9 (s,C-7′), 84.82 (d, *J* = 174.6 Hz, C-6′), 88.2 (d, *J* = 17.0 Hz, C-4′), 88.5 (s, C-1′), 125.7 (br. s, C-5), 127.7, 128.2, and 128.6 (s, C_{arom}), 137.2 (s, C-1″), 144.3 (d, *J* = 9.1 Hz, C-6), 148.17 (s, C-2), 153.65 (s, C-4). – NMR of β anomer: ^{1}H NMR ($CDCl_3$): δ = 1.98–2.74 (m, 8 H, H-2′ and H-3′ α/β), 3.54 (dd, *J* = 10.1 and 1.3 Hz,1 H, H-5′b), 3.75 (d, *J* = 10.1 Hz, H-5′a), 4.27 (dd, *J* = 46.9 and 9.7 Hz, 1 H, H-6′b), 4.31 (dd, *J* = 47.2 and 9.7 Hz, 1 H, H-6′a), 4.61 (d, *J* = 12.4 Hz, 1 H, H-7′b), 4.77 (d, *J* = 12.4 Hz, 1 H, H-7′a), 6.15 (dd, 1 H, *J* = 6.6 and 4.4 Hz, H-1′), 7.27–7.40 (m, 10 H, H_{arom} α/β), 8.46 (br. s, 1 H, NH), 9.64 (s, 1 H, H-6). – ^{13}C NMR ($CDCl_3$): δ = 26.06 (d, *J* = 3.5, C-3′ Hz), 33.55 (d, *J* = 1.3, C-2′), 70.5 (d, *J* = 5.6 Hz, C-5′), 74.0 (s, C-7′), 84.77 (d, *J* = 177.7 Hz, C-6′), 88.0 (d, *J* = 18.2 Hz, C-4′), 88.6 (s, C-1′), 125.6 (br. s, C-5), 128.0, 128.3, and 128.7 (s, C_{arom}), 136.9 (s, C-1″), 145.3 (s, C-6), 149.14 (s, C-2), 153.73 (s, C-4). – MS (MALDI): *m/z* = 402.6 $[M + Na]^+$. – IR (nujol): $\tilde{\nu}$ = 3450.84 cm^{-1}, 3174.60, 3073.65, 2834.79, 2364.67, 1729.29, 1703.33, 1605.07, 1512.68, 1458.62, 1342.93, 1331.04, 1273.37, 1101.52, 820.69, 743.59. – $C_{17}H_{18}FN_3O_6$ (379): calcd. C 53.83, H 4.78, N 11.08; found C 53.85, H 4.79, N 11.06. – Crystallization in ethanol afforded a mixture of α and β anomers that were carefully separated by pins in pure form. – β Anomer: $[\alpha]_D^{20}$ = +21.00 (*c* = 0.5, $CHCl_3$); m. p. 196°C (CH_3CH_2OH). – α Anomer: $[\alpha]_D^{20}$ = –19.71 (*c* = 0.4, $CHCl_3$); m. p. 76°C (CH_3CH_2OH).

9-[5-*O*-Benzyl-2,3-dideoxy-4-*C*-(fluoromethyl)-β/α-D-*glycero*-pentafuranosyl]-6-chloropurine (4): Starting from **6** and 6-chloro-9-(trimethylsilyl)purine in CH_2Cl_2, a 1:1 β/α mixture (^{1}H-NMR ratio) of monofluorobenzyl-protected 6-chloropurine analogues **4** was obtained (80% yield) and purified, but not resolved, by flash chromatography (*n*-hexane/ethyl acetate, 3:2) to give the product mixture as an oil, R_f = 0.35. – M. p. = 85°C ($CHCl_3$). – $[\alpha]_D^{20}$ = –10.28 (*c* = 0.4, $CHCl_3/CH_3COCH_3$ 1:1). – NMR of α anomer: ^{1}H NMR ($CDCl_3$): δ = 2.15–2.75 (m, 8 H, H-3′ and H-2′ α/β), 3.52 (m, 2 H, H-5′), 4.52 (dd, *J* = 46.8 and 9.9 Hz, 1 H, H-6′b), 4.59 (m, 2 H, H-7), 4.61 (dd, *J* = 47.8 and 9.9 Hz, 1 H, H-6′a), 6.43 (dd, *J* = 4.6 and 6.5 Hz, 1 H, H-1′), 7.10–7.40 (m, 5 H, H_{arom}), 8.38 (s, 1 H, H-8), 8.73 (s, 1 H, H-2). – ^{13}C NMR ($CDCl_3$): δ = 27.9 (d, *J* = 4.3 Hz, C-3′), 32.3 (s, C-2′), 71.9 (d, *J* = 5.9 Hz, C-5′), 73.8 (s, C-7′), 84.9 (d, *J* = 175.3 Hz, C-6′), 86.38 (s, C-1′), 87.00 (d, *J* = 17.4 Hz, C-4′), 127.66, 127.97, and 128.51 (s, C_{arom}), 132.21 (s, C-5), 137.52 (s, C-1″), 143.64 (d, *J* = 5.7 Hz, C-8), 151.03 or 151.09 (s, C-6), 151.85 (s, C-2). – NMR of β anomer: ^{1}H NMR ($CDCl_3$): δ = 2.15–2.75 (m, 8 H, H-3′ and H-2′ α/β), 3.55 (dd, *J* = 10.0 and 1.9 Hz, 1 H, H-5′b), 3.63 (dd, *J* = 10.0 and 1.8 Hz, 1 H, H-5′a), 4.40 (dd, *J* = 47.1 and 9.6 Hz, 1 H, H-6′b), 4.44 (dd, *J* = 47.5 and 9.6 Hz, 1 H, H-6′a), 4.54 (s, 2 H, H-7′), 6.44 (t, *J* = 5.5 Hz, 1 H, H-1′), 7.22–7.40 (m, 5 H, H_{arom}), 8.42 (s, 1 H, H-8), 8.70 (s, 1 H, H-2). – ^{13}C NMR ($CDCl_3$): δ = 28.1 (d, *J* = 3.5 Hz, C-3′), 32.2 (d, *J* = 1.3 Hz, C-2′), 71.5 (d, *J* = 5.3 Hz, C-5′), 73.7 (s, C-7′), 85.3 (d, *J* = 176.1 Hz, C-6′), 86.49 (s, C-1′), 86.91 (d, *J* = 17.9 Hz, C-4′), 127.78, 128.06, and 128.54 (s, C_{arom}), 132.21 (s, C-5), 143.9 (s, C-8), 151.03 or 151.09 (s, C-6), 151.83 (s, C-2). – MS (MALDI): *m/z* = 399.1 $[M + Na]^+$; 415.3 $[M + K]^+$. – IR (nujol): $\tilde{\nu}$ = 1592.81 cm^{-1}, 1560.02, 1339.99, 1203.00, 1128.68, 1055.70, 1030.82, 742.94, 635.02. – $C_{18}H_{18}ClFN_4O_2$ (377): calcd. C 57.37, H 4.81, N 14.87; found C 57.40, H 4.82, N 14.85.

Synthesis of the Inosyl Derivative 5: The 6-chloropurin-9-yl derivative **4** (1.0 mmol, 372 mg) was added to a solution of sodium hydroxide (100 mmol, 2.4 g) in methanol (24 mL) and water (2.0 mL). The solution was heated at reflux for 2 h, then diluted with water, the pH was adjusted to 3 by adding diluted acetic acid (ca. 0.1 M). The organic compounds were extracted with ethyl acetate (3 × 10 mL), dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue which was flash-chromatographed in ethyl acetate/2-propanol/methanol (50:5:1). A 1:1 mixture of the α/β anomers **5** was obtained (250 mg, 70% yield) as a pale yellow solid, R_f = 0.35. – M. p. 140°C (diisopropyl ether). – $[\alpha]_D^{20}$ = –11.93 (*c* = 0.5, CH_3COCH_3). – NMR of α anomer: ^{1}H NMR ([D_6]acetone): δ = 2.14–2.89 (m, 8 H, H-2′and H-3′ α/β) 3.62 (m, 2 H, H-5′), 4.56 (dd, *J* = 47.7 and 9.8 Hz, H-6′b), 4.62 (dd, *J* = 47.7 and 9.8 Hz, H-6′a), 4.62 (m, 2 H, H-7′), 6.37–6.43 (m, 2 H, H-1′ α/β), 7.10–7.45 (m, 5 H, H_{arom}), 8.09 (s, 1 H, H-8), 8.11 (s, 1 H, H-2). – ^{13}C NMR ([D_6]acetone): δ = 29.6 (d, *J* = 4.5 Hz, C-3′), 33.17 (s, C-2′), 73.5 (d, *J* = 5.4 Hz, C-5′), 74.9 (s, C-6′), 86.3 (d, *J* = 173.6 Hz, C-6′), 87.1 (s, C-1′), 87.9 (d, *J* = 17.5 Hz, C-4′), 126.85 (s, C-5), 129.07, 129.11, and 129.88 (s, C_{arom}), 139.3 (d, *J* = 3.2 Hz, C-8), 140.1 (s, C-1″), 146.9 (s, C-2), 158.08 (s, C-6). – NMR of β anomer: ^{1}H NMR ([D_6]acetone): δ = 2.10–2.50 (m, 8 H, H_2-2′, H_2-3′, α/β) 3.65 (dd, *J* = 9.8 and 1.7 Hz, 1 H, H-5′b), 3.71 (dd, *J* = 9.8 and 2.1 Hz, 1 H, H-5′a), 4.49 (d, *J* = 47.7 Hz, 2 H, H_2-6′), 4.57 (s, 2 H, H_2-7′), 6.39 (t, *J* = 6.0 Hz, 1 H, H-1′), 7.20–7.50 (m, 5 H, H_{arom}), 8.07 (s, 1 H, H-8), 8.13 (s, 1 H, H-2). – ^{13}C NMR ([D_6]acetone): δ = 29.7 (d, *J* = 4.1 Hz, C-3′), 33.14 (s, C-2′), 73.3 (d, *J* = 5.4 Hz, C-5′), 74.7 (s, C-6′), 86.7 (d, *J* = 173.6 Hz, C-6′), 87.2 (s, C-1′), 87.8 (d, *J* = 17.8 Hz, C-4′), 126.80 (s, C-5), 129.09, 129.18, and 129.85 (s, C_{arom}), 139.5 (s, C-8), 139.9 (s, C-1″), 146.8 (s, C-2), 158.06 (s, C-6). – MS (MALDI): *m/z* = 381.6 $[M + Na]^+$, 397.5 $[M + K]^+$. – IR (nujol): $\tilde{\nu}$ = 3449.92 cm^{-1}, 3049.48, 2864.59, 2138.74, 1705.07, 1586.42, 1344.05, 1204.43, 1119.29, 1025.61, 697.37. – $C_{18}H_{19}FN_4O_3$ (358): calcd. C 60.33, H 5.34, N 15.63; found C 60.30, H 5.32, N 15.65.

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[28] The pairwise correlation was reasonably linear, with satisfying r^2 factors (7 points, 0.902 and 0.921 for $^7J_{HF}$ and $^6J_{CF}$, respectively). The linearity improved dramatically if the point related to [D_4]methanol was excluded. This is not unexpected, as the value of Kamlet−Taft′s β for that solvent is less certain than for the others. Moreover, methanol is the only solvent, within the chosen set, with hydrogen bond donor properties, which is likely to introduce spurious effects which are not taken into account for by the β parameter. The main results of the regression analysis are as follows: (i) $^7J_{HF} = (-1.42 \pm 0.13)\ \beta + (3.17 \pm 0.08)$, $r^2 = 0.966$, $n = 6$ points; (ii) $^6J_{CF} = (-4.14 \pm 0.22)\ \beta + (8.93 \pm 0.14)$, $r^2 = 0.989$, $n = 6$ points.
[29] SCC is defined as the difference between the through-space J observed in the 5-Y-uracil derivative and that of the uracil nucleoside (Y = H) taken as reference: SCC = J(Y) − J(H). The data for the correlation are reported in Table 6. The equation obtained for HF and CF coupling constants are, respectively: SCS(HF) = (2.21 ± 0.14) σ_I − (0.10 ± 0.6), r^2 = 0.987 and SCS(CF) = (3.17 ± 0.54) σ_I − (0.06 ± 0.22), r^2 = 0.921. The results of these correlations can only be interpreted in a semiquantitative way, since the substituent set is mainly made up of functional groups with −I effect.
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