Synthesis, Structure, and Conformation of 2′,3′-Fused Oxathiane and Thiomorpholine Uridines

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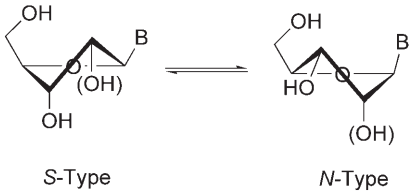
The syntheses of two 2′,3′-fused bicyclic nucleoside analogues, *i.e.*, 1-[(4a*R*,5*R*,7*R*,7a*S*)-hexahydro-5-(hydroxymethyl)-4,4-dioxidofuro[3,4-*b*][1,4]oxathiin-7-yl]pyrimidine-2,4(1*H*,3*H*)-dione (**1a**) and 1-[(4a*S*,5*R*,7*R*,7a*S*)-hexahydro-7-(hydroxymethyl)-1,1-dioxido-2*H*-furo[3,4-*b*][1,4]thiazin-5-yl]pyrimidine-2,4(1*H*,3*H*)-dione (**1b**), are described, the key step being an intramolecular hetero-*Michael* addition. Their structures and conformations, previously solved by X-ray crystallography, were analyzed in more detail, using 1D- and 2D-NMR as well as HR-MS analyses.

Introduction. – 2′,3′-Dideoxy nucleosides, including, *e.g.*, 3′-azido-3′-deoxythymidine (AZT; zidovudine) [1], 2′,3′-dideoxycytidine (ddC, zalcitabine) [2], 2′,3′-dideoxyinosine (ddI, didanosine) [3], and 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T, stavudine) [4], are an important class of antiviral drugs. The mechanism of action of these nucleosides requires their conversion by host cellular kinases into the corresponding triphosphate forms, which then serve as competitive inhibitors for HIV reverse transcriptase and/or as chain terminators due to the lack of a 3′-OH functionality for viral cDNA synthesis [5]. Therefore, a highly potent and selective nucleoside drug candidate should be structurally adaptable to the active sites of both the kinases and the reverse transcriptase, but display minimum affinity to cellular polymerases.

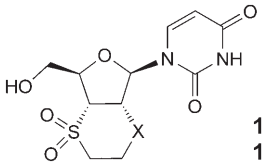
It is known that ribonucleosides predominantly exist in the *N*-type (C(3′)-*endo*) sugar conformation, while deoxyribonucleosides have *S*-type (C(3′)-*exo*) puckering (*Scheme 1*) [6]. A large number of 2′,3′-modified nucleosides have been synthesized and evaluated for their biological activities, revealing that the conformational equilibrium of the sugar moiety is a key factor in terms of biological effects [7]. 2′,3′-Fused bicyclic nucleosides as conformationally restricted sugar-ring analogues have

Scheme 1



been used to probe the conformational requirement of the key enzymes to maximize the therapeutic index of nucleoside-based antiviral agents [7][8].

In our research on the structure–activity relationship of sugar-modified nucleosides, we decided to synthesize and investigate the *S*,*S*-dioxo-1,4-oxathiane- and *S*,*S*-dioxothiomorpholine-fused nucleosides **1a** and **1b**, respectively. In these compounds, the 5′-OH group and the nucleobase are intact for phosphorylation and recognition, respectively. The conformation of the nucleoside moiety should be restricted by fusion at the 2′- and 3′-positions of the furanose ring, especially in the case of an additional six-membered ring (in chair conformation), which could result in a proper balance between the rigidity and flexibility of the sugar puckering. Compound **1b**, with an amino group linked to the 2′-position of the furanose moiety, would be an interesting building block for the synthesis and evaluation of conformationally restricted 2′,5′-linked oligonucleotides in antisense therapy [9].



1a X = O
1b X = NH

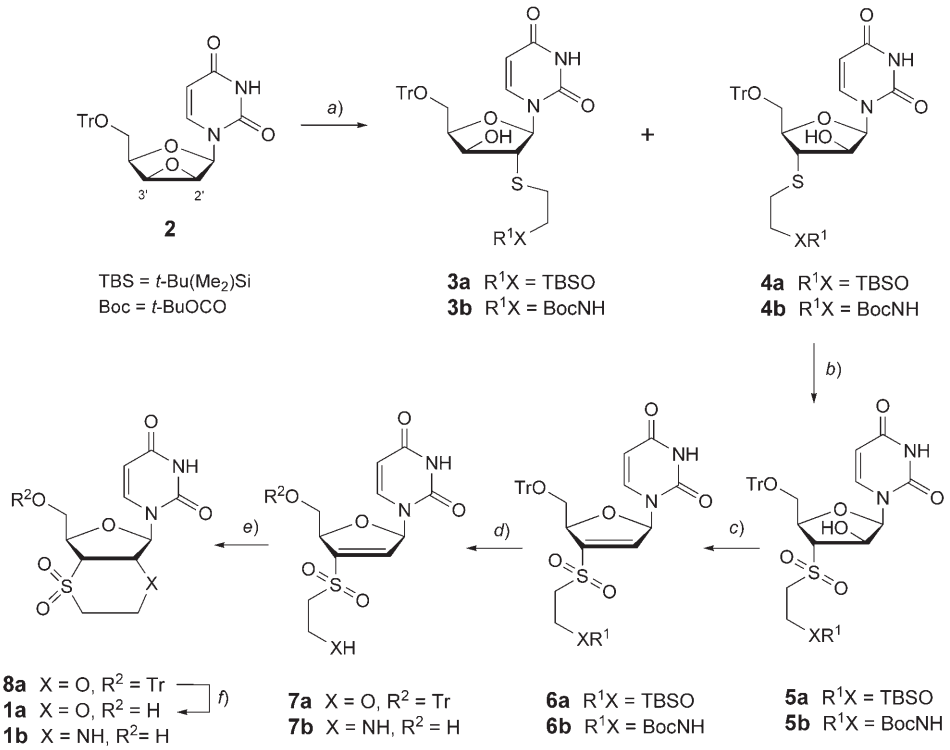
Many methods have been applied for the synthesis of bicyclic nucleosides such as intramolecular nucleophilic substitution [10], ring-closing metathesis [11], 1,3-dipolar addition [12], aldol reaction [13], or *Michael* addition. This latter method (*Michael* addition) has been developed by *Chattopadhyaya et al.* as a powerful means for the synthesis of a large variety of modified nucleosides, including bicyclic nucleosides [14]. Recently, *Pathak et al.* [15] reported the synthesis of 1,4-thiazinane (thiomorpholine)-fused uridine derivatives in 2′,3′-position *via Michael* addition of amines to bisvinylsulfonyl uridine. Intramolecular *Michael* addition has been employed to construct cyclic structures of natural and synthetic compounds, but no such application has been elaborated in the field of nucleoside chemistry [16].

Herein we report the synthesis and conformational properties of the uridine target compounds **1** prepared *via* intramolecular hetero-*Michael* addition to olefinic sulfones.

Results and Discussion. – The synthesis of **1a** is outlined in *Scheme 2* (series **a**). Thus, '2′,3′-*O*-anhydro-5′-*O*-trityl-*lyxo*-uridine' (**2**) [17] was reacted with 2-{[*tert*-butyl(dimethyl)silyl]oxy}ethane-1-thiol ($TBSOCH_2CH_2SH$) in the presence of 1,1,3,3-tetramethylguanidine (TMG) to generate a mixture of the substituted *xylo*- and *arabino*-configured uridines **3a** and **4a**, respectively, which were separated chromatographically to afford the pure compounds in 26 and 57% yield[1]). Next, oxidation of the sulfide **4a** with '*meta*-chloroperpenzoic acid' (MCPBA) in the presence of 10% $NaHCO_3$ as buffer afforded the corresponding sulfone **5a**. Subsequently, elimination of the 2′-OH group was effected by mesylation and, after workup, heating at 40° in pyridine, which resulted in the desired vinylsulfonyl uridine **6a** in 62% yield (over two

[1]) When the OH group of 2-mercaptoethanol was not protected, the regioisomeric products from the ring opening of the epoxide **2** could not be separated [14].

Scheme 2



a) For series **a**: $TBSOCH_2CH_2SH$, DMF, 1,1,3,3-tetramethylguanidine (TMG), 40°, 5 h; 26% of **3a**, 57% of **4a**; for series **b**: $BocNHCH_2CH_2SH$, DMF, TMG, 40°, 5 h; 23% of **3b**, 52% of **4b**. *b*) MCPBA, 10% aq. $NaHCO_3$, CH_2Cl_2, 0°, 2 h; 84% of **5a**, 87% of **5b**. *c*) 1. MsCl, pyridine, 0°, 6 h; 2. pyridine, 40°, 3 h; 62% of **6a**, 66% of **6b** (two steps). *d*) For **8a**: TBAF, THF, r.t., 1 h; 89%; for series **b**: 20% TFA in CH_2Cl_2, r.t., 4 h. *e*) For **1b**: K_2CO_3, MeOH, r.t., 3 h; 64% (two steps). *f*) 80% AcOH, r.t., 3 h; 67%.

steps). Deprotection of the TBS group by treatment with $Bu_4N^+F^-$ (TBAF) in THF led to compound **7a**, which underwent *in situ* cyclization *via* intramolecular *Michael* addition to afford directly **8a**. Finally, detritylation with 80% aqueous AcOH provided the bicyclic target nucleoside **1a** in 67% yield.

The synthesis of **1b** was performed similarly (*Scheme 2*, series **b**). Thus, **2** was attacked by $BocNHCH_2CH_2SH$ in the presence of TMG to afford **3b** and **4b** in 23 and 52% yield, respectively. Compound **4b** was oxidized with MCPBA to give the sulfone **5b**, which was mesylated and eliminated to afford the vinylsulfonyl uridine **6b**. The *tert*-butoxycarbonyl (Boc) and triphenylmethyl (trityl; Tr) protecting groups were then removed simultaneously by treatment with 20% CF_3COOH (TFA) in CH_2Cl_2 to afford the crude product **7b**, which was cyclized in the presence of K_2CO_3 to afford **1b** in 64% yield (over two steps).

The structures of **1a** and **1b** were determined by ^{1}H- and ^{13}C-NMR as well as by HR-ESI-MS studies (see *Exper. Part*), which confirmed the previously reported single-

crystal X-ray-diffraction analyses [18]. The configuration of the six-membered, fused rings were determined by 1D- and 2D-NMR experiments. Based on the NOESY cross-peaks shown in the *Figure*, the two rings in **1** are *cis*-fused and in α-position. Further, as previously reported, both bicyclic nucleoside analogues adopt the 4′-*exo*,3′-*endo* conformation [18]. Selected torsion angles and other conformational parameters of the sugar moiety are presented in the *Table*, based on the X-ray results [18].

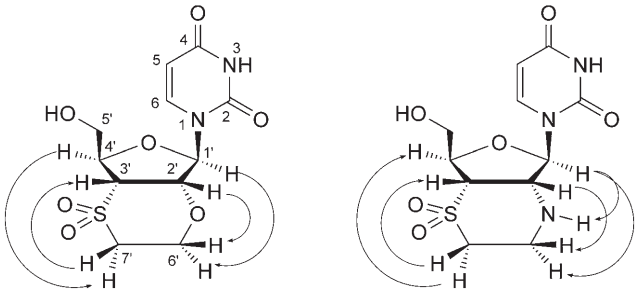


Figure. *Selected NOE correlations for compounds* **1a** *and* **1b**

Table. *Selected Conformational Parameters Determined from the X-Ray Structures of* **1a** *and* **1b**[a]) [18]. All values in degrees (°).

Parameter	**1a**	**1b**
C(4′)–O–C(1′)–C(2′)	– 6.1(3)	– 4.4(3)
O–C(1′)–C(2′)–C(3′)	27.8(2)	28.0(3)
C(1′)–C(2′)–C(3′)–C(4′)	38.0(2)	39.9(2)
C(2′)–C(3′)–C(4′)–O	– 35.3(2)	– 38.2(2)
C(3′)–C(4′)–O–C(1′)	18.5(3)	21.5(3)
C(3′)–C(4′)–C(5′)–O	– 169.8(2)	51.9(4)
O–C(3′)–C(4′)–C(5′)	82.3(2)	77.6(3)
O–C(1′)–N(1)–C(2)	– 163.2(1)	– 160.2(2)
P[b])	36.8(2)	36.9(2)
ν_m[c])	47.5(3)	49.9(3)

[a]) The crystallographic data of **1a** and **1b** have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication numbers CCDC-636232 and -636249, resp. Copies of the data can be obtained, free of charge, at http://www.ccdc.cam.ac.uk/data_request/cif. [b]) Pseudorotational phase angle. [c]) Puckering amplitude.

In conclusion, we have demonstrated that the intramolecular *Michael* addition of vinylsulfonyl nucleosides is a versatile method for the construction of 2′,3′-fused bicyclic nucleosides. The two target nucleosides **1a** and **1b** adopt the 4′-*exo*,3′-*endo* conformation, which shows, to some extent, a deviation from the classical *N*- or *S*-type conformations found in the majority of nucleosides in the solid state. The antiviral activities of the two novel compounds are currently investigated and will be reported elsewhere.

Experimental Part

General. All reactions were carried out under N_2 atmosphere. CH_2Cl_2 was dried over anh. $CaCl_2$. Compound **2** was prepared as described in [17]. All other reagents were commercially available and used as received. Melting points (m.p.) are uncorrected. Anal. TLC was performed with silica gel *GF254* (0.25 cm) plates. Column chromatography (CC) was performed on silica gel *G* (200–300 mesh; *Qingdao Haiyang Chemical Co.*, China). ^{1}H- and ^{13}C-NMR (^{1}H-decoupled) Spectra[2]) were recorded at 300 and 75 MHz, resp., in $CDCl_3$ or (D_6)DMSO; chemical shifts δ in ppm rel. to Me_4Si, coupling constants J in Hz. High-resolution mass spectrometry (HR-MS) was carried out on an *IonSpec 7.0 T Actively Shielded FT Ion-Cyclotron-Resonance* mass spectrometer equipped with an electrospray-ionization (ESI) source. Other mass spectra were recorded on an *Applied Biosystems ABI Q-Trap* mass spectrometer equipped with an atmospheric-pressure chemical-ionization (APCI) source.

*1-[2-*S*-(2-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}ethyl)-2-thio-5-*O*-(triphenylmethyl)-β-*D*-xylofuranosyl]pyrimidine-2,4(1*H*,3*H*)-dione* (**3a**) *and 1-[3-*S*-[2-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}ethyl]-3-thio-5-*O*-(triphenylmethyl)-β-*D*-arabinofuranosyl]pyrimidine-2,4(1*H*,3*H*)-dione* (**4a**). A mixture of 2-{[(*tert*-butyl(dimethyl)silyl]oxy}ethane-1-thiol ($TBSOCH_2CH_2OH$; 17.3 g, 0.09 mol), 1,1,3,3-tetramethylguanidine (TMG; 22.6 ml, 0.18 mol), and **2** (14.6 g, 0.03 mol) in anh. DMF (150 ml) was heated to 45–50° for 5 h. The mixture was cooled to r.t., poured on cold sat. aq. NH_4Cl soln. (300 ml), and extracted with AcOEt (3 × 200 ml). The combined org. phase was washed with brine (2 × 300 ml), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by CC (SiO_2; 0 → 5% MeOH in CH_2Cl_2) to afford **3a** (5.6 g, 28%) and **4a** (8.2 g, 41%).

Data of **3a**. M.p. 96–100°. ^{1}H-NMR ($CDCl_3$): 7.91 (*s*, H–N(3)); 7.72 (*d*, J = 8.1, H–C(6)); 7.49–7.20 (*m*, 15 arom. H); 6.01 (*s*, H–C(1′)); 5.52 (*d*, J = 8.1, H–C(5)); 4.44 (*s*, H–C(3′)); 4.20 (*s*, 3′-OH); 3.84 (*t*, J = 6.0, CH_2(6′)); 3.58–3.54 (*m*, H–C(4′)); 3.41–3.36 (*m*, H–C(4′)); 2.90–2.87 (*m*, CH_2(5′)), CH_2(7′)); 0.88 (*s*, *t*-Bu)); 0.06 (*s*, Me_2Si). ^{13}C-NMR ($CDCl_3$): 163.97; 162.49; 150.25; 143.30; 141.19; 128.46; 127.72; 126.98; 100.98; 91.45; 87.03; 82.74; 75.95; 62.71; 62.13; 56.24; 36.31; 34.24; 31.26; 25.72; 18.12; −5.48. APCI-MS: 659.5 ([M − H]$^-$), $C_{36}H_{43}N_2O_6SSi^-$; calc. 659.26).

Data of **4a**. M.p. 99–103°. ^{1}H-NMR ($CDCl_3$): 8.09 (*d*, J = 8.1, H–C(6)); 7.43–7.25 (*m*, 15 arom. H); 6.15 (*d*, J = 5.7, H–C(1′)); 5.34 (*d*, J = 8.1, H–C(5)); 4.49 (*m*, H–C(2′)); 3.84 (*s*, 2′-OH); 3.82–3.76 (*m*, CH_2(6′), H–C(4′)); 3.59–3.44 (*m*, CH_2(5′), H–C(3′)); 2.88–2.68 (*m*, CH_2(7′)); 0.88 (*s*, *t*-Bu)); 0.06 (*s*, Me_2Si). ^{13}C-NMR ($CDCl_3$): 164.00; 151.24; 143.35; 141.78; 128.94; 128.30; 127.69; 101.68; 87.79; 85.34; 81.72; 78.53; 63.76; 61.69; 48.05; 34.42; 26.18; 18.62; −5.2. APCI-MS: 659.5 ([M − H]$^-$), $C_{36}H_{43}N_2O_6SSi^-$; calc. 659.26).

*1-[2-*S*-(2-{[(1,1-Dimethylethoxy)carbonyl]amino}ethyl)-2-thio-5-*O*-(triphenylmethyl)-β-*D*-xylofuranosyl]pyrimidine-2,4(1*H*,3*H*)-dione* (**3b**) *and 1-[3-*S*-(2-{[(1,1-Dimethylethoxy)carbonyl]amino}ethyl)-3-thio-5-*O*-(triphenylmethyl)-β-*D*-arabinofuranosyl]pyrimidine-2,4(1*H*,3*H*)-dione* (**4b**). A mixture of *tert*-butyl 2-mercaptoethylcarbamate (15.5 g, 0.09 mol), TMG (22.6 ml, 0.18 mol), and **2** (14.6 g, 0.03 mol) in anh. DMF (150 ml) was heated at 35–40° for 3 h. The mixture was cooled to r.t., poured on cold sat. aq. NH_4Cl soln. (300 ml), and extracted with AcOEt (3 × 200 ml). The combined org. layers were washed with brine (2 × 300 ml), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by CC (SiO_2; 0 → 5% MeOH in CH_2Cl_2) to afford **3b** (4.8 g, 25%) and **4b** (5.1 g, 26%).

Data of **3b**. M.p. 109–111°. ^{1}H-NMR ($CDCl_3$): 7.68 (*d*, J = 8.1, H–C(6)); 7.48–7.23 (*m*, 15 arom. H); 5.97 (*s*, H–C(1′)); 5.45 (*d*, J = 8.1, H–C(5)); 5.14–5.12 (*m*, H–C(3′)); 4.42 (*s*, 3′-OH); 4.19 (*s*, H–C(2′)); 6.38–3.62 (*m*, H–C(4′)); 3.48–3.38 (*m*, CH_2(6′)); 2.96–2.99 (*m*, H_a–C(5′)); 2.79–2.72 (*m*, H_b–C(5′)); 1.98–1.80 (*m*, CH_2(7′)); 1.42 (*s*, *t*-Bu)). ^{13}C-NMR ($CDCl_3$): 163.9; 156.2; 150.4; 143.4; 141.1; 128.7; 128.0; 127.3; 109.8; 100.9; 91.7; 87.4; 83.1; 79.8; 76.2; 62.2; 55.5; 39.6; 31.8; 29.7; 28.4. APCI-MS: 644.5 ([M − H]$^-$), $C_{36}H_{40}N_2O_7S^-$; calc. 644.26).

Data of **4b**. M.p. 112–115°. ^{1}H-NMR ($CDCl_3$): 10.25 (*s*, H–N(3)); 8.14 (*d*, J = 8.1, H–C(6)); 7.41–7.30 (*m*, 15 arom. H); 6.17 (*s*, H–C(1′)); 5.36 (*d*, J = 8.1, H–C(5)); 5.11 (*s*, 3′-OH); 4.53 (*s*, H–C(2′))); 3.80 (*d*, J = 9.3, H–C(3′)) 3.61–3.31 (*m*, H–C(4′)), CH_2(5′), CH_2(6′)); 2.75–2.64 (*m*, CH_2(7′)); 1.40 (*s*, *t*-

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[2]) Arbitrary atom numbering (see *Figure*).

Bu). ^{13}C-NMR ($CDCl_3$): 164.26; 155.94; 143.00; 141.84; 128.60; 127.93; 127.31; 101.44; 87.24; 84.80; 81.20; 78.37; 77.84; 61.28; 46.95; 40.10; 31.95; 28.27. APCI-MS: 644.5 ($[M-H]^-$), $C_{36}H_{40}N_2O_7S^-$; calc. 644.26).

1-{3-Deoxy-3-[(2-{[(1,1-dimethylethyl)dimethylsilyl]oxy}ethyl)sulfonyl]-5-O-*(triphenylmethyl)-β*-D-*arabinofuranosyl}pyrimidine-2,4(1*H,*3*H*)-dione* (**5a**). 10% aq. $NaHCO_3$ (46 ml, 0.05 mmol) was added to a soln. of **4a** (6.61 g, 0.01 mol) in CH_2Cl_2 (100 ml), and the mixture was cooled to 0°. MCPBA (6.09 g, 0.03 mol) was added slowly, and the mixture was stirred in an ice bath for 2 h. Then, cold sat. aq. $NaHCO_3$ soln. (100 ml) and CH_2Cl_2 (100 ml) were added, the org. layer was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting residue was purified by CC (SiO_2; 0 → 8% MeOH in CH_2Cl_2). Yield. 5.82 g (84%). M.p. 112–114°. ^{1}H-NMR ($CDCl_3$): 11.11 (br. *s*, H–N(3)); 7.67 (*d*, *J* = 8.1, H–C(6)); 7.50–7.19 (*m*, 15 arom. H); 6.06 (*m*, H–C(1′)); 3.37 (*d*, *J* = 8.1, H–C(5)); 5.11 (*s*, 2′-OH); 4.85 (*m*, CH_2(6′)); 4.13 (*m*, H–C(2′)); 4.15–3.86 (*m*, H–C(4′), CH_2(7′)); 3.51–3.43 (*m*, CH_2(5′)); 3.22 (*m*, H–C(3′)); 0.84 (*s*, *t*-Bu)); 0.01 (*s*, Me_2Si). ^{13}C-NMR ($CDCl_3$): 165.97; 149.99; 143.51; 142.98; 128.69; 127.86; 127.15; 100.47; 87.79; 87.03; 74.53; 70.71; 69.46; 65.43; 57.36; 54.89; 25.81; 18.21; −5.57. APCI-MS: 691.5 ($[M-H]^-$, $C_{36}H_{43}N_2O_8SSi^-$; calc. 691.25).

*1-{(2*R,*5*R*)-4-[(2-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}ethyl)sulfonyl]-2,5-dihydro-5-[(triphenylmethoxy)methyl]furan-2-yl}pyrimidine-2,4(1*H,*3*H*)-dione* (**6a**). Compound **4a** (8.31 g, 12 mmol) was added to anh. pyridine (60 ml), and the soln. was cooled to 0°. Then, methanesulfonyl chloride (MsCl; 2.80 ml, 36 mmol) was slowly added, and the mixture was stirred at 0° for 24 h. Then, H_2O (4.8 ml) was added, and the mixture was heated to 40–50° for 2 h. Then, the mixture was poured into ice-water (500 ml), and the precipitate was filtered off, dried, and purified by CC (SiO_2; 0 → 3% MeOH in CH_2Cl_2). Yield: 5.01 g (62%, two steps). M.p. 103–107°. ^{1}H-NMR ($CDCl_3$): 8.63 (*s*, H–N(3)); 7.89 (*d*, *J* = 8.1, H–C(6)); 7.39–7.28 (*m*, 15 arom. H); 7.09–7.07 (*m*, H–C(2′)); 6.76 (*d*, *J* = 1.8, H–C(1′)); 5.18–5.20 (*m*, H–C(4′)); 4.74–4.78 (*m*, H–C(5)); 3.99–4.03 (*m*, CH_2(6′)); 3.77–3.71 (*m*, CH_2(7′)); 3.13–3.38 (*m*, CH_2(5′)); 0.85 (*s*, *t*-Bu); 0.04 (*s*, Me_2Si). ^{13}C-NMR ($CDCl_3$): 162.57; 150.04; 147.94; 142.41; 140.89; 136.94; 129.03; 128.01; 127.62; 102.75; 88.33; 87.36; 84.37; 62.67; 58.35; 56.90; 25.78; 18.27; −5.52. APCI-MS: 673.5 ($[M-H]^-$, $C_{36}H_{41}N_2O_7SSi^-$; calc. 673.24).

*1-{(4a*R,*5*R,*7*R,*7a*S*)-Hexahydro-4,4-dioxido-5-[(trityloxy)methyl]furo[3,4-*b*][1,4]oxathiin-7-yl}pyrimidine-2,4(1*H,*3*H*)-dione* (**8a**). Compound **6a** (4.5 g, 6.7 mmol) was added to 1M TBAF soln. in THF (65 ml), and the mixture was stirred at r.t. for 5 h. Then, H_2O (60 ml) and AcOEt (50 ml) were added, the layers were separated, and the aq. phase was re-extracted with AcOEt (3 × 50 ml). The combined org. layers were washed with brine (2 × 50 ml), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by CC (SiO_2; 0 → 5% MeOH in CH_2Cl_2). Yield: 3.33 g (89%). M.p. 162–166°. ^{1}H-NMR ($CDCl_3$): 8.41 (*s*, H–N(3)); 8.08 (*d*, *J* = 8.1, H–C(6)); 7.43–7.28 (*m*, 15 arom. H); 5.87 (*s*, H–C(1′)); 5.06 (*d*, *J* = 8.1, H–C(5)); 4.63 (*d*, *J* = 3.6, H–C(2′)); 4.55 (*d*, *J* = 11.1, H–C(4′)); 4.34–4.37 (*m*, H_{ax}–C(6′)); 4.15 (*d*, *J* = 12.0, H_{eq}–C(6′)); 3.99–3.94 (*m*, H–C(3′)); 3.87 (*m*, H_a–C(5′)); 3.64 (*d*, *J* = 11.4, H_b–C(5′)); 3.29–3.23 (*m*, H_{ax}–C(7′)); 3.06 (*m*, H_{eq}–C(7′)). ^{13}C-NMR ($CDCl_3$): 162.42; 149.71; 142.72; 139.44; 130.91; 128.66; 128.18; 127.61; 102.05; 89.18; 88.20; 83.65; 79.38; 64.94; 60.81; 59.22; 49.74; 19.16. APCI-MS: 559.4 ($[M-H]^-$), $C_{30}H_{27}N_2O_7S^-$; calc. 559.15).

*1-[(4a*R,*5*R,*7*R,*7a*S*)-Hexahydro-5-(hydroxymethyl)-4,4-dioxidofuro[3,4-*b*][1,4]oxathiin-7-yl]pyrimidine-2,4(1*H,*3*H*)-dione* (**1a**). Compound **8a** (2.0 g, 3.6 mmol) was added to 80% AcOH (40 ml), and the mixture was stirred at r.t. for 2 h. The solvent was evaporated, and the residue was washed with AcOEt and $CHCl_3$ to afford the title compound. Yield: 0.76 g (67%). Colorless powder. M.p. 303–310° (dec.). ^{1}H-NMR ((D_6)DMSO): 11.33 (*s*, H–N(3)); 8.08 (*d*, *J* = 8.1, H–C(6)); 5.72 (*s*, H–C(1′)); 5.57 (*d*, *J* = 8.1, H–C(5)); 5.51 (*t*, *J* = 4.5, 5′-OH); 4.68 (*d*, *J* = 3.6, H–C(2′)); 4.61 (*d*, *J* = 10.5, H–C(4′)); 4.34 (*d*, *J* = 12.9, H_{ax}–C(6′)); 3.91 (*t*, *J* = 12.0, H_{eq}–C(6′)), H_a–C(5′)); 3.73 (*m*, H–C(3′), H_b–C(5′)); 3.67–3.57 (*m*, H_{ax}–C(7′)); 3.31 (*d*, *J* = 14.7, H_{eq}–C(7′)). ^{13}C-NMR ((D_6)DMSO): 172.02; 163.31; 150.27; 140.17; 101.98; 89.04; 82.56; 79.95; 64.54; 59.38; 58.07; 48.83. HR-ESI-MS: 317.04469 ($[M-H]^-$, $C_{11}H_{13}N_2O_7S^-$; calc. 317.04435).

1-{3-Deoxy-3-[(2-{[(1,1-dimethylethoxy)carbonyl]amino}ethyl)sulfonyl]-5-O-*(triphenylmethyl)-β*-D-*arabinofuranosyl}pyrimidine-2,4(1*H,*3*H*)-dione* (**5b**). Prepared in analogy to **5a**. Yield: 3.7 g (87%). M.p. 128–132°. ^{1}H-NMR ($CDCl_3$): 7.93 (*d*, *J* = 8.1, H–N(3)); 7.47–7.23 (*m*, 15 arom. H); 6.11 (*d*, *J* = 4.5, H–C(1′)); 5.33 (*m*, H–C(5), 2′-OH)); 5.11 (*s*, H–C(2′)); 4.58 (*s*, H–C(3′)); 4.02–3.99 (*m*, H–C(4′)); 3.68–3.54 (*m*, CH_2(5′), CH_2(6′)); 3.49–3.45 (*m*, CH_2(7′)); 1.43 (*s*, *t*-Bu)). ^{13}C-NMR ($CDCl_3$): 164.89;

155.79; 150.60; 143.22; 142.27; 128.69; 128.05; 127.41; 101.27; 87.55; 85.93; 80.16; 74.60; 72.24; 66.04; 63.20; 53.06; 34.02; 29.69; 28.33. APCI-MS: 676.4 ($[M-H]^-$, $C_{35}H_{38}N_3O_9S^-$; calc. 676.23).

*1-{(2*R,*5*R*)-4-[(2-{[(1,1-Dimethylethoxy)carbonyl]amino}ethyl)sulfonyl]-2,5-dihydro-5-[(triphenylmethoxy)methyl]-2-furanyl}pyrimidine-2,4(1*H,*3*H*)-dione* (**6b**). Prepared in analogy to **6a**. Yield: 2.8 g (66%, two steps). M.p. 91–93°. ^{1}H-NMR ($CDCl_3$): 7.91 (*d*, *J* = 8.1, H–C(6)); 7.31–7.25 (*m*, 15 arom. H); 7.11 (*m*, H–C(2′)); 6.84 (*s*, H–C(1′)); 5.16 (*d*, *J* = 1.8, H–C(4′)); 5.08 (*s*, H–N(3)); 4.87 (*d*, *J* = 8.1, H–C(5)); 3.79–3.65 (*m*, CH_2(7′)); 3.49–3.46 (*m*, CH_2(6′)); 3.35–3.32 (*m*, H_a–C(5′)); 3.10–3.03 (*m*, H_b–C(5′)); 1.43 (*s*, *t*-Bu)). ^{13}C-NMR ($CDCl_3$): 163.02; 155.53; 150.29; 146.51; 142.19; 140.72; 138.58; 128.91; 128.05; 127.73; 102.99; 88.31; 87.59; 83.98; 80.30; 62.50; 54.52; 34.11; 28.28. APCI-MS: 658.9 ($[M-H]^-$), $C_{35}H_{36}N_3O_8S^-$; calc. 658.22).

*1-[(4a*S,*5*R,*7*R,*7a*S*)-Hexahydro-7-(hydroxymethyl)-1,1-dioxido-2*H*-furo[3,4-*b*][1,4]thiazin-5-yl]-pyrimidine-2,4(1*H,*3*H*)-dione* (**1b**). To compound **6b** (2 g, 3.0 mmol), 20% TFA in CH_2Cl_2 (40 ml) was added, and the mixture was stirred at r.t. for 3 h. The solvent was evaporated, the residue was dissolved in MeOH (50 ml), and K_2CO_3 (0.83 g, 6.0 mmol) was added. The mixture was stirred at r.t. for 2 h, and then concentrated *in vacuo*. The residue was purified by CC (SiO_2; 5 → 10% MeOH in CH_2Cl_2). Yield: 0.61 g (64%, two steps). M.p. 283–287° (dec.). ^{1}H-NMR ((D_6)DMSO): 11.35 (*s*, H–N(3)); 7.95 (*d*, *J* = 8.1, H–C(6)); 5.94 (*d*, *J* = 5.7, H–C(1′)); 5.64 (*d*, *J* = 8.1, H–C(5)); 5.48 (*s*, 5′-OH)); 4.55 (*m*, H–C(4′)); 3.91 (*m*, H–C(2′)); 3.80 (*d*, *J* = 12.0, H_a–C(5′)); 3.64 (*d*, *J* = 12.0, H_b–C(5′)); 3.57 (*m*, H–C(3′)); 3.25–3.05 (*m*, CH_2(6′)), CH_2(7′), 2′-NH). ^{13}C-NMR ((D_6)DMSO): 163.03; 150.66; 139.99; 101.69; 84.20; 76.60; 62.20; 61.74; 59.43; 49.91; 41.12. HR-ESI-MS: 316.06107 ($[M-H]^-$, $C_{11}H_{14}N_3O_6S^-$; calc. 316.06033).

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