O-2′,3′-Ketal-Nucleolipids of the Cytostatic 5-Fluorouridine: Synthesis, Lipophilicity, and Acidic Stability

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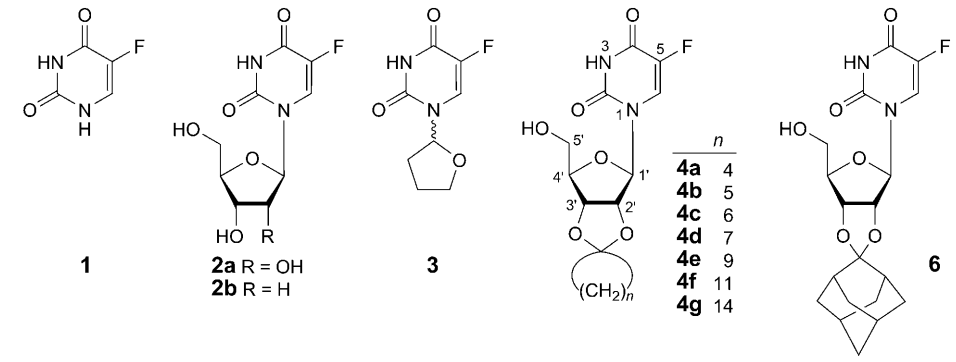
Dedicated to Prof. Dr. *Albert Eschenmoser*, ETH Zürich, on the occasion of his 85th birthday

The synthesis of a series of cyclic and acyclic *O*-2′,3′-ketal derivatives of the cancerostatic 5-fluorouridine (**2a**) is described. The novel compounds were characterized by ^{1}H- and ^{13}C-NMR, and UV spectroscopy, as well as by elemental analyses. The lipophilicity values (log *P*, retention times in *RP-18* HPLC) of the cyclic ketals were determined and related to the ring tensions as well as the acid stability of the spiro-linked ketal rings.

1. Introduction. – 5-Fluorouracil (**1**) as well as its β-D-ribo- and 2′-deoxy-β-D-ribonucleosides, **2a** and **2b**, respectively, possess antitumor activity 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]. The intrathecal use of 5-fluoro-2′-deoxyuridine (**2b**) has been studied for meningeal dissemination of malignant brain tumors, and it has been found that this nucleoside has an excellent antitumor activity and minimal neurotoxicity [3].

A large number of lipophilic prodrugs of 5-fluorouracil (**1**) and its nucleosides have been prepared and found to possess useful antitumor properties. Besides *Ftorafur* and its derivatives [4–10], 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 [11]. We now report the synthesis of lipophilic *O*-2′,3′-ketal nucleoside derivatives (nucleolipids) of compound **2a**, and their lipophilicity as well as their stability towards acid. The motivation for this is our intention to embed such nucleolipids into hydrophobized nanotube arrays, for example, of TiO_2 [12], and use them as implants for drug delivery.

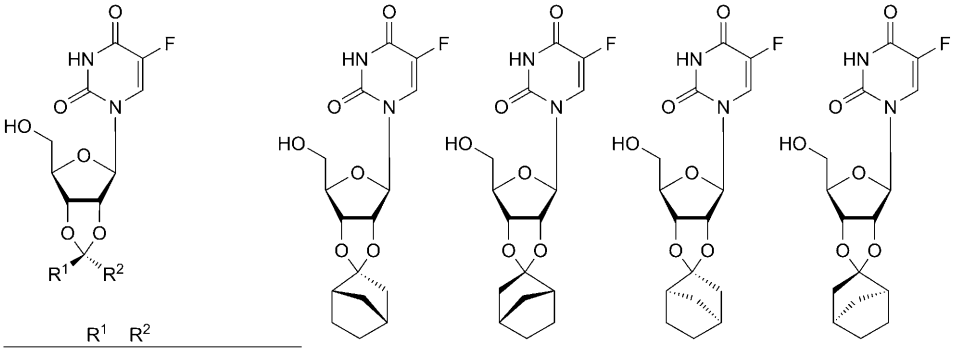
2. Results and Discussion. – 2.1. *Synthesis.* Recently, we reported the synthesis and crystal structures of *O*-2′,3′-cyclic cyclopentanone and cyclohexanone ketals of compound **2a** [13]. We now extend this work to the preparation of the corresponding cycloheptanone, cyclooctanone, cyclodecanone, cyclododecanone, cyclopentadecanone, norbornan-2-one, adamantan-2-one, as well as the acyclic heptan-4-one, ethyl levulinate, and 4-oxopentyl 4-methylbenzoate ketals, which all follow '*Lipinski*'s Rule of Five' for 5-fluorouridine [14]. Cyclododecanone and cyclopentadecanone



1 **2a** R = OH **2b** R = H **3**

	n
4a	4
4b	5
4c	6
4d	7
4e	9
4f	11
4g	14

6



	R^1	R^2
5a	Pr	Pr
5b (*R*)[a])	Me	$EtOOCCH_2CH_2$
5c (*R*)[a])	Me	$4\text{-}MeC_6H_4COO(CH_2)_3$

7a **7b** **7c** **7d**

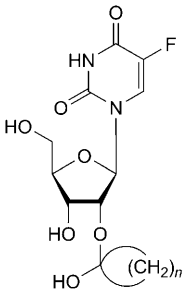
[a]) (*R*) Notation refers to the stereogenic center at the acetal C-atom.

(= *Exaltone*®) are important basic fragrances in scent industry [15–17]. Reaction of compound **2a** with the appropriate ketones in the presence of ethyl orthoformate and 4M HCl in 1,4-dioxane (DMF, 4 or 24 h, ambient temp.) gave, after workup, the ketals **4**–**7**, most of which were crystallized from $CHCl_3$ as thin colorless needles [13].

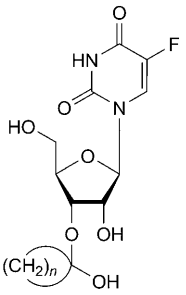
Ketalization of **2a** with norbornan-2-one led to products with three new stereogenic centers so that eight stereoisomers are conceivable; four of them, **7a**–**7d**, are displayed and could be tentatively assigned by NMR spectroscopy. The other diastereoisomers are characterized by interchange of *α-exo-* and *α-endo*-CH_2 groups of the spriro-linked ketals.

During the ketalizations of 5-fluorouridine with various cyclic ketones (→ **4a**–**4g**)[1]) it became evident that the reactions with small-to-medium sized ketones (ring size 5–8) was complete within 4 h, while large-ring ketones (ring size 10–15) require a reaction time of 24 h [13]. Workup of the reaction mixtures with cyclodecanone and cyclododecanone already after 4 h at ambient temperature afforded a mixture of the corresponding *O*-2′- and *O*-3′-half acetals **8a** and **8b**, respectively. This was evidenced

[1]) Cyclic ketal ring size = $n+1$; *e.g.*, 2′,3′-*O*-cycloheptane-1,1-diyl-5-fluorouridine (**4c**): $n=6$.



8a



8b

by the appearance of two sets of ^{1}H- and ^{13}C-NMR signals, both for the glyconic and the side-chain atoms, but not for the 5-fluorouracil atoms. The appearance of two 5′-OH *triplet*s at δ(H) 5.20 and 5.15 ppm indicated a half-acetal formation at both secondary OH groups.

At this point, it is also worthy to be mentioned that, in some cases, TLC inspection of the aqueous phase during workup of the corresponding reaction mixtures by partition between $CHCl_3$ and H_2O, traces of nucleolipid products could be detected. This points to the formation of micelles or liposomes of yet unknown structure which are back-extracted into the aqueous layer.

All novel compounds were characterized by ^{1}H- and ^{13}C-NMR, and UV spectroscopy, as well as by elemental analysis. ^{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). Moreover, compound **5a** was characterized by an X-ray-analysis (*Fig. 1*), the details of which will be published later[2]).

From the NMR spectra, it can be seen in all cases that the CH_2 or CH groups adjacent to the prochiral (or *pseudo*chiral) acetal C-atom (H–C(α') and H–C(α)) resonate at different chemical shifts.

The reason for this has been explained in detail in the preceding publication [13]. Inspection of the NMR spectra of all cyclic ketals, **4a**–**4g**, reveals now that the ^{13}C-NMR chemical shift differences of C(α') and C(α) ($\Delta\delta$) is influenced by the size of the spiro-linked ketal ring (*Fig. 2*). A comparison with the data presented in *Table 2* shows that the highest $\Delta\delta$ values (ring size 8 and 10) are found for those compounds with the highest ring tension as well as with the lowest acid stability of the ketal ring.

Next, we performed ketalizations of the nucleoside **2a** with ethyl levulinate as well as with 4-oxopentyl 4-methylbenzoate generating new stereogenic centers at the corresponding quaternary acetal C-atoms. The implication of these reactions was the preparation of two novel 5-fluorouridine derivatives which can be converted to compounds carrying different functional groups, *i.e.*, either a OH or a COOH group, at the end of the side chain upon saponification. Such derivatives may be used for covalent

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[2]) The X-ray-analysis was performed by Prof. Dr. *Hans Reuter*, Inorganic Chemistry/Structure Chemistry, Institute of Chemistry, University of Osnabrück, Germany. Experimental details will be published elsewhere.

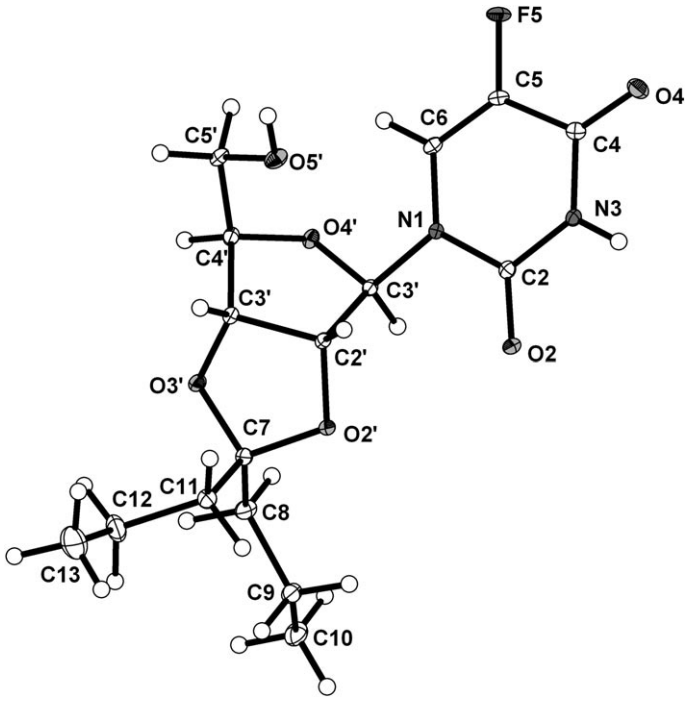

Fig. 1. *Ball-and-stick model of* **5a** *with the atomic numbering scheme used; with the exception of the H-atoms, which were represented by use of spheres with a common isotropic radius, all other atoms were represented as thermal displacement ellipsoids* (one octant: O-atom = grey, F-atom = white;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

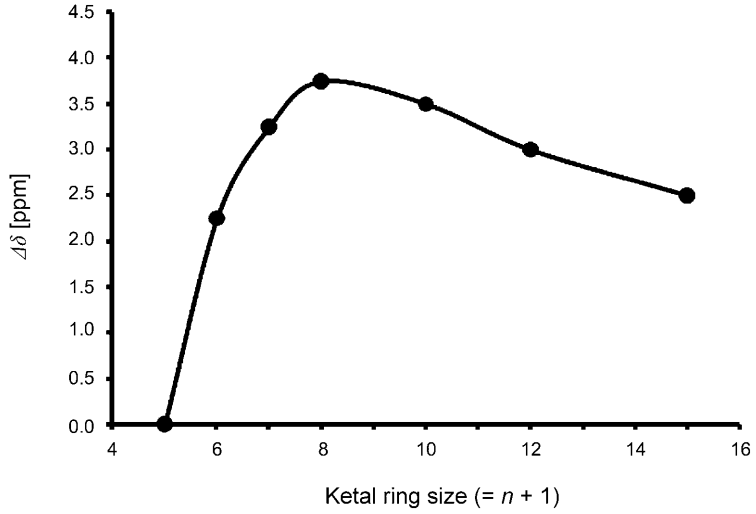

Fig. 2. *^{13}C-NMR Chemical shift difference* ($\Delta\delta$) *of C(α′) and C(α) of the cyclic ketals* **4a** – **4g** *as a function of the ring size.*

Table 1. *Calculated log* P, *Parachor, and Amphiphilic Ratio Values of 5-Fluorouridine Derivatives, as Well as of Cyclic Ketone Hydrates*

Compound	Calc. log *P* of **2**–**7**	Calc. log *P* of the corresponding ketone hydrates	Calc. parachor of **2a** and of the ketone hydrates [cm^3]	Amphiphilic ratio[a])
2a	−1.34 ± 0.46	–	452.5 ± 6.0	–
4a	+1.41 ± 0.67	−0.37 ± 0.26	218.0 ± 4.0	+7.5
4b	+1.97 ± 0.67	+0.19 ± 0.26	258.0 ± 4.0	−12.4
4c	+2.53 ± 0.67	+0.76 ± 0.26	298.1 ± 4.0	−2.7
4d	+3.10 ± 0.67	+1.36 ± 0.26	338.1 ± 4.0	−1.3
4e	+4.23 ± 0.67	+2.45 ± 0.26	418.2 ± 4.0	−0.6
4f	+5.36 ± 0.67	+3.58 ± 0.26	498.3 ± 4.0	−0.34
4g	+7.05 ± 0.67	+5.27 ± 0.26	618.4 ± 4.0	−0.19
5a	+2.62 ± 0.56	+0.90 ± 0.37	339.2 ± 4.0	−1.98
5b	+1.05 ± 0.58	+0.06 ± 0.63	363.9 ± 4.0	−27.8
5c	+3.70 ± 0.64	+1.81 ± 0.40	537.4 ± 4.0	−0.62
6	+2.81 ± 0.68	+1.03 ± 0.27	355.6 ± 4.0	−1.66
7a–**7d**	+1.82 ± 0.67	+0.05 ± 0.27	266.8 ± 4.0	−45.5

[a]) The amphiphilic ratio is defined as the ratio of the (log $P \cdot$ parachor) – value[3]) of the hydrophilic head group 5-fluorouridine (**2a**) divided by the (log $P \cdot$ parachor) – value of the lipophilic hydrate (= geminal diol) of the corresponding ketone, and it characterizes the balance of hydrophilicity and lipophilicity within the amphiphile.

coupling of 5-fluorouridine either to polymeric carriers or to a variety of reporter molecules.

Earlier, it had been shown that reaction of inosine with ($\omega - 1$)-keto esters such as ethyl levulinate or unsymmetrical ketones such as pentan-2-one leads to *O*-2′,3′-ketals with predominant or even exclusive formation of the (*R*)-configuration at the newly formed stereogenic center [18–22] (the (*R*)- and (*S*)-notation in this manuscript refers always to the configuration at the stereogenic center of the ketal moiety). Later, we reported that, in contrast to these almost stereoselective ketalizations, a reaction of inosine with 4-oxopentyl 4-methylbenzoate afforded both diastereoisomers ((*R*) and (*S*)) in nearly equal amounts [23]. TLC Monitoring of the ketalization of 5-fluorouridine (**2a**) and the NMR spectra of the products now revealed that the reaction with ethyl levulinate gave predominantly the (*R*)-diastereoisomer accompanied by *ca.* 30% of the (*S*)-isomer (assessed from an integration of the Me resonances of the corresponding ^{1}H-NMR spectrum). The diasteroisomers were separated by repeated silica-gel column chromatography. The ketalization of **2a** with 4-oxopentyl 4-methylbenzoate under the same reaction conditions as described above also gave a diastereoisomeric mixture containing 20% of the (*S*)-diastereoisomer which could be also separated by repeated silica-gel column chromatography. The results presented here and earlier imply that the ketalization reactions of β-D-ribonucleosides with unsymmetrical ketones are stereochemically difficult, and that the ratio of the diastereoisomers depends on both the nature of the ketone and that of the nucleoside.

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[3]) Parachor = $\gamma^{1/4} \cdot M/d$ with γ, surface tension; M, molar mass; d, density.

2.2. *Lipophilicity and Acidic Stability.* The lipophilicity of the novel hydrophobic nucleoside derivatives was characterized by two ways: *i*) log *P* values of the compounds were calculated (*Table 1*; see *Exper. Part*) and compared with those of the unmodified nucleoside **2a**, *ii*) the chromatographic mobilities of the compounds were determined in terms of retention times (t_R [min]) by *RP-18* HPLC. *Figs. 3–5* show *i*) a chromatographic profile of a mixture of compounds **4a**–**4g** (*Fig. 3*) as well as graphs displaying *ii*) the log *P* (*Fig. 4*), and *iii*) the t_R values (*Fig. 5*) as a function of the number of CH_2 groups of the cyclic ketal groups. The last row of *Table 1* lists the amphiphilic ratios of the novel nucleolipids of 5-fluorouridine. It characterizes the balance of hydrophilicity and lipophilicity within the amphiphile, and is defined by the ratio of the (log *P*· parachor) – value[3]) of the hydrophilic head group 5-fluorouridine (**2a**) devided by the (log *P*· parachor) – value of the lipophilic hydrate (= geminal diol) of the corresponding ketone [24].

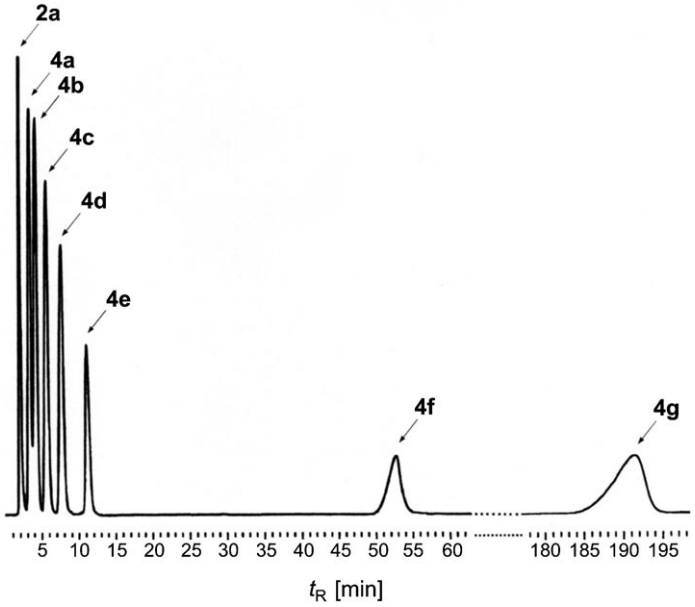

Fig. 3. RP-18 *HPLC Elution profile of a mixture of compounds* **4a**–**4g** (for details, see *Exper. Part.*).

As can be seen, the calculated log *P* (*Table 1* and *Fig. 4*) values increase linearly with the number of CH_2 groups; the retention times of the cyclododecanone and the cyclopentadecanone derivatives, **4f** and **4g**, however, are significantly longer than expected and point to a particular physicochemical behavior of such derivatives which will be the subject of a later contribution. These results are in line with the finding that the large-ring ketals are highly toxic in an MTT (= 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide) assay (*Table 2*).

Acid stability was determined by incubating compounds **4a**–**4g** as well as **5a**, for comparison, (2 mg, each) in 1N aqueous HCl/MeCN 1:1 (*v*/*v*), neutralization with

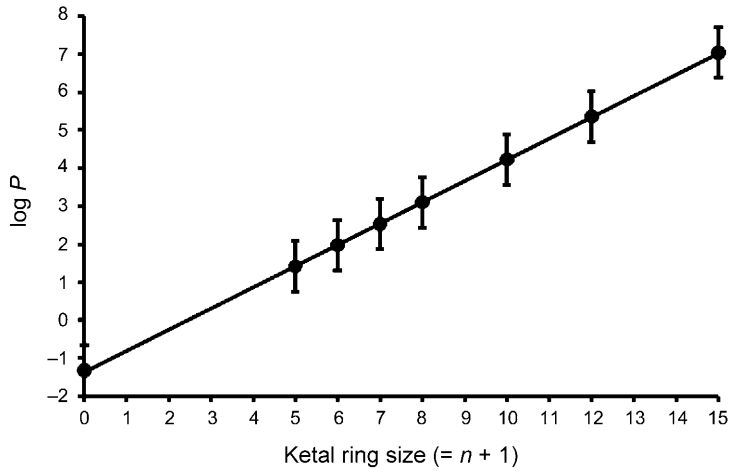

Fig. 4. *log* P *Values of the cyclic ketals* **4a**–**g** *as a function of the ring size*

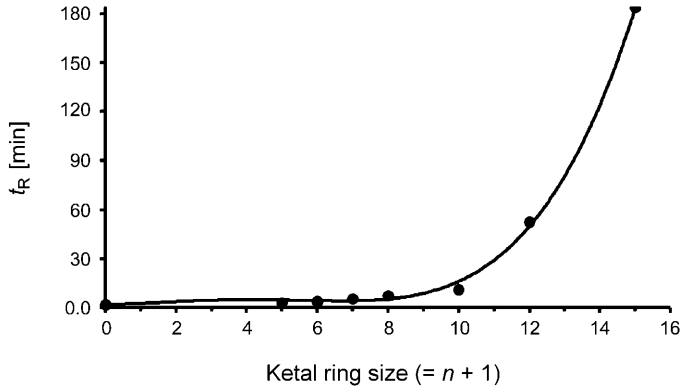

Fig. 5. *Retention times* (t_R [min]) *of the cyclic ketals* **4a**–**4c** *as a function of the ring size* (for details, see *Exper. Part.*)

Et_3N, and subsequent *RP-18* HPLC analysis as described in the *Exper. Part*. The half-life values were calculated graphically from plots of the peak integrals of both the residual ketals and 5-fluorouridine (**2a**) *vs.* reaction time. From all chromatographic profiles, it can be clearly seen that only the nucleoside **2a** and no 5-fluorouracil (**1**) is formed upon hydrolysis. Inspection of the data listed in *Table 2* shows that, within the series of cyclic ketals **4a**–**4g**, acidic stability islands exist for the cyclohexanone and the cyclododecanone derivatives.

It is recommended to compare our results (reaction time, yield, and acidic stability), particularly for the reactions of various cycloketones to the corresponding cycloketals, **4a**–**4g**, with old pioneering findings of *Ruzicka et al.* [25], as well as of *K. Ziegler* and *R. Aurnhammer* [26] concerning '*die Bildungstendenz cyclischer Verbindungen*' and about the '*relative Bildungsleichtigkeit, die relative Beständigkeit und den räumlichen Bau der gesättigten Kohlenstoffringe*' (from acyclic precursors).

Table 2. *Ring Tension* (E_S) *of the Spiro-Linked Ketal Rings of Compounds* **4a**–**4g** *as Well as of Compound* **5a**, *Half-Life Values* τ *of the Ketal Rings in* 1N *aq. HCl/MeCN 1:1, and Toxicity of the Compounds in an MTT Assay*

Ring size	Ring tension (E_S) [kJ/mol]	τ [min]	Toxicity in an MTT assay
5	27.2	24	neutral
6	0.4	540	neutral
7	26.8	10	neutral
8	41.8	15	neutral
10	50.3	76	n.d.
12	10.0	1260	high toxicity
15	0.0	340	n.d.[a])
Heptan-4-one	–	130	neutral

[a]) n.d.: Not determined.

The results presented in this article provide the synthetic basis for a broader study aiming at the physicochemical behavior of the compounds described, *e.g.*, their interaction with biological bilayers as well as at the biomedical application of nucleolipids [27] carrying pharmacologically active nucleosides such as 5-fluorouridine.

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Experimental Part

General. All chemicals were purchased from *Sigma-Aldrich* (D-Deisenhofen) or from *TCI – Europe* (B-Zwijndrecht). Solvents were of laboratory grade and distilled before use. TLC: aluminum sheets, silica gel (SiO_2) *60* F_{254}, 0.2-mm layer (*Merck*, Germany). M.p.: *Büchi SMP-20*; uncorrected. UV Spectra: *Cary 1E* spectrophotometer (*Varian*, D-Darmstadt); λ_{max} (log ε) in nm. NMR Spectra: *AMX-500* spectrometer (*Bruker*, D-Rheinstetten) at 500.14 (^{1}H) and 125.76 (^{13}C) MHz; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. Elemental analyses (C, H, N): *VarioMICRO* instrument (Fa. *Elementar*, D-Hanau) with crystallized compounds. log *P* and parachor values were calculated using the program suite *ChemSketch* (version 12.0; *Advanced Chemistry Developments Inc.*, Toronto, Canada, http://www.acdlabs.com). A quant. yield means that, in repeated experiments, the yield of almost pure material was always higher than 95% before crystallization.

RP-18 HPLC and Acid Stability Measurements of Compounds **4a**–**4g**. *RP-18* HPLC of **4a**–**4g** was carried out on a 250 × 4 mm *RP-18* column (*Merck*, Germany) on a *Merck-Hitachi* HPLC apparatus with one pump (*Model 655A-12*) connected with a proportioning valve, a variable wavelength monitor (*Model 655 A*), a controller (*Model L-5000*), and an integrator (*Model D-2000*). Solvent: MeCN/0.1M $Et_3NH^+ \cdot AcO^-$ 35:65 (pH 7.0). The mixture, including the nucleoside **2a**, was prepared by dissolving each crystalline nucleolipid as well as **2a** (2 mg, each) in MeCN (2 ml, each). From the **2a** soln., an aliquot of 50 µl and aliquots of 100 µl (each) of the nucleolipid solns. were taken and mixed. From this mixture, 100 µl aliquots were injected onto the HPLC column.

Determination of the acid stability of the ketals was performed by incubation of appropriate amounts of compounds **4a**–**4g** (2 mg, each) in 1N aq. HCl/MeCN 1:1 (2 ml). Aliquots (100 µl) were taken after various times and neutralized by addition of Et_3N/MeCN 1:5 (200 µl). Aliquots (100 µl) were then taken and submitted to *RP18* analysis as described above. Only in case of compounds **4f** and **4g**, the solvent was changed to MeCN/0.1M $Et_3NH^+ \cdot AcO^-$ 65:35 because of a lower t_R value of the residual ketals (7–8 min).

*2′,3′-*O*-Cycloheptane-1,1-diyl-5-fluorouridine* (*= 5-Fluoro-1-[(3a′*R*,4′*R*,6′*R*,6a′*R*)-3a′,4′,6′,6a′-tetrahydro-6′-(hydroxymethyl)spiro[cycloheptane-1,2′-furo[3,4-*d*][1,3]dioxol]-4′-yl]pyrimidine-2,4(1*H*,3*H*)-dione*; **4c**). Anh. *5-fluorouridine* (**2a**; 1 g, 3.82 mmol, dried for 48 h at 75° over $CaCl_2$ under high vacuum) was dissolved in anh. DMF, and cycloheptanone (0.9 ml, 7.63 mmol), $CH(OEt)_3$ (1 ml, 5.73 mmol), and 4M HCl in 1,4-dioxane (1.7 ml) were added. After stirring for 4 h at r.t., the mixture was partitioned between $CHCl_3$ (350 ml) and a sat. aq. $NaHCO_3$ soln. The org. layer was washed with H_2O (350 ml), dried (Na_2SO_4), and filtered. After evaporation of the solvents on a rotary evaporator, DMF was removed under high vacuum at 60° (24 h). The residue was crystallized from $CHCl_3$/acetone 5:1 at 4° to give **4c** (1.2 g, 88%). Colorless needles. M.p. 188°. R_f ($CHCl_3$/MeOH 9:1) 0.5. UV (MeOH): 265 (12,500). ^{1}H-NMR ((D$_6$)DMSO): 11.85 (*s*, NH); 8.17 (*d*, ^3J(F, H–C(6)) = 7.0, H–C(6)); 5.83 (*d*, $^3J(1',2') = 1.3$, H–C(1′)); 5.17 (*t*, ^3J(HO–C(5′),CH_2(5′)) = 5.0, HO–C(5′)); 4.84 (*dd*, $^3J(2',1') = 1.3$, $^3J(2',3') = 6.0$, H–C(2′); 4.72 (*dd*, $^3J(3',2') = 6.5$, $^3J(3',4') = 3.5$, H–C(3′)); 4.09 (*Ψdd*, $^3J(4',3') = 3.0$, $^3J(4',5') = 7.0$, H–C(4′)); 3.62 (*m*, $J_{AB} = -12.0$, CH_2(5′)); 1.93 (*m*, 2 H_{endo}–C(α′)); 1.73 (*m*, 2 H–C(α,*exo*)); 1.53 (*s*, 2 H_{endo}–C(β′), 2 H–C(γ), 2 H–C(γ′)); 1.44 (*m*, 2 H_{exo}–C(β)). ^{13}C-NMR ((D$_6$)DMSO): 157.00 (*d*, ^2J(C(4),F) = 26.1, C(4)); 148.97 (C(2)); 139.42 (*d*, ^1J(C(5),F) = 230.0, C(5)); 125.79 (*d*, ^2J(C(6),F) = 34.6, C(6)); 117.57 (C(acetal)); 90.85 (C(1′)); 86.42 (C(4′)); 83.40 (C(2′)); 80.04 (C(3′)); 61.18 (C(5′)); 39.75 (C(α′)); 36.54 (C(α)); 28.099 (C(γ′)); 27.934 (C(γ)); 21.71 (C(β′)); 21.19 (C(β)). Anal. calc. for $C_{16}H_{21}FN_2O_6$ (356.35): C 53.93, H 5.94, N 7.86; found: C 53.86, H 5.94, N 7.83.

*2′,3′-*O*-Cyclooctane-1,1-diyl-5-fluorouridine* (*= 5-Fluoro-1-[(3a′*R*,4′*R*,6′*R*,6a′*R*)-3a′,4′,6′,6a′-tetrahydro-6′-(hydroxymethyl)spiro[cyclooctane-1,2′-furo[3,4-*d*][1,3]dioxol]-4′-yl]pyrimidine-2,4(1*H*,3*H*)-dione*; **4d**). Anh. **2a** (1 g, 3.82 mmol) was reacted with cyclooctanone (1 g, 7.92 mmol), and the mixture was worked up as described for **4c**. Yield (quant.). Colorless needles ($CHCl_3$). M.p. 166°. R_f ($CHCl_3$/MeOH 9:1) 0.4. UV (MeOH): 266 (13,500). ^{1}H-NMR ((D$_6$)DMSO): 11.86 (*s*, NH); 8.17 (*d*, ^2J(H–C(6),F) = 7.0, H–C(6)); 5.84 (*s*, $^3J(1',2') = 1.4$, H–C(1′)); 5.19 (*t*, ^3J(HO–C(5′), H–C(5′)) = 5.0, HO–C(5′)); 4.86 (*dd*, $^3J(2',1')) = 1.7$, $^3J(2',3') = 6.3$, H–C(2′)); 4.74 (*dd*, $^3J(3',2') = 6.2$, $^3J(3',4') = 3.4$, H–C(3′)); 4.09 (*dt*, $^3J(4',3') = 3.7$, $^3J(4',5') = 3.6$, H–C(4′)); 3.64–3.57 (*m*, $J_{AB} = -12.0$, CH_2(5′)); 1.92 (*m*, 2 H_{endo}–C(α′)); 1.73 (*m*, 2 H_{exo}–C(α)); 1.60 (*m*, 2 H_{endo}–C(β′)); 1.50 (*m*, 2 H_{exo}–C(β), 2 H–C(γ), 2 H–C(γ′), 2 H–C(δ)). ^{13}C-NMR ((D$_6$)DMSO): 157.0 (*d*, ^2J(C(4), F) = 26.3, C(4)); 148.97 (C(2)); 139.4 (*d*, ^1J(C(5),F) = 230.6, C(5)); 125.85 (*d*, ^2J(C(6), F) = 34.6, C(6)); 117.12 (C(acetal)); 90.97 (C(1′)); 86.58 (C(4′)); 83.50 (C(2′)); 80.07 (C(3′)); 61.19 (C(5′)); 36.20 (C(α′)); 32.49 (C(α)); 27.56 (C(γ′)); 27.08 (C(γ)); 23.00 (C(δ)); 21.76 (C(β′)); 21.54 (C(β)). Anal. calc. for $C_{17}H_{23}FN_2O_6$ (370.37): C 55.13, H 6.26, N 7.56; found: C 55.20, H 6.30, N 7.51.

*2′,3′-*O*-Cyclodecane-1,1-diyl-5-fluorouridine* (*= 5-Fluoro-1-[(3a′*R*,4′*R*,6′*R*,6a′*R*)-3a′,4′,6′,6a′-tetrahydro-6′-(hydroxymethyl)spiro[cyclodecane-1,2′-furo[3,4-*d*][1,3]dioxol]-4′-yl]pyrimidine-2,4(1*H*,3*H*)-dione*; **4e**). Anh. **2a** (1 g, 3.82 mmol) was reacted with cyclodecanone (1.2 ml, 7.63 mmol) as described for **4c**, but for a period of 24 h. The mixture was partitioned between $CHCl_3$ (175 ml) and an aq. sat. $NaHCO_3$ soln. (50 ml). The org. layer was washed with H_2O (3 × 100 ml), whereby a white precipitate, formed at the liquid–liquid interface, was transferred into the org. phase, where it went into soln. Oily material, adhering to the inner glass wall of the separating funnel, was purged into the org. phase using $CHCl_3$. The last two aq. layers were back-extracted with $CHCl_3$ (25 ml). All org. layers were combined, checked by TLC, and, in case of the appearance of further impurities, again washed with H_2O (175 ml). After drying (Na_2SO_4) and filtration of the org. phase, the solvents were evaporated, and DMF was removed under high vacuum (65°, 24 h). The residual solid material was submitted to flash-chromatography (FC; SiO_2 column: 6 × 10 cm, $CHCl_3$/MeOH 95:5, 0.2 bar). The main fractions were pooled, and the solvent was evaporated to dryness. Compound **4e** was crystallized from $CHCl_3$ at 4° (1.47 g; 95%). Colorless stars. M.p. 184°. R_f ($CHCl_3$/MeOH 9:1) 0.5. UV (MeOH): 266 (12,600). ^{1}H-NMR ((D$_6$)DMSO): 11.85 (br. *s*, NH); 8.17 (*d*, ^3J(H–C(6),F) = 10.0, H–C(6)); 5.83 (*d*, $^3J(1',2') =$

2.0, H–C(1′)); 5.16 (*t*, ^3J(HO–C(5′), H–C(5′)) = 5.0, HO–C(5′)); 4.87 (*dd*, ^3J(2′,1′)) = 2.5, ^3J(2′,3′) = 6.0, H–C(2′)); 4.74 (*dd*, ^3J(3′,2′) = 6.0, ^3J(3′,4′) = 3.2, H–C(3′)); 4.09 (*m*, ^3J(4′,3′) = 3.5, H–C(4′)); 3.66–3.55 (*m*, J_{AB} = –12.0, CH_2(5′)); 1.88 (*m*, 2 H_{endo}–C(α′)); 1.72 (*m*, 2 H_{exo}–C(α)); 1.60 (*m*, 2 H_{endo}–C(β′)); 1.55–1.38 (*m*, 6 CH_2). ^{13}C-NMR ((D$_6$)DMSO): 157.0 (*d*, ^2J(C(4),F) = 26.3, C(4)); 148.92 (C(2)); 139.88 (*d*, ^1J(C(5),F) = 230.4, C(5)); 125.85 (*d*, ^2J(C(6),F) = 34.8, C(6)); 117.67 (C(acetal)); 90.96 (C(1′)); 86.58 (C(4′)); 83.54 (C(2′)); 80.15 (C(3′)); 61.20 (C(5′)); 33.955 (C(α′)); 30.504 (C(α)); 25.62, 24.97, 24.592, 22.738, 22.599, 21.106, 21.036 (7 CH_2). Anal. calc. for $C_{19}H_{27}FN_2O_6 \cdot 0.1$ DMF (405.74): C 56.25, H 6.71, N 6.90; found: C 56.55, H 6.82, N 6.90.

*2′,3′-*O*-Cyclododecane-1,1-diyl-5-fluorouridine* (*= 5-Fluoro-1-[(3a′*R*,4′*R*,6′*R*,6a′*R*)-3a′,4′,6′,6a′-tetrahydro-6′-(hydroxymethyl)spiro[cyclododecane-1,2′-furo[3,4-*d*][1,3]dioxol]-4′-yl]pyrimidine-2,4-(1*H*,3*H*)-dione*; **4f**). Anh. **2a** (1 g, 3.82 mmol) was reacted with cyclododecanone (1.4 g, 7.63 mmol), and the mixture was worked up as described for **4e**. Upon removal of DMF under high vacuum at 65°, non-reacted cyclododecanone was simultaneously sublimated off at 50°. Crystallization of the fluffy residue from $CHCl_3$ at 4° gave **4f** (1.03 g, 63%). Thin colorless needles. M.p. 231°. R_f ($CHCl_3$/MeOH 9:1) 0.5. UV (MeOH): 265 (12,500). ^{1}H-NMR ((D$_6$)DMSO): 11.86 (*s*, NH); 8.17 (*d*, ^3J(H–C(6),F) = 10.0, H–C(6)); 5.84 (*d*, ^3J(1′,2′) = 2.4, H–C(1′)); 5.17 (*t*, ^3J(HO–C(5′), H–C(5′)) = 5.1, HO–C(5′)); 4.88 (*dd*, ^3J(2′,1′)) = 2.7, ^3J(2′,3′) = 6.2, H–C(2′)); 4.75 (*dd*, ^3J(3′,2′) = 6.2, ^3J(3′,4′) = 3.3, H–C(3′)); 4.10 (*m*, ^3J(4′,3′) = 3.7, H–C(4′)); 3.65–3.58 (*m*, J_{AB} = –12.0, CH_2(5′)); 1.74 (*m*, 2 H_{endo}–C(α′)); 1.58 (*m*, 2 H_{exo}–C(α)); 1.45 (*m*, 2 H_{endo}–C(β′)); 1.33–1.32 (*m*, 8 CH_2). ^{13}C-NMR ((D$_6$)DMSO): 156.95 (*d*, ^2J(C(4),F) = 26.3, C(4)); 148.91 (C(2)); 139.87 (*d*, ^1J(C(5),F) = 229.6, C(5)); 125.80 (*d*, ^2J(C(6),F) = 34.8, C(6)); 117.07 (C(acetal)); 90.90 (C(1′)); 86.49 (C(4′)); 83.40 (C(2′)); 80.04 (C(3′)); 61.15 (C(5′)); 33.47 (C(α′)); 30.46 (C(α)); 25.66, 25.54, 25.37, 21.93, 21.71, 21.57, 19.79, 19.68 (9 CH_2). Anal. calc. for $C_{21}H_{31}FN_2O_6$ (426.48) · 0.15 $CHCl_3$: C 56.76, H 7.03, N 6.30; found: C 56.56, H 7.10, N 6.34.

*2′,3′-*O*-Cyclopentadecane-1,1-diyl-5-fluorouridine* (*= 5-Fluoro-1-[(3a′*R*,4′*R*,6′*R*,6a′*R*)-3a′,4′,6′,6a′-tetrahydro-6′-(hydroxymethyl)spiro[cyclopentadecane-1,2′-furo[3,4-*d*][1,3]dioxol]-4′-yl]pyrimidine-2,4(1*H*,3*H*)-dione*; **4g**). Anh. **2a** (1 g, 3.82 mmol) was reacted with cyclopentadecanone (1.72 g, 7.64 mmol) for 21 h, and the mixture was worked up as described for **4e**. Upon removal of DMF under high vacuum at 65°, non-reacted cyclopentadecanone was simultaneously sublimated off. Crystallization of the fluffy residue from $CHCl_3$ at 4° gave **4g** as thin colorless needles ($CHCl_3$) without any intensive characteristic scent. Yield (quant.). M.p. 208°. R_f ($CHCl_3$/MeOH 9:1) 0.7. UV (MeOH): 266 (12,400). ^{1}H-NMR ((D$_6$)DMSO): 11.85 (*s*, NH); 8.16 (*d*, ^3J(H–C(6),F) = 10.0, H–C(6)); 5.84 (*d*, ^3J(1′,2′) = 2.0, H–C(1′)); 5.15 (*t*, ^3J(HO–C(5′), H–C(5′)) = 4.5, HO–C(5′)); 4.88 (*dd*, ^3J(2′,1′)) = 2.5, ^3J(2′,3′) = 6.0, H–C(2′)); 4.75 (*dd*, ^3J(3′,2′) = 6.0, ^3J(3′,4′) = 3.2, H–C(3′)); 4.09 (*m*, ^3J(4′,3′) = 4.0, H–C(4′)); 3.64–3.54 (*m*, J_{AB} = –12.0, CH_2(5′)); 1.69 (*t*, ^3J(H_{endo}–C(α′), H_{endo}–C(β′)) = 6.5, 2 H_{endo}–C(α′)); 1.54 (*t*, ^3J(H_{exo}–C(α), H_{exo}–C(β)) = 6.5, 2 H_{exo}–C(α)); 1.37–1.24 (*m*, 12 CH_2). ^{13}C-NMR ((D$_6$)DMSO): 157.0 (*d*, ^2J(C(4),F) = 26.5, C(4)); 149.0 (C(2)); 140.00 (*d*, ^1J(C(5),F) = 230.6, C(5)); 125.90 (*d*, ^2J(C(6),F) = 34.0, C(6)); 116.70 (C(acetal)); 90.98 (C(1′)); 86.60 (C(4′)); 83.55 (C(2′)); 80.13 (C(3′)); 61.20 (C(5′)); 36.57 (C(α′)); 34.26 (C(α)); 2 × 26.94, 26.39, 26.38, 26.29, 3 × 26.08, 2 × 26.01, 22.07, 22.00 (12 CH_2). Anal. calc. for $C_{24}H_{37}FN_2O_6$ (468.56): C 61.52, H 7.96, N 5.98; found: C 61.40, H 7.78, N 5.89.

*5-Fluoro-1-[(1*S*,2*S*,3a′*R*,4*R*,4′*R*,6′*R*,6a′*R*)-3a′,4′,6′,6a′-tetrahydro-6′-(hydroxymethyl)spiro[bicyclo[2.2.1]heptane-2,2′-furo[3,4-*d*][1,3]dioxol]-4′-yl]pyrimidine-2,4(1*H*,3*H*)-dione* (**7a**), *5-Fluoro-1-[(1*R*,2*R*,3a′*R*,4*S*,4′*R*,6′*R*,6a′*R*)-3a′,4′,6′,6a′-tetrahydro-6′-(hydroxymethyl)spiro[bicyclo[2.2.1]heptane-2,2′-furo[3,4-*d*][1,3]dioxol]-4′-yl]pyrimidine-2,4(1*H*,3*H*)-dione* (**7b**), *5-Fluoro-1-[(1*R*,2*S*,3a′*R*,4*S*,4′*R*,6′*R*,6a′*R*)-3a′,4′,6′,6a′-tetrahydro-6′-(hydroxymethyl)spiro[bicyclo[2.2.1]heptane-2,2′-furo[3,4-*d*][1,3]dioxol]-4′-yl]pyrimidine-2,4(1*H*,3*H*)-dione* (**7c**), *and 5-Fluoro-1-[(1*S*,2*R*,3a′*R*,4*R*,4′*R*,6′*R*,6a′*R*)-3a′,4′,6′,6a′-tetrahydro-6′-(hydroxymethyl)spiro[bicyclo[2.2.1]heptane-2,2′-furo[3,4-*d*][1,3]dioxol]-4′-yl]pyrimidine-2,4(1*H*,3*H*)-dione* (**7d**); *Isomeric Mixture.* Anh. **2a** (1 g, 3.82 mmol) was reacted with norbornan-2-one (0.84 g, 7.64 mmol) for 21 h, and the mixture was worked up as described for **4e**. Upon removal of DMF under high vacuum at 65°, non-reacted norbornan-2-one was simultaneously sublimated off. Crystallization of the fluffy residue from $CHCl_3$ at 4° gave a mixture of **7a**–**7d** (1.27 g, 94%). Thin colorless needles. M.p. 217°. R_f ($CHCl_3$/MeOH 9:1) 0.5. UV (MeOH): 266 (12,400). ^{1}H-NMR ((D$_6$)DMSO): 11.87 (*s*, 4 NH); 8.21–8.18 (*m*, 4 H–C(6)); 5.85–5.83 (*m*, 4 H–C(1′)); 5.21–5.18 (*m*, 4 HO–C(5′)); 4.88–4.85, 4.82–4.78 (2*m*, 4 H–C(2′)); 4.75–4.71, 4.68–4.64 (2*m*, 4 H–C(3′)); 4.17–4.15, 4.13–4.10,

4.09–4.07 (3*m*, 4 H–C(4′)); 3.65–3.58 (*m*, 4 CH_2(5′)); 2.06–1.18 (several *m*, 10 H, 4 norbornyl). ^{13}C-NMR ((D$_6$)DMSO): 157.03 (*d*, ^2J(C(4),F) = 26.4, 4 C(4)); 148.99, 148.97 (2*s*, 4 C(2)); 139.92 (2*d*, ^1J(C(5),F) = 230.5, 4 C(5)); 126.34–125.69 (3*d*, ^2J(C(6),F) = 34.0, 4 C(6)); 120.33, 120.25, 119.89, 119.81 (4*s*, 4 C(acetal)); 91.72, 90.85, 90.78, 90.58 (4*s*, 4 C(1′)); 86.75, 86.33, 86.25, 85.99 (4*s*, 4 C(4′)); 83.79, 83.72, 83.32, 83.13 (4*s*, 4 C(2′)); 80.69, 80.64, 80.22, 79.89 (4*s*, 4 C(3′)); 61.36, 61.35, 61.21, 61.15 (4*s*, 4 C(5′)); 45.41, 43.41, 35.73, 35.09, 35.02, 34.92, 34.79, 30.74 (8*s*, 8 CH(norbornylidene)); 44.58, 44.39, 44.35, 43.02, 42.99, 37.24, 37.12, 37.05, 36.96, 27.60, 27.55, 26.63, 23.65, 21.86, 21.83, 21.29 (16*s*, 16 CH_2(norbornylidene)). Anal. calc. for $C_{16}H_{19}FN_2O_6$ (354.33): C 54.24, H 5.40, N 7.91; found: C 54.14, H 5.43, N 7.89.

*5-Fluoro-1-[(1′*R*,3′*S*,3a*R*,4*R*,6*R*,6a*R*)-3a,4,6,6a-tetrahydro-6-(hydroxymethyl)spiro[furo[3,4-*d*][1,3]dioxole-2,2′-tricyclo[3.3.1.1^{3,7}]decan]-4-yl]pyrimidine-2,4(1*H*,3*H*)-dione* (**6**). Anh. **2a** (1 g, 3.82 mmol) was reacted with adamantan-2-one (1.15 g, 7.64 mmol) for 22 h, and the mixture was worked up as described for **4e**. Upon removal of DMF under high vacuum at 65°, non-reacted adamantan-2-one was simultaneously sublimated off overnight. Crystallization of the fluffy residue from $CHCl_3$ at 4° gave **6** (1.40 g, 93%). Thin colorless stars. M.p. 239°. R_f ($CHCl_3$/MeOH 9:1) 0.4. UV (MeOH): 266 (12.400). ^{1}H-NMR ((D$_6$)DMSO): 11.85 (*s*, NH); 8.19 (*d*, ^3J(H–C(6),F) = 7.0, H–C(6)); 5.81 (*d*, ^3J(1′,2′) = 2.0, H–C(1′)); 5.18 (*t*, ^3J(HO–C(5′), H–C(5′)) = 5.0, HO–C(5′)); 4.90 (*dd*, ^3J(2′,1′) = 3.0, ^3J(2′,3′) = 6.5, H–C(2′)); 4.78 (*dd*, ^3J(3′,2′) = 6.0, ^3J(3′,4′) = 3.0, H–C(3′)); 4.11 (*Ψq*, ^3J(4′,3′) = 3.0, ^3J(4′,5′) = 3.5, H–C(4′)); 3.66–3.57 (*m*, J_{AB} = –12.0, CH_2(5′)); 2.39 (br. *s*, H_{endo}–C(*α*′)); 2.05–1.62 (*m*, 13 adamantylidene H). ^{13}C-NMR ((D$_6$)DMSO): 157.04 (*d*, ^2J(C(4),F) = 26.4, C(4)); 149.01 (C(2)); 139.95 (*d*, ^1J(C(5),F) = 230.4, C(5)); 125.93 (*d*, ^2J(C(6),F) = 34.7, C(6)); 115.76 (C(acetal)); 91.05 (C(1′)); 86.68 (C(4′)); 83.27 (C(2′)); 80.01 (C(3′)); 61.21 (C(5′)); 37.83 (C(*α*′)); 36.13 (C(*β*′)); 35.12 (C(*α*)); 34.22 (C(*β*), C(*γ*′)); 33.75 (C(*γ*)); 33.68 (C(*ε*)); 25.89 (C(*δ*), C(*δ*′)). Anal. calc. for $C_{19}H_{23}FN_2O_6$ (394.40): C 57.86, H 5.88, N 7.10; found: C 57.67, H 5.85, N 7.08.

5-Fluoro-2′,3′-O*-(1-propylbutylidene)uridine* (= *5-Fluoro-1-[(3a*R*,4*R*,6*R*,6a*R*)-3a,4,6,6a-tetrahydro-6-(hydroxymethyl)-2,2-dipropylfuro[3,4-*d*][1,3]dioxol-4-yl]pyrimidine-2,4(1*H*,3*H*)-dione*; **5a**). Anh. **2a** (1 g, 3.82 mmol) was dissolved in anh. DMF, and heptan-4-one (1.1 ml, 7.64 mmol), $CH(OEt)_3$ (1 ml, 5.73 mmol), and 4M HCl in 1,4-dioxane (2.6 ml) were added. After stirring for 20 h at r.t., the mixture was partitioned between $CHCl_3$ (175 ml) and a sat. aq. $NaHCO_3$ soln. (50 ml). The org. layer was washed with H_2O (175 ml), dried (Na_2SO_4), and filtered. After evaporation of the solvents on a rotary evaporator, DMF was removed under high vacuum at 65° (24 h). The residue was crystallized from $CHCl_3$ to give **5a** (0.92 g, 67%). Colorless needles. M.p. 155°. R_f ($CHCl_3$/MeOH 9:1) 0.4. UV (MeOH): 266 (12,600). ^{1}H-NMR ((D$_6$)DMSO): 11.88 (*s*, NH); 8.15 (*d*, ^3J(H–C(6),F) = 5.0, H–C(6)); 5.81 (*s*, H–C(1′)); 5.18 (*t*, ^3J(HO–C(5′), H–C(5′)) = 5.0, HO–C(5′)); 4.88 (*dd*, ^3J(2′,1′) < 1, ^3J(2′,3′) = 6.5, H–C(2′)); 4.74 (*dd*, ^3J(3′,2′) = 6.5, ^3J(3′,4′) = 3.5, H–C(3′)); 4.08 (*m*, H–C(4′)); 3.57 (*m*, CH_2(5′)); 1.64 (*m*, 2 H_{endo}–C(*α*′)); 1.48 (*m*, 2 H_{exo}–C(*α*)); 1.40–1.32 (*m*, 2 H_{endo}–C(*β*′), 2 H_{exo}–C(*β*)); 0.84 (*t*, 3 H_{endo}–C(*γ*′), 3 H_{exo}–C(*γ*)). ^{13}C-NMR ((D$_6$)DMSO): 157.1 (*d*, ^2J(C(4),F) = 26.4, C(4)); 148.99 (C(2)); 139.0 (*d*, ^1J(C(5),F) = 230.1, C(5)); 126.0 (*d*, ^2J(C(6),F) = 34.0, C(6)); 116.44 (C(acetal)); 91.16 (C(1′)); 86.73 (C(4′)); 83.93 (C(3′)); 80.52 (C(2′)); 61.25 (C(5′)); 38.58 (C(*α*′)); 38.04 (C(*α*)); 17.01 (C(*β*′)); 16.32 (C(*β*)); 14.2 (C(*γ*′), C(*γ*)). Anal. calc. for $C_{16}H_{23}FN_2O_6$ (358.36): C 53.62, H 6.47, N 7.82; found: C 53.39, H 6.44, N 7.53.

2′,3′-O*-[(1*R*)-4-Ethoxy-1-methyl-4-oxobutylidene]-5-fluorouridine* (= *Ethyl 3-[(2*R*,3a*R*,4*R*,6-*R*,6a*R*)-4-(5-Fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3a,4,6,6a-tetrahydro-6-(hydroxymethyl)-2-methylfuro[3,4-*d*][1,3]dioxol-2-yl]propanoate*; **5b**). Anh. **2a** (1 g, 3.82 mmol) was dissolved in dry DMF (15 ml). Ethyl levulinate (1.1 ml, 7.6 mmol), $CH(OEt)_3$ (1 ml, 5.73 mmol), and HCl (4M in dry 1,4-dioxane, 3.4 ml) were then added. The soln. was stored at r.t. for 24 h and then partitioned between $CHCl_3$ (175 ml) and an aq. sat. $NaHCO_3$ soln. (50 ml). The aq. phase was then extracted with $CHCl_3$ (2 × 25 ml), whereby a semi-solid precipitate at the interphase was pooled into the org. layer. The combined org. layers were washed with H_2O, dried (Na_2SO_4), filtered, and evaporated to dryness. The residual slightly yellowish, oily residue (1.38 g, 93%) was flash-chromatographed (SiO_2 *60*, column: 6 × 8 cm, $CHCl_3$/MeOH 95:5, 0.2 bar). The fractions of the main zone were pooled and evaporated to give 1.4 g of (1*R*)- and (1*S*)-**5b** as a slightly yellowish glass. R_f ($CHCl_3$/MeOH 9:1) 0.3/0.35. UV (MeOH): 265 (12,400). Repeated FC (SiO_2 *60*, column: 6 × 20 cm, $CHCl_3$/MeOH 95:5, 0.2 bar) gave the separated diastereoisomers. Anal. calc. for $C_{16}H_{21}FN_2O_8$ (388.345): C 49.48, H 5.45, N 7.21; found: C 49.14, H 5.67, N 7.09.

(1R)-**5b**. ^{1}H-NMR ((D$_6$)DMSO): 11.91 (*s*, NH); 8.15 (*d*, ^3J(H–C(6),F) = 7.0, H–C(6)); 5.82 (*d*, ^3J(1′,2′) = 1.5, H–C(1′)); 5.21 (*t*, ^3J(HO–C(5′), H–C(5′)) = 5.0, HO–C(5′)); 4.92 (*dd*, ^3J(2′,1′)) = 3.0, ^3J(2′,3′) = 7.0, H–C(2′)); 4.77 (*dd*, ^3J(3′,2′) = 6.5, ^3J(3′,4′) = 3.5, H–C(3′)); 4.10 (*Ψq*, ^3J(4′,3′) = 3.5, ^3J(4′,5′) = 4.0, H–C(4′)); 4.05 (*q*, ^3J = 7.0, CH$_2$(ester)); 3.61–3.56 (*m*, CH$_2$(5′)); 2.40 (*t*, ^3J = 7.0, CH$_2$–C=O); 2.02 (*t*, ^3J = 7.0, CH$_2$); 1.26 (*s*, Me(acetal)); 1.17 (*t*, ^3J = 7.0, Me(ester)). ^{13}C-NMR ((D$_6$)DMSO): 172.50 (ester C=O); 157.00 (*d*, ^2J(C(4),F) = 26.3, C(4)); 148.93 (C(2)); 139.10 (*d*, ^1J(C(5),F) = 230.5, C(5)); 125.92 (*d*, ^2J(C(6),F) = 34.8, C(6)); 113.69 (C(acetal)); 90.82 (C(1′)); 86.39 (C(4′)); 83.80 (C(2′)); 80.20 (C(3′)); 61.13 (C(5′)); 59.88 (CH$_2$(ester)); 33.32 (*C*H$_2$–C=O); 28.11 (CH$_2$(acetal)); 23.54 (Me(acetal)); 14.02 (Me(ester)).

(1S)-**5b**. ^{1}H-NMR ((D$_6$)DMSO): 11.86 (*s*, NH); 8.16 (*d*, ^3J(H–C(6),F) = 7.2, H–C(6)); 5.83 (*d*, ^3J(1′,2′) = 1.5, H–C(1′)); 5.16 (*t*, ^3J(HO–C(5′), H–C(5′)) = 5.0, HO–C(5′)); 4.89 (*dd*, ^3J(2′,1′)) = 2.5, ^3J(2′,3′) = 6.5, H–C(2′)); 4.76 (*dd*, ^3J(3′,2′) = 6.5, ^3J(3′,4′) = 3.5, H–C(3′)); 4.09–4.09 (*m*, H–C(4′)); 4.04 (*q*, ^3J = 7.0, CH$_2$(ester)) 3.64–3.61 (*m*, CH$_2$(5′)); 2.30 (*t*, ^3J = 7.0, CH$_2$–C=O); 1.86 (*t*, ^3J = 7.0, CH$_2$); 1.44 (*s*, Me(acetal)); 1.20 (*t*, ^3J = 7.0, Me(ester)). ^{13}C-NMR ((D$_6$)DMSO): 172.40 (ester C=O); 157.03 (*d*, ^2J(C(4),F) = 26.3, C(4)); 148.94 (C(2)); 139.89 (*d*, ^1J(C(5),F) = 230.5, C(5)); 125.91 (*d*, ^2J(C(6),F) = 34.6, C(6)); 114.03 (C(acetal)); 91.20 (C(1′)); 86.73 (C(4′)); 84.22 (C(2′)); 80.76 (C(3′)); 61.16 (C(5′)); 59.85 (CH$_2$(ester)); 33.34 (*C*H$_2$–C=O); 28.97 (CH$_2$(acetal)); 24.87 (Me(acetal)); 14.02 (Me(ester)).

5-Fluoro-2′,3′-O-*((1*R*)-1-methyl-4-{[(4-methylphenyl)carbonyl]oxy}butylidene)uridine* (= *3-[(2*R*,3a*R*,4*R*,6*R*,6a*R*)-4-(5-Fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3a,4,6,6a-tetrahydro-6-(hydroxymethyl)-2-methylfuro[3,4-*d*][1,3]dioxol-2-yl]propyl 4-Methylbenzoate, Diastereoisomer Mixture*; **5c**). Anh. **2a** (1.0 g, 3.82 mmol) was dissolved in anh. DMF (15 ml), and 4-oxopentyl 4-methylbenzoate (1.7 g, 7.63 mmol) and CH(OEt)$_3$ (1.0 ml, 5.73 mmol) were added. After addition of 4M HCl in 1,4-dioxane (3.4 ml), the mixture was stirred at r.t. for 24 h. Workup was performed as described for **4e**. A first FC (SiO$_2$ *60*, 6 × 15 cm; CHCl$_3$/MeOH 94:6, 0.2 bar) afforded one main fraction from which a diastereoisomer mixture of **5c** was obtained as a turbid, opalescent foam in 87% (1.54 g) yield after evaporation of the solvent. R_f (CHCl$_3$/MeOH 9:1) 0.6. UV (MeOH): 265 (12,400). Anal. calc. for C$_{22}$H$_{25}$FN$_2$O$_8$ (464.44): C 56.89, H 5.43, N 6.03; found: C 57.01, H 5.73, N 6.06. Repeated FC (SiO$_2$ *60*, column: 6 × 20 cm, CHCl$_3$/MeOH 94:6, 0.2 bar) gave the separated diastereoisomers as turbid, opalescent foams.

(1R)-**5c**. 11.86 (*s*, NH); 8.16 (*d*, ^3J(H–C(6),F) = 7.1, H–C(6)); 7.86 (*d*, ^3J(H, H) = 8.0, 2 arom. H); 7.33 (*d*, ^3J(H, H) = 8.0, 2 arom. H); 5.58 (*d*, ^3J(1′,2′) = 1.5, H–C(1′)); 5.18 (*t*, ^3J(HO–C(5′), H–C(5′)) = 5.0, HO–C(5′)); 4.94 (*dd*, ^3J(2′,1′)) = 2.0, ^3J(2′,3′) = 6.5, H–C(2′)); 4.80 (*dd*, ^3J(3′,2′) = 6.5, ^3J(3′,4′) = 3.5, H–C(3′)); 4.30 (*t*, ^3J = 5.5, CH$_2$); 4.13 (*Ψq*, ^3J(4′,3′) = 3.5, ^3J(4′,5′) = 4.0, H–C(4′)); 3.64–3.56 (*m*, CH$_2$(5′)); 2.38 (*s*, Me(tolyl)); 1.88–1.87 (*m*, 2 CH$_2$); 1.29 (*s*, Me(acetal)). ^{13}C-NMR ((D$_6$)DMSO): 165.69 (ester C=O); 157.05 (*d*, ^2J(C(4),F) = 26.3, C(4)); 148.96 (C(2)); 143.49 (arom. C); 139.88 (*d*, ^1J(C(5),F) = 230.5, C(5)); 129.26, 129.13 (arom. C); 127.12 (arom. C); 125.88 (*d*, ^2J(C(6),F) = 35.0, C(6)); 114.20 (C(acetal)); 91.09 (C(1′)); 86.58 (C(4′)); 83.76 (C(2′)); 80.25 (C(3′)); 64.36 (CH$_2$O); 61.18 (C(5′)); 35.20 (CH$_2$(acetal)); 23.55 (Me(acetal)); 22.80 (CH$_2$); 21.11 (Me(tolyl)).

(1S)-**5c**. 11.86 (*s*, NH); 8.15 (*d*, ^3J(H–C(6),F) = 6.5, H–C(6)); 7.84 (*d*, ^3J(H, H) = 8.0, 2 arom. H); 7.31 (*d*, ^3J(H, H) = 8.0, 2 arom. H); 5.85 (*d*, ^3J(1′,2′) = 1.5, H–C(1′)); 5.17 (br. *s*, HO–C(5′)); 4.91 (*dd*, ^3J(2′,1′)) = 2.6, ^3J(2′,3′) = 6.4, H–C(2′)); 4.79 (*dd*, ^3J(3′,2′) = 6.5, ^3J(3′,4′) = 3.5, H–C(3′)); 4.24 (*t*, ^3J = 5.5, CH$_2$); 4.13 (*Ψq*, ^3J(4′,3′) = 3.5, ^3J(4′,5′) = 4.0, H–C(4′)); 3.64–3.56 (*m*, CH$_2$(5′)); 2.38 (*s*, Me(tolul)); 1.73–1.71 (*m*, 2 CH$_2$); 1.478 (*s*, Me(acetal)). ^{13}C-NMR ((D$_6$)DMSO): 165.66 (ester C=O); 157.11 (*d*, ^2J(C(4),F) = 26.3, C(4)); 148.96 (C(2)); 143.51 (arom. C); 139.88 (*d*, ^1J(C(5),F) = 230.3, C(5)); 129.13, 129.09 (arom. C); 127.09 (arom. C); 125.88 (*d*, ^2J(C(6),F) = 35.0, C(6)); 114.61 (C(acetal)); 91.18 (C(1′)); 86.77 (C(4′)); 84.19 (C(2′)); 80.70 (C(3′)); 64.29 (CH$_2$O); 61.18 (C(5′)); 34.65 (CH$_2$(acetal)); 25.05 (Me(acetal)); 23.42 (CH$_2$)); 21.11 (Me(tolyl)).

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