Synthesis and Crystal Structures of *O*-2′,3′-Cyclic Cyclopentanone and Cyclohexanone Ketals of the Cytostatic 5-Fluorouridine

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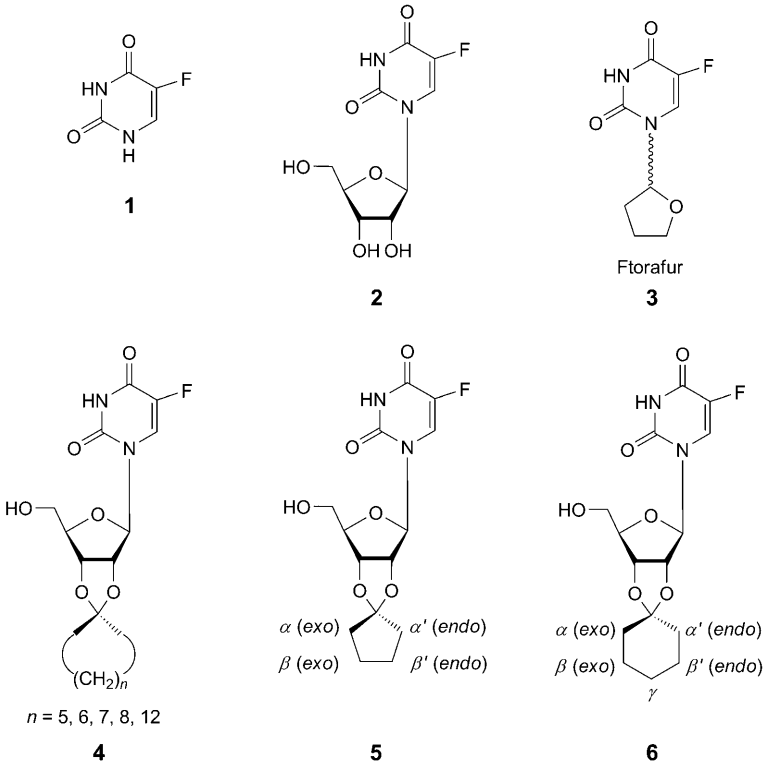
Dedicated to Prof. Dr. *Andrea Vasella*, ETH-Zürich in gratitude

The synthesis of two *O*-2′,3′-cyclic ketals, *i.e.*, **5** and **6**, of the cytostatic 5-fluorouridine (**2**), carrying a cyclopentane and/or a cyclohexane ring, respectively, is described. The novel compounds were characterized by ^{1}H-, ^{19}F-, and ^{13}C-NMR, and UV spectroscopy, as well as by elemental analyses. Their crystal structures were determined by X-ray analysis. Both compounds **5** and **6** show an *anti*-conformation at the *N*-glycosidic bond which is biased from $+ac$ to $+ap$ compared to the parent nucleoside **2**. The sugar puckering is changed from $^{2'}E$ to $_{3'}E$ going along with a reduction of the puckering amplitude τ_m by *ca.* 10–13° due to the ketalization. The conformation about the sugar exocyclic bond C(4′)–C(5′) of **5** and **6** remains unchanged, *i.e.*, g^+, compared with compound **2**.

1. Introduction. – 5-Fluorouracil (**1**) as well as its β-D-ribo- (**2**) and 2′-deoxy-β-D-ribonucleosides possess antitumor activities against various types of carcinomas, particularly of the breast and the gastrointestinal tract. Furthermore, positive results have been obtained in the topical treatment of premalignant keratosis of the skin and basal cell carcinomas [1][2]. One of the most prominent lipophilic derivatives of **1** is 5-fluoro-1-(tetrahydrofuran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (*Tegafur*, *Ftorafur*; **3**), first synthesized by *R. Zhuk*, based on an idea of *S. Hiller*. This prodrug is slowly broken down in muscle and liver; given intravenously, it has the same spectrum of application as 5-fluorouracil [3–8]. A large number of lipophilic prodrugs have been prepared and found to possess antitumor properties. Besides *Ftorafur* (**3**) and its derivatives, recently 5-fluoro-5′-uridylic acid mono[2-(decyloxy)-3-(dodecylsulfanyl)propyl]ester and its salts (*Fosfluridine*, *Tidoxil*) have been used for the treatment of intraepithelial proliferative diseases. This nucleolipid drug was developed by the chemists of the company *Heidelberg Pharma* (*Ladenburg*, Germany) [9]. Many biochemical mechanisms seem to be responsible for the cytotoxicity of 5-fluorouracil, *e.g.*, *i*) inhibition of thymidylate synthase, following its conversion to 5-fluoro-2′-deoxyuridine 5′-monophosphate; *ii*) conversion to 5-fluorouridine 5′-triphosphate and its incorporation into RNA; *iii*) its incorporation into DNA, leading to an impairment of the integrity of DNA [10].

During our studies [11][12] on the synthesis and structure of lipophilic nucleoside derivatives (nucleolipids) with pharmacological activity, we prepared recently a series

of *O*-2′,3′-cyclic ketal derivatives (*i.e.*, **4**) as potential prodrugs of 5-fluorouridine. Here, we report the three-dimensional structures of the cyclopentanone and the cyclohexanone derivatives, **5** and **6**, respectively, of 5-fluorouridine obtained by X-ray crystallography.



2. Results and Discussion. – 2.1. *Synthesis.* Condensation of either unsymmetrical ketones such as pentan-2-one or ($\omega-1$)-oxo esters such as ethyl levulinate with ribonucleosides in the presence of $CH(OEt)_3$ leads to (*R*)- and (*S*)-*O*-2′,3′-alkylidene ketals, which have been used for various purposes [13–15]. In all cases, predominantly the (*R*)-diastereoisomers are formed. Reaction of cyclic ketones with 5-fluorouridine (**2**) under analogous reaction conditions gives cyclic, spiro-linked *O*-2′,3′-alkylidene ketals of the general structure **4** having – in contrast to the derivatives mentioned above – no additional stereogenic center. Compounds of this type are potentially of pharmacological interest, as they present lipophilic prodrugs of the cytostatic nucleoside which can be catabolized in a slightly acidic medium.

Reaction of compound **2** with cyclopentanone in the presence of ethyl orthoformate and 4M HCl in 1,4-dioxane (solvent: DMF) gave, after workup, compound **5**, which was crystallized from $CHCl_3$ as colorless needles. Starting from cyclohexanone, compound **6** was prepared by the same route; this derivative was crystallized from $CHCl_3$/acetone

4:1 (*v*/*v*). Both compounds were characterized by ^{1}H-, ^{19}F-, and ^{13}C-NMR spectroscopy. ^{1}H- and ^{13}C-NMR resonances were unequivocally assigned by gradient-selected homo- and heteronuclear correlation spectroscopy (*Bruker* pulse programs, ^{1}H,^{13}C: HSQCETGP; ^{1}H,^{1}H: COSYGPSW). From the ^{1}H- and ^{13}C-NMR spectra, it can be seen in both cases that the CH_2 groups adjacent to the prochiral (or *pseudo*chiral) acetal C-atom (=C(10); see *Fig. 1*, below) resonate at different chemical shifts. This has already been found earlier for *O*-2′,3′-isopropylidene-protected ribonucleosides as well as for other unsymmetrical *O*-2′,3′-alkylidene-ribonucleoside derivatives. The reason for these findings is that one of the alkyl groups adjacent to the sp^3 acetal C-atom is *endo*-oriented and positioned beneath the ribose ring and thereby exposed to an electrical field effect of the N-heterocycle, while the other one is *exo*-positioned. An X-ray analysis of (*R*)-*O*-2′,3′-(3-carboxy-1-methylpropylidene)adenosine allowed an unequivocal assignment of the ^{1}H- and ^{13}C-NMR chemical shifts of the alkylidene residue [15] and showed that, for the unsymmetrical, (*R*)-configured compounds, the Me group is *exo*-oriented and resonates at higher field. In the case of *O*-2′,3′-isopropylidene-adenosine, the chemical-shift differences for both Me groups amounts to 0.31 (for ^{1}H) and 2.0 ppm (for ^{13}C). Inspection of the NMR spectra of compound **5** revealed a $\Delta\delta$ value of 0.21 ppm for the *exo*- and *endo*-CH_2 H-atoms adjacent to the prochiral center, and of 0.16 ppm for the corresponding H-atoms of compound **6**, both fitting to *Imbachs* rule for β-D-ribonucleosides. The β-CH_2 H-atoms, CH_2(12) and CH_2(13), of compound **5** almost coincide to a *multiplet*. The ^3J(H,H) coupling between the α- and β-CH_2 H-atoms, *i.e.*, CH_2(11) and CH_2(12), and CH_2(14) and CH_2(13), respectively, amounts for both cases to 7.1 Hz, and is therewith in the range of a torsion angle of 40° (±5°) with a staggered conformation at the C(11)–C(12) as well as at the C(13)–C(14) axis. In the case of compound **6**, the corresponding ^3J coupling amounts to 5.7 Hz, which implies a torsion angle of 57° (±5°) and an almost perfect *gauche*-conformation. Both compounds differ in the ^{13}C-NMR chemical-shift differences of their C(α') (*endo*) and C(α) (*exo*) resonances: in compound **5**, this value amounts to only 0.03 ppm, while, in compound **6** the $\Delta\delta$ value is 2.3 ppm. The chemical-shift differences of the β-C-atoms (**5**: C(12)/C(13); **6**: C(13)/C(14)) amount to 0.3 and 0.4 ppm, respectively.

2.2. *Crystallography.* In *Tables 1–4*, the crystallographic data as well as torsion angles, intermolecular bond distances, and bond angles of 5-fluorouridine (**2**) together with those of compounds **5** and **6** are collected. *Fig. 1* displays the ball-and-stick models of the compounds, while *Fig. 2* shows their sugar puckering. The data clearly show that the structural parameters of both ketals are almost identical, but that they differ partly from those of the parent nucleoside. While the torsion angle χ(C(2)–N(1)–C(1′)–O(4′)) [16] around the N-glycosidic bond of 5-fluorouridine (**2**) lies in the +*ac* region, it is biased towards antiperiplanar (+*ap*) for compounds **5** and **6**. Also the sugar puckering is slightly changed: while the parent nucleoside adopts a C(2′) *endo*-($^{2'}E$) conformation, the ketals **5** and **6** exhibit both a C(3′) *exo*-($_{3'}E$)-conformation (*Fig. 2*) with a phase angle *P* of pseudorotation of 204.06° for **5** and 204.27° for **6**, and pseudorotational amplitudes τ_m of 24.3° for **5** and 21.5° for **6**. The amplitude is thus reduced by *ca.* 10–13° compared with that of **2** (P = 166.3°, τ_m = 34.5°), due to the ketalization. The conformation across the sugar exocyclic bond is in each case g^+ and hence identical with that of 5-fluorouridine.

Table 1. *Crystallographic Data for Compounds* **5** *and* **6**

	5	**6**
Empirical formula	$C_{14}H_{17}FN_2O_6$	$C_{15}H_{19}FN_2O_6$
Formula weight [g mol^{-1}]	328.30	342.32
Temp. [K]	100 (2)	100 (2)
Wavelength [Å]	0.71073	0.71073
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a [Å]	5.3090(4)	5.9586(4)
b [Å]	13.5604(7)	13.2524(7)
c [Å]	19.9728(8)	19.4723(9)
V [Å^3]	1437.89(14)	1537.64(15)
Z	4	4
D_x [g cm^{-3}]	1.517	1.479
μ (MoK_α) [mm^{-1}]	0.127	0.122
F (000)	688	720
Crystal size [mm]	$0.33 \times 0.32 \times 0.21$	$0.49 \times 0.21 \times 0.13$
Crystal description	Bloc	Needle
θ Range for data collection [°]	1.82–27.99	1.86–28.00
Limiting indices	$-6 \le h \le 6$ $-17 \le k \le 17$ $-25 \le l \le 25$	$-7 \le h \le 7$ $-17 \le k \le 17$ $-25 \le l \le 25$
Reflection collected/unique	54649/1988	87416/2147
R_{int}	0.0304	0.0397
Completeness to $\theta = 27.99$ [%]	98.4	100.0
Transmission factors [min; max]	0.9591; 0.9738	0.9427; 0.9845
Data/restraints/parameters	1988/0/213	2147/0/220
Goodness-of-fit on F^2	1.041	1.058
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0297$, $wR2 = 0.0755$	$R1 = 0.0276$, $wR2 = 0.0704$
Final R indices [all data]	$R1 = 0.0318$, $wR2 = 0.0769$	$R1 = 0.0306$, $wR2 = 0.0727$
Extinction coefficient	0.0017 (13)	None
Largest diff. peak and hole [e Å^{-3}]	0.224 and -0.194	0.314 and -0.243

Table 2. *Torsion Angles* [°] *of 5-Fluorouridine* (**2**) *and Its Derivatives* **5** *and* **6**

Torsion angle	Symbol	F^{5}Urd (**2**)	**5**	**6**
C(2)–N(1)–C(1′)–O(4′)	X[a])	−122.7	−164.6(2)	−167.9(1)
C(2′)–C(1′)–O(4′)–C(4′)	ζ_0	−15.8	2.4(2)	2.1(2)
O(4′)–C(1′)–C(2′)–C(3′)	ζ_1	30.9	12.5(2)	11.2(2)
C(1′)–C(2′)–C(3′)–C(4′)	ζ_2	−33.0	−22.2(2)	−19.6(2)
C(2′)–C(3′)–C(4′)–O(4′)	ζ_3	25.1[b])	24.1(2)	21.4(2)
C(3′)–C(4′)–O(4′)–C(1′)	ζ_4	−6.3	−16.5(2)	−14.9(2)
O(5′)–C(5′)–C(4′)–C(3′)	Φ_{oc}	49.1	53.9(2)	52.2(2)
O(5′)–C(5′)–C(4′)–O(4′)	Φ_{oo}	−69.3	−64.3(2)	−66.0(2)

[a]) The originally published value amounts to 53.1° [10] and refers to an *N*-glycosidic torsion angle C(6)–N(1)–C(1′)–O(4′) but not to C(2)–N(1)–C(1′)–O(4′) as defined for X in [16]. [b]) This value has been corrected according to the originally deposited data [10].

Table 3. *Intramolecular Bond Distances* [Å] *in Molecules* **2**, **5**, *and* **6**

Bond	F^{5}Urd (**2**)	**5**	**6**
N(1)–C(2)	1.387(4)	1.377(2)	1.374(2)
N(1)–C(6)	1.374(4)	1.375(2)	1.376(2)
N(1)–C(1′)	1.473(3)	1.495(2)	1.495(2)
C(2)–O(2)	1.210(4)	1.222(2)	1.224(2)
C(2)–N(3)	1.387(3)	1.377(2)	1.379(2)
N(3)–C(4)	1.378(4)	1.385(2)	1.379(2)
C(4)–O(4)	1.231(3)	1.223(2)	1.224(2)
C(4)–C(5)	1.420(5)	1.438(3)	1.444(2)
C(5)–C(6)	1.336(3)	1.330(3)	1.336(2)
C(5)–F(5)	[a])	1.354(2)	1.353(2)
C(1′)–O(4′)	1.400(3)	1.406(2)	1.402(2)
C(1′)–C(2′)	1.524(4)	1.544(2)	1.546(2)
C(2′)–O(2′)	1.404(3)	1.422(2)	1.426(2)
C(2′)–C(3′)	1.542(3)	1.522(2)	1.532(2)
O(2′)–C(10)	[a])	1.434(2)	1.435(2)
C(3′)–O(3′)	1.425(4)	1.432(2)	1.431(2)
C(3′)–C(4′)	1.540(4)	1.514(2)	1.518(2)
O(3′)–C(10)	[a])	1.426(2)	1.433(2)
C(4′)–O(4′)	1.447(4)	1.456(2)	1.453(2)
C(4′)–C(5′)	1.492(6)	1.506(2)	1.506(2)
C(5′)–O(5′)	1.423(6)	1.422(2)	1.418(2)

[a]) Not reported.

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Experimental Part

General. All chemicals were purchased from *Sigma-Aldrich* (D-Deisenhofen, Germany) or from *TCI–Europe* (B-Zwijndrecht). Solvents were of laboratory grade. TLC: aluminium sheets, silica gel *60 F_{254}*, 0.2-mm layer (*Merck*, Germany). M.p. *Büchi SMP-20*, uncorrected. UV Spectra: *Cary 1E* UV spectrophotometer (*Varian*, D-Darmstadt); in MeOH; λ_{max} in nm (ε in $M^{-1}cm^{-1}$). NMR Spectra: *AMX-500* spectrometer (*Bruker*, D-Rheinstetten); ^{1}H: 500.14, ^{13}C: 125.1, ^{19}F: 235.4 MHz; chemical shifts in ppm rel. to TMS as internal standard for ^{1}H and ^{13}C nuclei, and $CFCl_3$ for ^{19}F; *J* in Hz.

*5-Fluoro-1-[(3a′*R*,4′*R*,6′*R*,6a′*R*)-3a′,4′,6′,6a′-tetrahydro-6′-(hydroxymethyl)spiro[cyclopentane-1,2′-furo[3,4-*d*][1,3]dioxol]-4′-yl]pyrimidine-2,4(1*H*,3*H*)-dione* (**5**). 5-Fluorouridine (1.0 g, 3.82 mmol) was dissolved in dry DMF (15 ml). Cyclopentanone (0.7 ml, 7.63 mmol), $CH(OEt)_3$ (1 ml, 5.72 mmol), and HCl (4M in dry 1,4-dioxane, 3.4 ml) were then added. The soln. was stored at r.t. for 4 h. The soln. was partitioned between $CHCl_3$ and sat. aq. $NaHCO_3$. The org. layer was separated, washed with H_2O, dried (Na_2SO_4), filtered, evaporated, and dried (high vacuum, 55°) to yield **5** in almost quant. yield (> 95%) in repeated experiments. Colorless oil. This residual oil was crystallized twice from $CHCl_3$. Colorless needles suitable for X-ray analysis were obtained by slow evaporation of a dil. soln. of **5** from $CHCl_3$. M.p. 200°. TLC ($CHCl_3$/MeOH 9:1 (*v*/*v*)): R_f 0.5. UV (MeOH): 266 (12.100). ^{1}H-NMR ((D$_6$)DMSO): 11.93 (*d*, ^4J(NH,F) = 2.8, NH); 8.21 (*d*, ^3J(F, H–C(6)) = 7.1, H–C(6)); 5.83 (*d*, ^3J(H–C(1′), H–C(2′)) = 1.3, H–C(1′)); 5.25 (*t*, *J* = 5.0, C(5′)–OH); 4.84 (*dd*, ^3J(H–C(2′), H–C(1′)) = 2.6; ^3J(H–C(2′),

Table 4. *Intramolecular Bond Angles* [°] *in Molecules* **2**, **5**, *and* **6**

Bond angle	F^{5}Urd (**2**)	**5**	**6**
C(2)–N(1)–C(6)	122.2(2)	121.32(15)	121.91(14)
C(2)–N(1)–C(1′)	113.4(2)	115.97(13)	114.96(12)
C(6)–N(1)–C(1′)	119.3(3)	122.47(14)	122.73(13)
O(2)–C(2)–N(1)	124.2(3)	122.26(16)	122.29(14)
O(2)–C(2)–N(3)	121.3(3)	122.06(16)	122.05(14)
N(1)–C(2)–N(3)	114.3(3)	115.67(14)	115.67(13)
C(4)–N(3)–C(2)	127.3(3)	126.99(15)	127.09(14)
O(4)–C(4)–N(3)	126.4(2)	121.77(17)	121.91(15)
O(4)–C(4)–C(5)	116.6(2)	126.24(15)	125.79(15)
N(3)–C(4)–C(5)	113.1(2)	111.99(15)	112.30(14)
C(6)–C(5)–F(5)	120.6(4)	120.40(16)	120.80(15)
C(6)–C(5)–C(4)	122.7(3)	123.31(15)	123.06(14)
F(5)–C(5)–C(4)	[a])	116.30(15)	116.13(14)
C(5)–C(6)–N(1)	120.3(3)	120.29(16)	119.93(15)
O(4′)–C(1′)–N(1)	[a])	108.16(13)	109.32(12)
O(4′)–C(1′)–C(2′)	107.5(3)	108.48(13)	108.75(12)
N(1)–C(1′)–C(2′)	[a])	114.55(14)	112.97(12)
O(2′)–C(2′)–C(3′)	115.4(2)	105.15(13)	105.43(12)
O(2′)–C(2′)–C(1′)	109.3(3)	111.45(14)	109.93(12)
C(3′)–C(2′)–C(1′)	101.7(3)	102.81(13)	103.33(12)
C(2′)–O(2′)–C(10)	[a])	108.29(13)	107.98(11)
O(3′)–C(3′)–C(4′)	108.4(2)	108.94(14)	110.63(14)
O(3′)–C(3′)–C(2′)	110.6(2)	101.81(13)	102.57(12)
C(4′)–C(3′)–C(2′)	102.3(3)	106.61(14)	105.91(12)
C(3′)–O(3′)–C(10)	[a])	105.51(13)	105.59(12)
O(4′)–C(4′)–C(5′)	109.6(2)	111.85(14)	110.30(13)
O(4′)–C(4′)–C(3′)	106.2(2)	104.68(13)	105.92(12)
C(1′)–O(4′)–C(4′)	[a])	111.61(12)	111.49(11)
O(5′)–C(5′)–C(4′)	110.2(3)	109.82(15)	108.79(14)
O(3′)–C(10)–O(2′)	[a])	104.90(12)	104.65(11)

[a]) Not reported.

H–C(3′)) = 6.4, H–C(2′)); 4.71 (*dd*, ^3J(H–C(3′), H–C(2′)) = 6.3; ^3J(H–C(3′), H–C(4′)) = 3.2, H–C(3′)); 4.12 (ψq, ^3J(H–C(4′), CH$_2$(5′)) = 3.6, H–C(4′)); 3.65–3.56 (*m*, ^2J(H–C(5′), H–C(5″) = –12.1, CH$_2$(5′)); 1.90 (*t*, ^3J(CH$_2$(*α*, *endo*), CH$_2$(*β*, *endo*)) = 7.1, CH$_2$(*α*, *endo*)); 1.69 (*t*, ^3J((CH$_2$ (*α*′, *exo*), CH$_2$ (*β*′, *exo*)) = 7.1, CH$_2$(*α*′, *exo*)); 1.66–1.59 (*m*, CH$_2$(*β*, *endo*), CH$_2$(*β*, *exo*)). ^{13}C-NMR ((D$_6$)DMSO): 162.27 (C(2)); 157.0 (*d*, ^2J(C(4), F) = 26.4, C(4)); 140.0 (*d*, ^1J(C(5), F) = 230.2, C(5)); 125.9 (*d*, ^2J(C(6), F) = 34.0, C(6)); 122.15 (C(acetal)); 90.81 (C(1′)); 86.16 (C(4′)); 83.51 (C(2′)); 80.35 (C(3′)); 61.16 (C(5′)); 35.94, 35.91 (C(*α*), C(*α*′)); 22.95, 22.62 (C(*β*), C(*β*′)). ^{19}F-NMR ((D$_6$)DMSO): –167.71. Anal. calc. for $C_{14}H_{17}FN_2O_6$ (328.293): C 51.22, H 5.22, N 8.53; found: C 50.89, H 5.37, N 8.59.

*5-Fluoro-1-[(3a′*R*,4′*R*,6′*R*,6a′*R*)-3a′,4′,6′,6a′–tetrahydro-6′-(hydroxymethyl)spiro[cyclohexane-1,2′-furo[3,4-*d*][1,3]dioxol]-4′-yl]pyrimidine-2,4(1*H*,3*H*)-dione* (**6**). Compound **6** was prepared as described for **5**, but using cyclohexanone instead of cyclopentanone. An almost quant. yield (> 95%) of pure **6** was obtained in repeated experiments. The oily material was crystallized several times from $CHCl_3$. Colorless needles suitable for X-ray analysis were obtained by slow evaporation of a dil. soln. of **6** in $CHCl_3$/acetone 3:1 (*v*/*v*). M.p. 210°. TLC ($CHCl_3$/MeOH 9:1 (*v*/*v*)): R_f 0.6. UV: 266 (12.300). ^{1}H-NMR ((D$_6$)DMSO): 11.90 (*d*, ^4J(NH, F) = 2.8, NH); 8.19 (*d*, ^3J(H–C(6), F) = 7.1, C–C(6)); 5.82 (*d*,

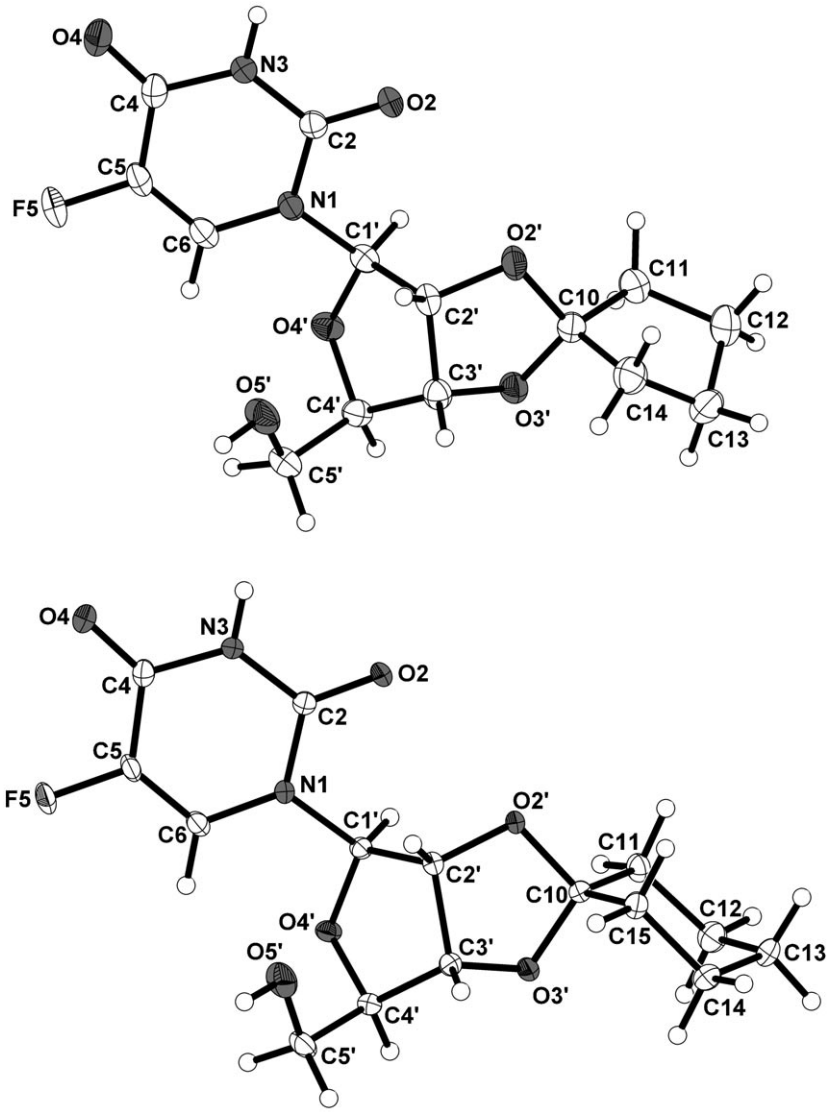

Fig. 1. *Ball-and-stick model of* **5** *and* **6** *with the atomic numbering scheme used*. With the exception of the H-atoms, which were represented by use of spheres with a common isotropic radius, all other atoms were represented as thermal displacement ellipsoids (one octant: oxygen = grey, fluorine = white; cross: nitrogen = grey, carbon = white) showing 50% of the probability of the corresponding atom.

^3J(H–C(1′), H–C(2′)) = 1.1, H–C(1′)); 5.22 (*t*, ^3J = 5.0, C(5′)–OH); 4.87 (*dd*, ^3J(H–C(2′), H–C(1′)) = 2.6, ^3J(H–C(2′), H–C(3′)) = 6.2, H–C(2′)); 4.74 (*dd*, ^3J(H–C(3′), H–C(2′)) = 6.2, ^3J(H–C(3′), H–C(4′)) = 3.4, H–C(3′)); 4.09 (ψq, ^3J(H–C(4′), H–C(3′)) = 3.6, H–C(4′)); 3.63 – 3.55 (*m*, ^2J(H–C(5′), H–C(5″)) = – 11.3, CH_2(5′)); 1.72 (*t*, ^3J(H–C(α', *endo*), H–C(β', *endo*)) = 5.7, H–C(α', *endo*)); 1.59 (*m*, H–C(β', *endo*)); 1.56 (*m*, ^3J(H–C(α, *exo*), H–C(β, *exo*)) = 5.9, H–C(α, *exo*)); 1.49 (*m*,

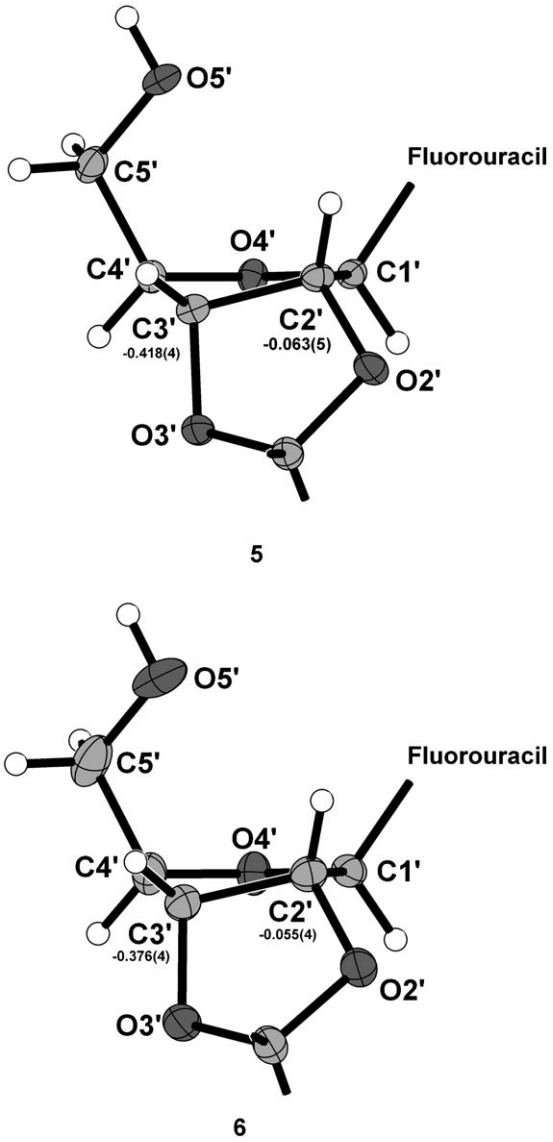

Fig. 2. *Sugar puckering of compounds* **5** *and* **6**. For details, see *Fig. 1.*

H–C(*β*, *exo*)); 1.36 (*m*, H–C(*γ*)). ^{13}C-NMR ((D$_6$)DMSO): 157.0 (*d*, ^2J(C(4), F) = 26.2, C(4)); 149.00 (C(2)); 139.93 (*d*, ^1J(C(5), F) = 230.2, C(5)); 125.91 (*d*, ^2J(C(6), F) = 125.9, C(6)); 113.46 (C(acetal)); 90.99 (C(1′)); 86.60 (C(4′)); 83.30 (C(2′)); 79.88 (C(3′)); 61.15 (C(5′)); 36.56 (C(*α*′)); 34.26 (C(*α*)); 24.42 (C(*γ*)); 23.63 (C(*β*′)); 23.22 (C(*β*)). ^{19}F-NMR ((D$_6$)DMSO): –167.53. Anal. calc. for $C_{15}H_{19}FN_2O_6$ (342.32): C 52.63, H 5.59, N 8.18; found: C 52.52, H 5.85, N 8.03.

X-Ray Crystallography. Suitable single crystals of **5** and **6** were selected under a polarization microscope and mounted on a 50-μm *MicroMesh MiTeGen Micromount*™ using *FROMBLIN Y*

perfluoropolyether (*LVAC 16/6*, *Aldrich*). The crystallographic data for **5** and **6** are given in *Table 1*. All measurements were conducted at 100 K on a *Bruker Kappa APEXII* single-crystal diffractometer with CCD area-detector using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and *KRYOFLEX* low-temp. equipment. Unit-cell dimensions were determined using the *APEX 2* software suite [17]. Data reduction was performed with SAINT [18]. The intensities were corrected for *Lorentz* and polarization effects. For both compounds, an empirical absorption correction was applied using SADABS [19], which is based on an analysis of symmetry-equivalent reflections in the highly redundant data set. Each structure was solved by direct methods using SHELXS [20], which revealed most of the non-H-atoms of the molecules. All remaining non-H-atoms were located in subsequent difference *Fourier* maps.

The non-H-atoms in each structure were refined anisotropically. All H-atoms including those of the OH groups were found in difference *Fourier* maps. To reduce the number of refined parameters, they were placed in geometrically calculated positions and constrained to ride on their parent atoms. Three common isotropic displacement parameters for the H-atoms of the benzene, sugar, and ketal groups were refined.

The refinement of each structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2)$. Corrections for secondary extinction were applied for **5**. In both cases, the largest peaks of residual electron density were without chemical significance. In the absence of heavy atoms, *Friedel* reflections were merged. Because of the same reason the calculated *Flack* parameters [21] were too low and without any significant information about the absolute structure. The correct configurations were established by the known absolute configuration of the educts. All calculations were performed using SHELXL 97 [20]. The figures were drawn using *Diamond* [22]. Pseudorotational parameters (P, τ_m) were calculated according to [16].

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