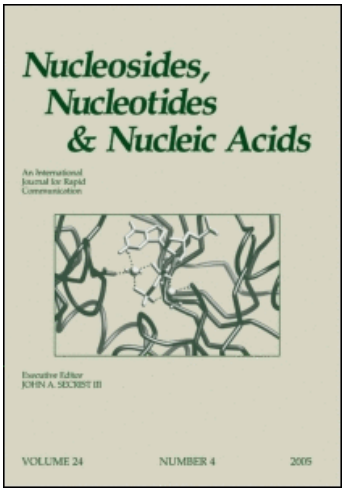

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Thiosugars. XII. Synthesis of New 3′-*O*-Substituted 2′,5′-Anhydro-2′-thio-α-D-pentofuranosyl Nucleoside Analogues[#]

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ABSTRACT

Methyl 2,5-anhydro-3-*O*-(2-methoxyethyl)-2-thio-β-D-arabinofuranoside and methyl 2,5-anhydro-3-*O*-(2-fluorobenzyl)-2-thio-α-D-lyxofuranoside were transformed into the corresponding uridine, thymidine, cytidine and adenosine analogues, which exclusively exhibited the α-configuration irrespective of the anomeric configuration of the donor. The structure, configuration, and conformation of the products was elucidated by X-ray structure analyses. The nucleoside analogues were tested for antiviral activities.

Key Words: Thiosugars; Nucleosides; 2,5-Anhydro-2-thiopentofuranosides; Configurations; X-ray structure; Biological tests.

[#]Part XI: See Ref. [11].

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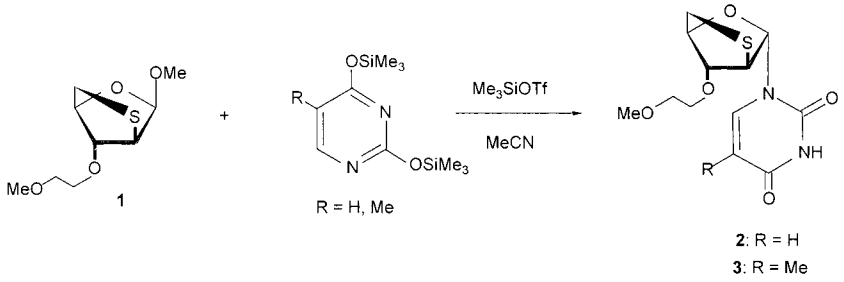
INTRODUCTION

Certain nucleoside analogues containing unnatural sugar or base moieties are known to be potent antiviral and antitumor agents.[1–3] Among these compounds also anhydro derivatives have been studied. However, 3′,5′-anhydro-3′-thio-D-xylofuranosyl nucleosides did not exhibit cytotoxic or antiviral activity[4] and also 1-(2,5-anhydro-β-D-arabinofuranosyl)cytosine[5,6] was not as effective in the therapy of acute myeloblastic leukemia[7] as the well known 1-β-D-arabinofuranosylcytosine (''araC'').[8,9] The introduction of sulfur into the carbohydrate moiety of a nucleoside could, however, modify its biological activity.[3] We were therefore interested in the synthesis and antiviral properties of the related 2′,5′-anhydro-2′-thiopentofuranosyl nucleoside analogues and present our results here.

RESULTS AND DISCUSSION

The methyl glycosides of bicyclic 2-thiopentofuranoses should be suitable starting materials for the preparation of 2′,5′-anhydro-2′-thio nucleoside analogues since we could successfully apply the related 2′,5′-anhydro-2′-seleno derivatives[10] for this synthesis. Expectedly, the preparation of several nucleoside analogues starting from two glycosyl donors of this type: methyl 2,5-anhydro-3-*O*-(2-methoxyethyl)-2-thio-β-D-arabinofuranoside (**1**) and methyl 2,5-anhydro-3-*O*-(2-fluorobenzyl)-2-thio-α-D-lyxofuranoside (**8**), was possible. The preparation of the donor **1** is described in Refs. [11,12]. Compound **8** was obtained with 85% yield by the reaction of methyl 2-thio-2,5-anhydro-α-D-lyxofuranoside (**7**)[11,12] with 2-fluorobenzyl bromide. Its *ortho*-fluorobenzyl substituent could possibly induce an interesting biological activity in a nucleoside analogue since related monocyclic[13] and, in particular, oxabicyclic 2-fluorobenzyl ethers, are well known herbicides.[13–17]

Coupling of the glycosyl donors with silylated pyrimidine bases[18,19] was accomplished under the Vorbrüggen conditions by use of trimethylsilyl trifluoromethanesulfonate (TMSOTf).[20] Reaction of **1** led to the uridine analogue **2** with 78% yield and the thymidine analogue **3** with 77% yield (Scheme 1). The nucleoside analogues **2** and **3** were obtained as the pure α-anomers. The exclusive attack of the nucleobase from one side of the furanosyl carbenium ion can be explained by the anomeric effect



Scheme 1.

and steric hindrance of an approach from the β-side by the 2,5-anhydro-2-thio substructure. After crystallization from ethyl acetate both nucleoside analogues were obtained as single crystals. The X-ray structure analyses of the compounds revealed the α-configuration at the anomeric center as demonstrated for **2** in Fig. 1. The sugar moiety of both **2** and **3** exhibits an envelope conformation (E_3).[21,22] The plane of the nucleobase in **2** and **3** is twisted by an angle of only 10° with respect to the O-C1-C2-plane of the sugar.

The uridine derivative **2** was used to synthesize its 4-thio analogue **4** by heating it with Lawesson's reagent in 1,2-dichloroethane[23] to yield 78% **4** (Scheme 2). The corresponding cytidine derivative **6** was prepared in two steps from **2** by use of a literature procedure.[24] First **2** was transformed into the 1,2,4-triazole derivative **5** with 49% yield. Subsequent treatment of **5** with aqueous ammonia yielded the cytidine analogue **6** although with a low yield of 12% (Scheme 2). It could be crystallized from methanol. The structure was confirmed by an X-ray structure analysis, which also revealed the same envelope conformation (E_3)[21,22] of the sugar moiety in **6** as in **2** and **3**.

Analogously, the glycoside **8** which we obtained from **7**[11,12] was coupled with silylated uracil and thymine to give the uridine and thymidine analogues **9** and **10** with yields of 23% and 56%, respectively. The adenosine derivative **11** was obtained with 10% yield by coupling **8** with adenine (Scheme 3). All the three nucleosides were obtained as pure anomers. They could be crystallized and their configuration and

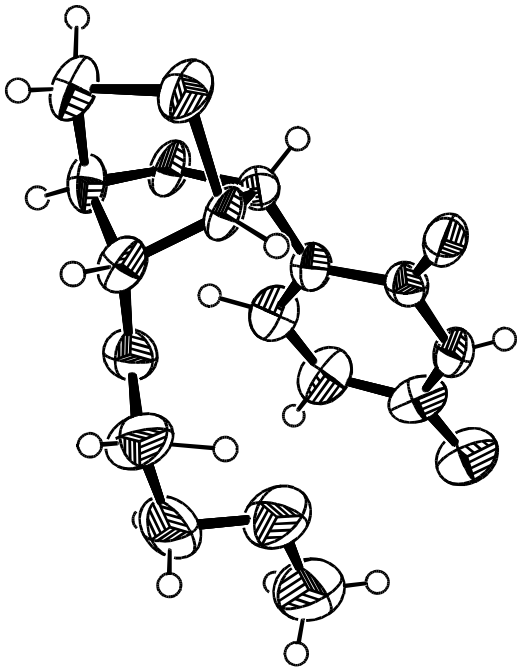
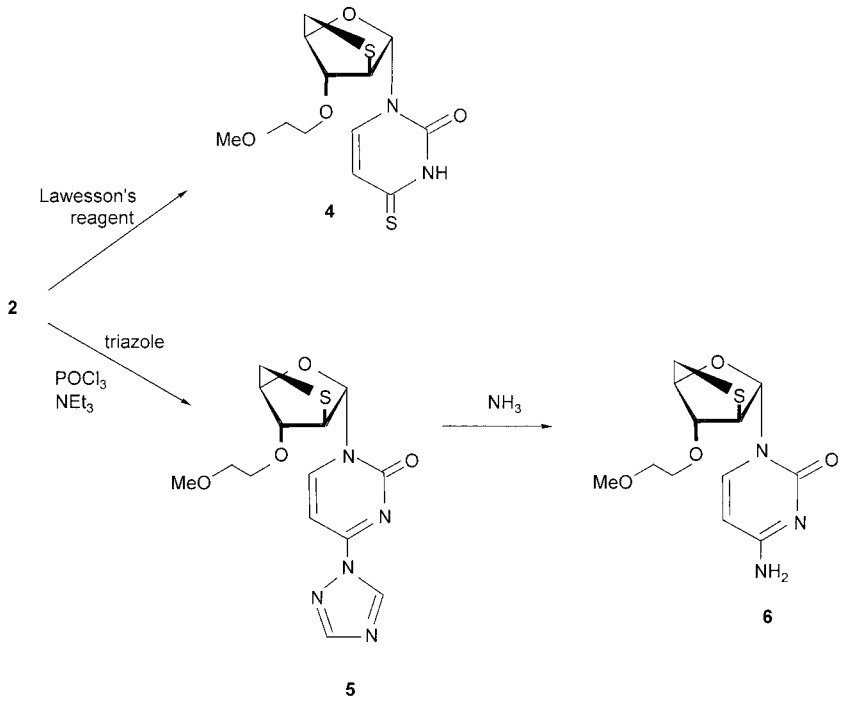


Figure 1. ORTEP view of the X-ray diffraction structure of thionucleoside **2**. Thermal ellipsoids are drawn at the 50% probability level.



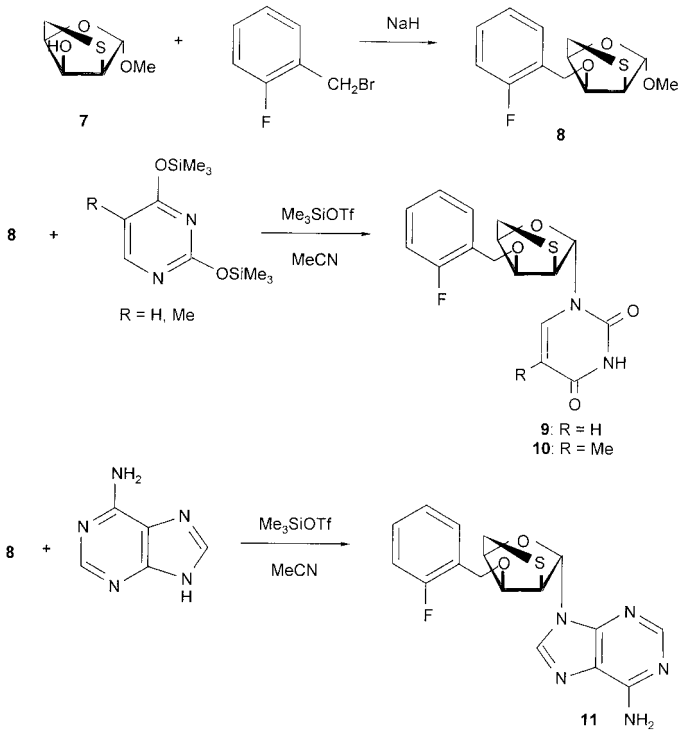
Scheme 2.

conformation was determined by X-ray structure analyses (cf. Fig. 2 and Fig. 3), which revealed the expected α-configuration for **9**, **10** and **11**. Interestingly, the analogues of thymidine **10** and adenosine **11** exist in two different conformers in the asymmetric unit of the crystal, whereas for the uridine derivative **9** only one conformer is found. Maybe, the steric demand of the methyl group at C-5 in **10** and of the large purine moiety in **11** prevents the more systematic arrangement of only one conformer in the crystal lattice.

It seems worthwhile to mention that the methyl 3,5-anhydro-3-thiofuranoside **12**[11,12] did not react with silylated uracil or thymine in the presence of trimethylsilyl triflate. Even after a prolonged reaction time of 24 h or at an elevated temperature of 50°C, the expected products **13** and **14** were not formed (Scheme 4). Instead, only the starting material **12** was recovered quantitatively.

Biological Tests

The nucleoside derivatives **2**, **3**, **6**, **9**, **10** and **11** were biologically tested. The compounds did not exhibit antiviral activity against the cytopathogenicity of HIV-1 (III_B) and HIV-2 (ROD) in human T-lymphocyte (CEM) cells at concentrations of 250 μM. They were also inactive against HSV-1 (KOS, TK^-KOS ACV^r and TK^-VMW 1837), HSV-2 (G), Vaccinia virus, Vesicular stomatitis virus, Coxsackie virus B4, Respiratory syncytial virus, Parainfluenza 3 virus, Reovirus-1, Sindbis virus and Punta



Scheme 3.

Toro virus at concentrations of 250 μg/ml. None of the compounds was cytotoxic at a concentration of 400 μg/ml. The nucleoside analogues **2**, **3**, **9** and **10** did not exhibit significant antiviral activity ($IC_{50} > 200$ μM) against Cytomegalovirus (strain AS-169 and Davis) or Varicella zoster virus (TK^+VZV, strain YS and OKO and TK^-VZV, strain 07/1 and YS/R) in HEL cells. Compounds **6** and **11** were not inhibitory ($IC_{50} > 100$ μM) to human tumor cell (L1210/0, Molt4/C8, CEM/0, CEM/TK^-) proliferation.

EXPERIMENTAL

Melting points (corrected) were measured with an Electrothermal apparatus. IR spectra (KBr) were measured with an ATI Mattson Genesis spectrometer. NMR spectra were recorded with Bruker AMX 400 and DRX 500 spectrometers in $CDCl_3$ as solvent. Chemical shifts (ppm) are related to Me_4Si (^1H and ^{13}C). Standard correlation techniques were used for assignments. Mass spectra were measured on Varian CH 7 (EI, 70 eV) and VG Analytical 70–250 S (HRMS, FAB, 3-nitrobenzyl alcohol matrix) apparatus. Optical rotations were measured in $CHCl_3$ (*c* 1.0) on the Perkin Elmer polarimeter 341. TLC was carried out on E. Merck PF_{254} foils (detection: UV light and iodine vapor, $EtOH/H_2SO_4$ spray/200°C), and column chromatography on Merck

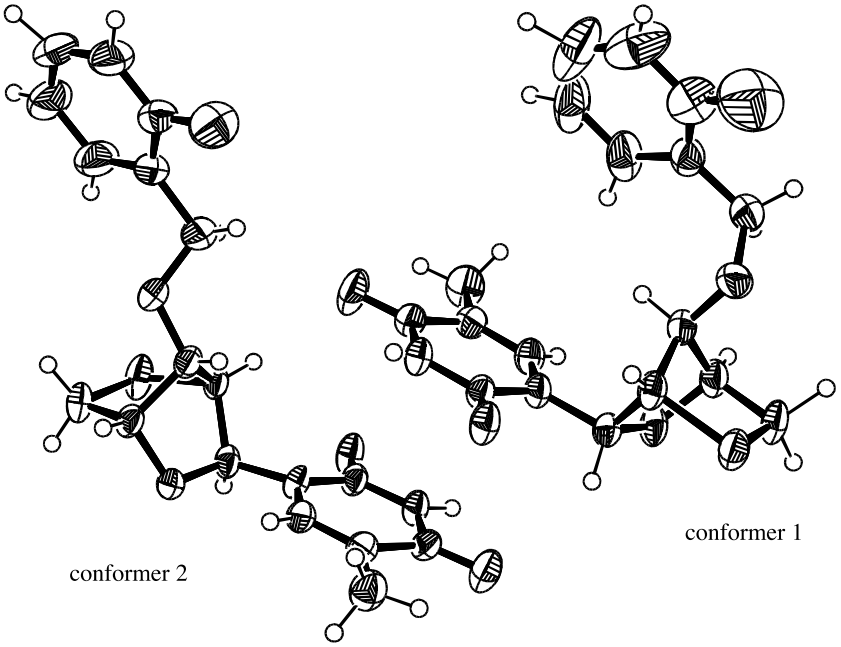


Figure 2. ORTEP view of the X-ray diffraction structure of thionucleoside **10**. Thermal ellipsoids are drawn at the 50% probability level.

silicagel 60 (70–230 mesh). Solvents (PE = petroleum ether, EA = ethyl acetate) were purified and dried according to standard laboratory procedures.[25] Analytical HPLC was performed with Merck-Hitachi equipment (LiChroCART 250-3 column with Lichrosphere 100-3 RP 8, 5 μm filling; solvent gradient: 0–20 min/0–60% MeCN/H_2O, 20–23 min/60–100% MeCN/H_2O, UV detection at 260 nm).

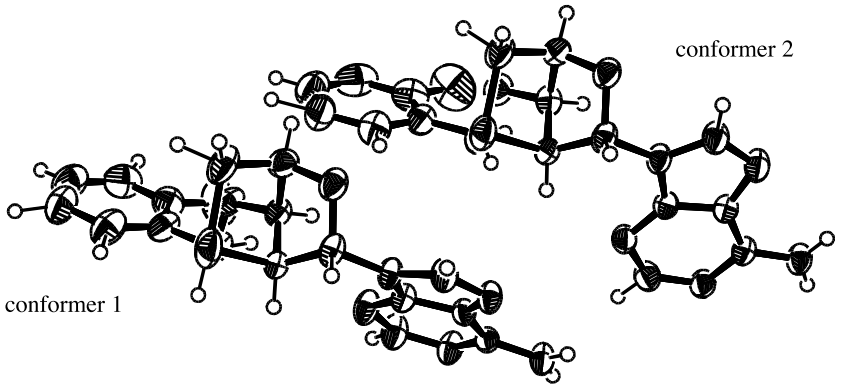
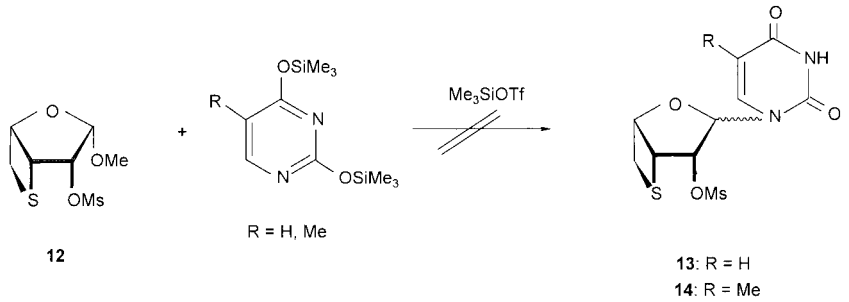


Figure 3. ORTEP view of the X-ray diffraction structure of thionucleoside **11**. Thermal ellipsoids are drawn at the 50% probability level.



Scheme 4.

X-Ray Structure Analyses

The crystal data and a summary of experimental details are given in Tables 1 and 2. The data collection for **2**, **3**, **9**, **10**, and **11** was performed on a Kappa CCD Nonius diffractometer, with graphite monochromated MoK_α radiation (λ = 0.71070 Å) in the Rotation Φ scan mode at 293 K. The data collection for **6** was performed on an Enraf-Nonius CAD4 diffractometer, with graphite monochromated CuK_α radiation (λ = 1.54178 Å) in the $2\theta/\omega$ scan mode at 173 K. The structures were solved by direct methods using the SIR-97[26] program, and refined by full-matrix-block least-squares on F^2 using all data and the SHELXL-97[27] program. Full crystallographic details, excluding structure features, have been deposited with the Cambridge Crystallographic Data Centre. These data may be obtained, on request, from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Tel. +44-1223-336408, Fax +44-1223-336033, E-mail deposit@ccdc.cam.ac.uk. Deposition number CCDC 144005 (**2**), 144006 (**3**), 144158 (**6**), 144007 (**9**), 144008 (**10**) and 144009 (**11**).

1-[2,5-Anhydro-3-*O*-(2-methoxyethyl)-2-thio-α-D-arabinofuranosyl]uracil (2): TMSOTf (0.20 mL, 246 mg, 1.11 mmol) was added to a cooled solution (−18°C) of **1**[11] (105 mg, 0.45 mmol), 2,4-bis-*O*-trimethylsilyluracil[18] (250 mg, 1.0 mmol) and 4 Å molecular sieves (50 mg) in MeCN (8.0 mL). The solution was stirred for 1.5 h and the temperature was allowed to rise from −18°C to +10°C. Satd. aq. $NaHCO_3$ solution (20 mL) was added and stirring was continued for another 0.5 h. After filtration the aq. phase was extracted with $CHCl_3$, the organic phase was separated, dried with $MgSO_4$ and evaporated. The crude product was purified by column chromatography ($CHCl_3$/MeOH 4:1, R_f 0.58) and recrystallisation from EA to yield **2** [111 mg, 78%, purity 98% (HPLC)] as tiny colorless needles. A single crystal was suitable for an X-ray structural analysis. M.p. 162°C. $[\alpha]_D^{20}$ = −41.4. IR: ν 1705 (C=O) cm^{-1}. ^1H NMR (500 MHz): δ 2.89 (dd, 1H, H-5′$_a$), 2.90 (dd, 1H, H-5′$_b$), 3.31 (s, 3H, OCH_3), 3.38−3.40 (m, 2H, $CH_2CH_2OCH_3$), 3.50 (ddd, 1H, $CH_aH_bCH_2OCH_3$, ^3J = 3.0, 4.9, ^2J = 11.0 Hz), 3.60 (ddd, 1H, $CH_aH_bCH_2OCH_3$, ^3J = 3.1, 6.5, ^2J = 11.0 Hz), 3.73 (d, 1H, H-2′), 4.24 (d, 1H, H-3′), 4.86 (dd, 1H, H-4′), 5.64 (d, 1H, H-5), 5.93 (s, 1H, H-1′), 7.71 (d, 1H, H-6), 10.12 (bs, 1H, NH). $J_{2',3'}$ = 1.2, $J_{4',5'a}$ = 1.4, $J_{4',5'b}$ = 1.7, $J_{5'a,5'b}$ = 10.9, $J_{5,6}$ = 8.2 Hz. ^{13}C NMR (126 MHz): δ 32.2 (C-5′), 45.7 (C-2′), 58.0 (OCH_3), 69.5 ($CH_2CH_2OCH_3$), 71.4 ($CH_2CH_2OCH_3$), 80.6 (C-4′), 85.2 (C-3′), 92.2 (C-1′), 99.4 (C-5),

Table 1. Crystal data and structure refinement for **2**, **3** and **6**.

Compound	**2**	**3**	**6**
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a [pm]	550.20 (10)	560.10 (10)	706.41 (9)
b [pm]	1201.70 (10)	1235.40 (10)	823.37 (16)
c [pm]	2103.40 (2)	2109.10 (10)	2335.4 (8)
Z	4	4	4
F_{000}	632	664	632
μ [mm^{-1}]	0.254	0.245	2.295
Crystal size [mm]	0.41 × 0.33 × 0.19	0.45 × 0.33 × 0.21	0.50 × 0.20 × 0.20
$\rho_{calcd.}$ [g cm^{-3}]	1.434	1.431	1.464
$h/k/l$ limits	0,6/0,14/−24,24	0,6/0,15/− 25,26	−8,0/−10,1/−29,0
θ limits [°]	3.36/25.18	1.91/26.08	3.79/76.21
Number of reflections	9174	10509	1697
Independent reflections	2462	2868	1671
Reflections with $I \leq 2\sigma(I)$	1574	2389	1291
Weighting scheme $[\Sigma w(F_0^2-F_c^2)^2]$; $P = (F_0^2+2F_c^2)/3$	$w = 1/[\sigma^2(F_02) + (0.0634P)^2 + 1.8650P]$	$w = 1/[\sigma^2(F_0^2) + (0.1140P)^2 + 0.1542P]$	$w = 1/[\sigma^2(F_0^2) + (0.1844P)^2 + 2.3960P]$
Number of parameters	234	203	200
Final R indices [$I \leq 2\sigma(I)$]	$R_1 = 0.0673$ $R_w = 0.1469$	$R_1 = 0.0635$ $R_w = 0.1518$	$R_1 = 0.0811$ $R_w = 0.2226$
R indices (all data)	$R_1 = 0.1233$ $R_w = 0.1727$	$R_1 = 0.0855$ $R_w = 0.1864$	$R_1 = 0.1179$ $R_w = 0.2711$
Goodness-of-fit on F^2	0.997	1.191	1.082
Largest difference peak and hole [e Å^{-3}]	0.257/−0.237	0.819/−0.521	0.805/−0.723
Absolute structure parameter	−0.3 (2)	0.08 (16)	0.00 (9)
Refinement of H-atoms	Geom	Geom	Geom

Table 2. Crystal data and structure refinement for **9**, **10** and **11**.

Compound	**9**	**10**	**11**
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	$P2_1$	$P1$	$P2_1$
a [pm]	995.3 (1)	578.30 (10)	1188.00 (10)
b [pm]	630.7 (1)	941.80 (10)	811.60 (10)
c [pm]	1291.2 (1)	1545.50 (10)	1797.90 (10)
α [°]		89.340 (10)	
β [°]	104.92 (1)	79.980 (10)	91.300 (10)
γ [°]		88.570 (10)	
Z	2	2	4
F_{000}	364	380	776
μ [mm^{-1}]	0.242	0.231	0.220
Crystal size [mm]	0.35 × 0.25 × 0.10	0.44 × 0.38 × 0.28	0.30 × 0.26 × 0.19
$\rho_{calcd.}$ [g cm^{-3}]	1.486	1.460	1.431
$h/k/l$ limits	0,12/−8,8/−16,16	−6,6/−11,11/−18,18	0,14/−10,10/−22,22
θ limits [°]	2.12/27.53	1.34/25.07	2.03/26.03
Number of reflections	12573	10872	13559
Independent of reflections	3585	5794	6754
Reflections with $I \leq 2\sigma(I)$	3418	5631	5734
Weighting scheme $[\Sigma w(F_0^2-F_c^2)^2]$; $P = (F_0^2+2F_c^2)/3$	$w = 1/[\sigma^2(F_0^2) + (0.1148P)^2 + 0.2269P]$	$w = 1/[\sigma^2(F_0^2) + (0.1148P)^2 + 0.2269P]$	$w = 1/[\sigma^2(F_0^2) + (0.0777P)^2 + 0.0919P]$
Number of parameters	278	548	582
Final R indices [$I \leq 2\sigma(I)$]	$R_1 = 0.0495$	$R_1 = 0.0508$	$R_1 = 0.0487$
	$R_w = 0.1445$	$R_w = 0.1410$	$R_w = 0.1187$
R indices (all data)	$R_1 = 0.0517$	$R_1 = 0.0565$	$R_1 = 0.0615$
	$R_w = 0.1488$	$R_w = 0.1590$	$R_w = 0.1316$
Goodness-of-fit on F^2	0.936	1.196	1.161
Largest difference peak and hole [e Å^{-3}]	0.827/−0.279	0.684/−0.412	0.357/−0.359
Absolute structure parameter	0.01 (11)	−0.02 (8)	−0.00 (7)
Refinement of H-atoms	Difmap/geom	Difmap/geom	Geom

141.3 (C-6), 150.6 (2-CO), 164.4 (4-CO). FAB MS; *m/z*: 301 $[M + H]^+$. FAB HRMS: calcd. 301.0858 ($C_{12}H_{17}N_2O_5S$); found 301.0868.

1-[2,5-Anhydro-3-*O*-(2-methoxyethyl)-2-thio-α-D-arabinofuranosyl]thymine (3): Compound **3** was prepared as described for **2** from **1**[11] (209 mg, 0.95 mmol), 2,4-bis-*O*-trimethylsilylthymine[19] (486 mg, 1.80 mmol), TMSOTf (0.40 mL, 492 mg, 2.21 mmol) and 4 Å molecular sieves (95 mg) in MeCN (8.0 mL). After work up, column chromatography ($CHCl_3$/MeOH 4:1, R_f = 0.64) and recrystallisation from EA **3** [231 mg, 77%, purity 99% (HPLC)] was obtained as colorless needles. A single crystal was suitable for an X-ray structure analysis. M.p. 189–191°C (decomp.). $[\alpha]_D^{20} = -3.9$. IR: ν 3166 (NH), 1667 (C = O) cm^{-1}. ^1H NMR (400 MHz): δ 1.93 (d, 3H, CH_3), 2.89 (dd, 1H, H-5′$_a$), 2.95 (dd, 1H, H-5′$_b$), 3.30 (s, 3H, OCH_3), 3.32–3.35 (m, 2H, $CH_2CH_2OCH_3$), 3.45 (ddd, 1H, $CH_aH_bCH_2OCH_3$, ^3J = 3.0, 4.9, ^2J = 11.0 Hz), 3.57 (ddd, 1H, $CH_aH_bCH_2OCH_3$, ^3J = 3.1, 6.5, ^2J = 11.0 Hz), 3.72 (dd, 1H, H-2′), 4.23 (dd, 1H, H-3′), 4.86 (dddd, 1H, H-4′), 5.93 (s, 1H, H-1′), 7.53 (q, 1H, H-6), 9.29 (bs, 1H, NH). $J_{2',3'}$ = 1.3, $J_{2',4'}$ = 0.5, $J_{3',4'} < 0.5$, $J_{4',5'a}$ = 1.3, $J_{4',5'b}$ = 1.7, $J_{5'a,5'b}$ = 10.9, $J_{6,Me}$ = 1.2 Hz. ^{13}C NMR (101 MHz): δ 12.5 (CH_3), 32.2 (C-5′), 45.7 (C-2′), 59.1 (OCH_3), 69.4 ($CH_2CH_2OCH_3$), 71.4 ($CH_2CH_2OCH_3$), 80.7 (C-4′), 85.2 (C-3′), 92.1 (C-1′), 107.5 (C-5), 137.0 (C-6), 150.4 (2-CO), 164.4 (4-CO). FAB MS; *m/z*: 315 $[M + H]^+$. FAB HRMS: calcd. 315.1015 ($C_{13}H_{19}N_2O_5S$); found 315.1019.

1-[2,5-Anhydro-3-*O*-(2-methoxyethyl)-2-thio-α-D-arabinofuranosyl]-4-thiouracil (4): A solution of **2** (51 mg, 0.17 mmol) and Lawesson's reagent[28] (40 mg, 0.10 mmol) in dry 1,2-dichloroethane (7.0 mL) was heated for 2.5 h at 83°C. After cooling to room temperature the solvent was evaporated. The residue was dissolved in $CHCl_3$, extracted with water, the organic phase was separated and dried with $MgSO_4$ and concentrated. The crude product was purified by column chromatography ($CHCl_3$/MeOH 10:1, R_f = 0.73) and recrystallised from EA to yield **4** (42 mg, 78%) as yellow crystals. M.p. 108°C. $[\alpha]_D^{20} = -110.5$. IR: ν 3105 (NH), 1707 (C=O), 1606 (thioamide B) cm^{-1}. ^1H NMR (500 MHz): δ 2.90 (dd, 1H, H-5′$_a$), 2.95 (dd, 1H, H-5′$_b$), 3.31 (s, 3H, OCH_3), 3.35–3.37 (m, 2H, $CH_2CH_2OCH_3$), 3.49 (ddd, 1H, $CH_aH_bCH_2OCH_3$, ^3J = 3.8, 4.3, ^2J = 11.0 Hz), 3.60 (ddd, 1H, $CH_aH_bCH_2OCH_3$, ^3J = 4.4, 5.2, ^2J = 11.0 Hz), 3.71 (d, 1H, H-2′), 4.22 (d, 1H, H-3′), 4.86 (dd, 1H, H-4′), 5.89 (s, 1H, H-1′), 6.35 (d, 1H, H-5), 7.55 (d, 1H, H-6), 9.61 (bs, 1H, NH). $J_{2',3'}$ = 1.5, $J_{4',5'a}$ = 1.5, $J_{4',5'b}$ = 1.9, $J_{5'a,5'b}$ = 11.0, $J_{5,6}$ = 7.7 Hz. ^{13}C NMR (101 MHz): δ 32.2 (C-5′), 45.6 (C-2′), 59.0 (OCH_3), 69.7 ($CH_2CH_2OCH_3$), 71.3 ($CH_2CH_2OCH_3$), 80.8 (C-4′), 85.3 (C-3′), 92.4 (C-1′), 110.9 (C-5), 136.3 (C-6), 147.6 (2-CO), 189.4 (4-CS). FAB MS; *m/z*: 317 $[M + H]^+$. FAB HRMS: calcd. 317.0630 ($C_{12}H_{17}N_2O_4S_2$); found 317.0626.

1-[2,5-Anhydro-3-*O*-(2-methoxyethyl)-2-thio-α-D-arabinofuranosyl]-4-(triazole-1-yl)-pyrimidine-2(1*H*)-one (5): $POCl_3$ (2.30 mL, 3.86 g, 25.20 mmol) was added to a suspension of 1,2,4-triazole (8.10 g, 117 mmol) in anhydrous MeCN (30 mL) at room temperature and the suspension was cooled to 0°C. Triethylamine (15.4 mL, 11.24 g, 111 mmol) was added to the suspension, then a solution of **2** (584 mg, 1.94 mmol) in MeCN (15 mL) was added and the mixture was stirred at room temperature for 3.5 h. After the reaction was completed triethylamine (10.6 mL) and

water (2.8 mL) were added and stirring was continued for 0.5 h. Solid components were filtered off, the solvents were removed under reduced pressure, the residue was dissolved in $CHCl_3$ and extracted with satd. aq. $NaHCO_3$ solution (40 mL) and water (40 mL). The organic phase was dried with $MgSO_4$, concentrated and the resulting crude product was purified by column chromatography ($CHCl_3$/MeOH 19:1, R_f 0.39) to yield **5** (332 mg, 49%) as a colorless solid. M.p. 153°C. $[\alpha]_D^{20} = -36.2$. ^{1}H NMR (400 MHz): δ 2.97 (dd, 1H, H-5′$_a$), 3.00 (dd, 1H, H-5′$_b$), 3.23 (s, 3H, OCH_3), 3.24–3.31 (m, 2H, $CH_2CH_2OCH_3$), 3.40 (ddd, 1H, $CH_aH_bCH_2OCH_3$, ^3J = 3.0, 4.9, ^2J = 11.0 Hz), 3.54 (ddd, 1H, $CH_aH_bCH_2OCH_3$, ^3J = 3.1, 6.5, ^2J = 11.0 Hz), 3.91 (d, 1H, H-2′), 4.25 (d, 1H, H-3′), 4.94 (dd, 1H, H-4′), 6.07 (s, 1H, H-1′), 6.95 (d, 1H, H-5), 8.12 (s, 1H, $CH_{triazole}$), 8.36 (s, 1H, H-6), 9.28 (s, 1H, $CH_{triazole}$). $J_{2',3'}$ = 1.5, $J_{4',5'a}$ = 1.4, $J_{4',5'b}$ = 1.9, $J_{5'a,5'b}$ = 10.9, $J_{5,6}$ = 7.3 Hz. ^{13}C NMR (101 MHz): δ 32.2 (C-5′), 45.4 (C-2′), 58.9 (OCH_3), 69.5 ($CH_2CH_2OCH_3$), 71.4 ($CH_2CH_2OCH_3$), 81.1 (C-4′), 85.6 (C-3′), 92.7 (C-5), 93.5 (C-1′), 143.2 ($CH_{triazole}$), 148.4 (C-6), 153.1 ($CH_{triazole}$), 154.6, 159.3 (2-CO, C-4). FAB MS; *m/z*: 352 $[M + H]^+$.

1-[2,5-Anhydro-3-*O*-(2-methoxyethyl)-2-thio-α-D-arabinofuranosyl]cytosine (6): A solution of **5** (328 mg, 0.93 mmol) in 1,4-dioxane (11 mL) and 25% aq. NH_3 (5.4 mL) was stirred at room temperature for 24 h. The solvents were evaporated. The residue was dissolved in $CHCl_3$ and extracted with water. The organic phase was separated, dried with $MgSO_4$ and concentrated. The crude product was purified by column chromatography ($CHCl_3$/MeOH 9:1, R_f 0.08) and recrystallised from MeOH to yield **6** [33 mg, 12%, purity 97% (HPLC)] as colorless platelets. M.p. 198°C. $[\alpha]_D^{20} = -48.2$. IR: ν 3451 (NH_2), 3337 (NH_2), 1645 (C=O) cm^{-1}. ^{1}H NMR (400 MHz): δ 2.85 (dd, 1H, H-5′$_a$), 3.01 (dd, 1H, H-5′$_b$), 3.27 (s, 3H, OCH_3), 3.33–3.35 (m, 2H, $CH_2CH_2OCH_3$), 3.42 (ddd, 1H, $CH_aH_bCH_2OCH_3$, ^3J = 3.9, 4.5, ^2J = 10.9 Hz), 3.59 (ddd, 1H, $CH_aH_bCH_2OCH_3$, ^3J = 4.6, 5.0, ^2J = 10.9 Hz), 3.69 (dd, 1H, H-2′), 4.25 (d, 1H, H-3′), 4.74–4.79 (m, 1H, H-4′), 5.80 (d, 1H, H-5), 5.87 (s, 1H, H-1′), 7.80 (d, 1H, H-6). $J_{2',3'}$ = 1.5, $J_{2',4'}$ = 0.6, $J_{4',5'a}$ = 1.3, $J_{4',5'b}$ = 2.0, $J_{5'a,5'b}$ = 10.8, $J_{5,6}$ = 7.5 Hz. ^{13}C NMR (101 MHz): δ 33.0 (C-5′), 47.0 (C-2′), 59.1 (OCH_3), 70.2 ($CH_2CH_2OCH_3$), 72.6 ($CH_2CH_2OCH_3$), 81.8 (C-4′), 86.7 (C-3′), 93.7 (C-5), 94.3 (C-1′), 148.6 (C-6), 158.9, 167.9 (2-CO, C-4). FAB MS; *m/z*: 300 $[M + H]^+$. FAB HRMS: calcd. 300.1018 ($C_{12}H_{18}N_3O_4S$); found 300.1054.

Methyl 2,5-anhydro-3-*O*-(2-fluorobenzyl)-2-thio-α-D-lyxofuranoside (8): A suspension of NaH (60% dispersion in mineral oil, 300 mg, 7.5 mmol) and methyl 2,5-anhydro-2-thio-α-D-lyxofuranoside (**7**)[11] (940 mg, 5.79 mmol) in dry THF (30 mL) was stirred for 5 min. Then 2-fluorobenzyl bromide (1.2 mL, 1.87 g, 9.89 mmol) was added. After 1 h the reaction mixture was filtered, the solvent was evaporated and the crude product was purified by column chromatography (PE/EA 4:1, R_f 0.45) to yield **8** (1.33 g, 85%) as a pale yellow syrup. ^{1}H NMR (500 MHz): δ 2.78 (dd, 1H, H-5$_a$), 3.03 (dd, 1H, H-5$_b$), 3.34 (s, 3H, OCH_3), 3.35 (d, 1H, H-2), 4.41 (ddd, 1H, H-4), 4.50 (dd, 1H, H-3), 4.61, 4.65 (AB-system, 2H, $CH_aH_bC_6H_4F$), 4.90 (s, 1H, H-1), 7.04 (ddd, 1H, H$_{ar}$-3), 7.13 (ddd, 1H, H$_{ar}$-5), 7.28 (dddd, 1H, H$_{ar}$-4), 7.28 (ddd, 1H, H$_{ar}$-6). $J_{2',3'}$ = 2.2, $J_{3',4'}$ = 2.9, $J_{4',5'a}$ = 1.4, $J_{4',5'b}$ = 1.7, $J_{5'a,5'b}$ = 10.1, $J_{CHa,F} < 0.5$, $J_{CHb,F}$ = 0.9, J_{AB} = 11.7, $J_{3ar,4ar}$ = 8.2, $J_{3ar,5ar}$ = 1.2, $J_{3ar,F}$ = 10.1, $J_{4ar,5ar}$ = 7.7, $J_{4ar,6ar}$ = 1.8, $J_{4ar,F}$ = 5.3, $J_{5ar,6ar}$ = 7.5, $J_{6ar,F}$ = 7.5 Hz. ^{13}C NMR (126 MHz): δ 34.9 (C-5), 48.6

(C-2), 55.0 (CH_3), 65.4 (d, $CH_2C_6H_4F$), 76.0 (C-4), 79.9 (C-3), 109.7 (C-1), 115.3 (d, C-3′), 124.2 (d, C-5′), 124.6 (d, C-1′), 129.7 (d, C-4′), 130.2 (d, C-6′), 160.6 (d, C-2′). $J_{CH2,F}$ 3.6, $J_{1,F}$ 14.5, $J_{2,F}$ 247.1, $J_{3,F}$ 21.8, $J_{4,F}$ 8.5, $J_{5,F}$ 3.6, $J_{6,F}$ 3.6 Hz. MS: *m/z* (%): 270 (0.9) $[M]^{+\cdot}$, 239 (2) $[M-OCH_3]^+$, 210 (2), 195 (2), 177 (2), 165 (2), 163 (3), 141 (4), 123 (3), 110 (10), 109 (100) $[C_7H_6F]^{+\cdot}$, 101 (12), 89 (2), 87 (4), 86 (10), 85 (35), 84 (9), 83 (10), 73 (11), 68 (3), 59 (3), 45 (6). $C_{13}H_{15}FO_3S$ (270.32) calcd. C, 57.76; H, 5.59; F, 7.03; found C, 57.99; H, 5.69; F, 6.26.

1-[2,5-Anhydro-3-*O*-(2-fluorobenzyl)-2-thio-α-D-lyxofuranosyl]uracil (9): Compound **9** was prepared as described for **2** from **8** (150 mg, 0.55 mmol), 2,4-bis-*O*-trimethylsilyluracil[18] (600 mg, 2.34 mmol), TMSOTf (0.33 mL, 406 mg, 1.83 mmol) and 4 Å molecular sieves (30 mg) in MeCN (7.0 mL). After chromatographic work up (PE/EA 1:1, R_f = 0.07) and recrystallisation from EtOH **9** [44 mg, 23%, purity 99% (HPLC)] was obtained as colorless needles. A single crystal was suitable for an X-ray structural analysis. M.p. 146°C. $[\alpha]_D^{20} = -100.8$. IR: ν 3148 (NH), 1694 (C=O) cm^{-1}. ^1H NMR (500 MHz): δ 3.00 (dd, 1H, H-5′$_a$), 3.14 (dd, 1H, H-5′$_b$), 3.84 (d, 1H, H-2′), 4.10 (dd, 1H, H-3′), 4.59, 4.64 (AB-system, 2H, $CH_2C_6H_4F$), 4.67 (ddd, 1H, H-4′), 5.72 (d, 1H, H-5), 5.79 (s, 1H, H-1′), 7.06 (ddd, 1H, H$_{ar}$-3), 7.16 (ddd, 1H, H$_{ar}$-5), 7.32 (dddd, 1H, H$_{ar}$-4), 7.39 (ddd, 1H, H$_{ar}$-6), 7.50 (d, 1H, H-6), 9.49 (bs, 1H, NH). $J_{2',3'} = 2.3$ $J_{3',4'} = 2.7$ $J_{4',5'a} = 1.2$, $J_{4',5'b} = 1.6$, $J_{5'a,5'b} = 10.7$, $J_{CH2,F} = 1.2$ $J_{AB} = 11.6$, $J_{5,6} = 8.1$, $J_{5,6} = 8.1$, $J_{3ar,4ar} = 8.2$, $J_{3ar,5ar} = 1.0$, $J_{3ar,F} = 9.9$, $J_{4ar,5ar} = 7.7$, $J_{4ar,6ar} = 2.0$, $J_{4ar,F} = 5.6$, $J_{5ar,6ar} = 7.5$, $J_{6ar,F} = 7.5$ Hz. ^{13}C NMR (126 MHz): δ 34.9 (C-5′), 49.0 (C-2′), 65.8 (d, $CH_2C_6H_4F$), 77.9 (C-3′), 78.3 (C-4′), 92.5 (C-1′), 101.4 (C-5), 115.5 (d, C$_{ar}$-3), 123.8 (d, C$_{ar}$-1), 124.6 (d, C$_{ar}$-5), 130.5 (d, C$_{ar}$-4), 130.8 (d, C$_{ar}$-6), 138.9 (C-6), 150.3 (2-CO), 160.9 (d, C$_{ar}$-2), 164.4 (4-CO). $J_{1ar,F} = 14.8$, $J_{2ar,F} = 247.0$, $J_{3ar,F} = 21.5$, $J_{4ar,F} = 8.3$, $J_{5ar,F} = 3.7$, $J_{6ar,F} = 3.9$, $J_{CH2,F} = 3.6$ Hz. FAB-MS; *m/z*: 351 $[M + H]^+$. FAB HRMS: calcd. 351.0815 ($C_{16}H_{16}FN_2O_4S$); found 351.0844.

1-[2,5-Anhydro-3-*O*-(2-fluorobenzyl)-2-thio-α-D-lyxofuranosyl]thymine (10): Compound **10** was prepared as described for **2** from **8** (150 mg, 0.55 mmol), 2,4-bis-*O*-trimethylsilylthymine[19] (630 mg, 2.33 mmol), TMSOTf (0.33 mL, 406 mg, 1.83 mmol) and 4 Å molecular sieves (30 mg) in MeCN (7.0 mL). After chromatographic work up (PE/EA 1:1, R_f = 0.12) and recrystallisation from EtOH **10** [114 mg, 56%, purity 98% (HPLC)] was obtained as colorless needles. A single crystal was suitable for an X-ray structural analysis. M.p. 194°C. $[\alpha]_D^{20} = -69.8$. IR: ν 3168 (NH), 1681(C = O) cm^{-1}. ^1H NMR (500 MHz): δ 1.94 (d, 3H, CH_3), 2.99 (dd, 1H, H-5′$_a$), 3.14 (dd, 1H, H-5′$_b$), 3.84 (d, 1H, H-2′), 4.11 (dd, 1H, H-3′), 4.59, 4.62 (AB-system, 2H, $CH_2C_6H_4F$), 4.65 (ddd, 1H, H-4′), 5.79 (s, 1H, H-1′), 7.04 (ddd, 1H, H$_{ar}$-3), 7.15 (ddd, 1H, H$_{ar}$-5), 7.25 (q, 1H, H-6), 7.32 (dddd, 1H, H$_{ar}$-4), 7.39 (ddd, 1H, H$_{ar}$-6), 8.89 (bs, 1H, NH). $J_{2',3'} = 2.3$, $J_{3',4'} = 2.7$, $J_{4',5'a} = 1.4$, $J_{4',5'b} = 1.6$, $J_{5'a,5'b} = 10.6$, $J_{CH2,F} = 1.1$, $J_{AB} = 11.7$, $J_{6,Me} = 1.2$, $J_{3ar,4ar} = 8.4$, $J_{3ar,5ar} = 1.2$, $J_{3ar,F} = 9.9$, $J_{4ar,5ar} = 7.5$, $J_{4ar,6ar} = 1.8$, $J_{4ar,F} = 5.4$, $J_{5ar,6ar} = 7.5$, $J_{6ar,F} = 7.5$ Hz. ^{13}C NMR (126 MHz): δ 12.7 (CH_3), 34.9 (C-5′), 48.9 (C-2′), 65.6 (d, $CH_2C_6H_4F$), 77.7 (C-3′), 78.2 (C-4′), 92.4 (C-1′), 109.9 C-5), 115.4 d, (C$_{ar}$-3), 123.7 (d, C$_{ar}$-1), 124.5 (d, C$_{ar}$-5), 130.5 (d, C$_{ar}$-4), 130.8 (d, C$_{ar}$-6), 134.2 (C-6), 149.8 (2-CO), 160.8 (d, C$_{ar}$-2), 163.7 (4-CO). $J_{1ar,F} = 14.8$, $J_{2ar,F} = 247.1$, $J_{3ar,F} = 21.4$, $J_{4ar,F} = 8.3$, $J_{5ar,F} = 3.6$, $J_{6ar,F} = 3.9$, $J_{CH2,F} = 3.6$ Hz. FAB MS; *m/z*: 365 $[M + H]^+$. FAB HRMS: calcd. 365.0971

($C_{17}H_{18}FN_2O_4S$); found 365.0952. $C_{17}H_{17}FN_2O_4S$ (364.40) calcd. C, 56.03; H, 4.70; F, 5.21; N, 7.69; found C, 56.21; H, 4.77; F, 5.01; N, 7.31.

9-[2,5-Anhydro-3-*O*-(2-fluorobenzyl)-2-thio-α-D-lyxofuranosyl]adenine (11): Compound **11** was prepared as described for **2** from **8** (150 mg, 0.55 mmol), adenine (135 mg, 1.10 mmol), TMSOTf (0.52 mL, 640 mg, 2.88 mmol) and 4 Å molecular sieves (40 mg) in MeCN (10 mL). After chromatographic work up ($CHCl_3$/MeOH 12:1, R_f = 0.19) recrystallisation from EtOH **11** [21 mg, 10%, purity 99% (HPLC)] was obtained as colorless platelets. A single crystal was suitable for an X-ray structure analysis. M.p. 181°C. $[\alpha]_D^{20} = -76.4$. IR: ν 3436 (NH_2), 3138 (NH), 1673 (C=N) cm^{-1}. ^{1}H NMR (400 MHz): δ 3.06 (dd, 1H, H-5′$_a$), 3.21 (dd, 1H, H-5′$_b$), 4.15 (d, 1H, H-2′), 4.40 (dd, 1H, H-3′), 4.56, 4.64 (AB-system, 2H, CH_aH_bC$_6$H$_4$F), 4.70 (ddd, 1H, H-4′), 6.21 (s, 1H, H-1′), 7.00 (ddd, 1H, H$_{ar}$-3), 7.10 (ddd, 1H, H$_{ar}$-5), 7.26–7.32 (m, 1H, H$_{ar}$-4), 7.36 (ddd, 1H, H$_{ar}$-6), 7.94 (s, 1H, H-2), 8.31 (s, 1H, H-8). $J_{2',3'}$ = 2.3, $J_{3',4'}$ = 2.8, $J_{4',5'a}$ = 1.4, $J_{4',5'b}$ = 1.7, $J_{5'a,5'b}$ = 10.6, $J_{CHa,F}$ = 0.6, $J_{CHb,F}$ = 1.1, J_{AB} = 11.7, $J_{3ar,4ar}$ = 8.5, $J_{3ar,5ar}$ = 1.2, $J_{3ar,F}$ = 9.9, $J_{4ar,5ar}$ = 7.5, $J_{4ar,6ar}$ = 1.8, $J_{5ar,6ar}$ = 7.5, $J_{6ar,F}$ = 7.5 Hz. ^{13}C NMR (101 MHz): δ 35.2 (C-5′), 48.8 (C-2′), 65.7 (d, *C*H$_2$C$_6$H$_4$F), 77.8 (C-4′), 78.8 (C-3′), 91.6 (C-1′), 115.4 (d, C$_{ar}$-3), 119.8 (C-5), 123.8 (d, C$_{ar}$-1), 124.4 (d, C$_{ar}$-5), 130.3 (d, C$_{ar}$-4), 130.6 (d, C$_{ar}$-6), 137.8 (C-2), 148.4 (C-4), 152.5 (C-8), 155.2 (C-6), 160.8 (d, C$_{ar}$-2). $J_{1ar,F}$ = 14.6, $J_{2ar,F}$ = 247.3, $J_{3ar,F}$ = 21.5, $J_{4ar,F}$ = 8.4, $J_{5ar,F}$ = 3.6, $J_{6ar,F}$ = 4.1, $J_{CH2,F}$ = 2.0 Hz. FAB MS; *m/z*: 374 $[M + H]^+$. FAB HRMS: calcd. 374.1087 ($C_{17}H_{17}FN_5O_2S$); found 374.1094.

Attempted preparation of the nucleoside analogues **13** and **14**. The reaction of methyl 3,5-anhydro-2-*O*-mesyl-3-thio-β-L-lyxofuranoside (**12**)[11,12] with 2,4-bis-*O*-trimethylsilyluracil[18] or -thymine[19] in the presence of TMSOTf and 4 Å molecular sieves in MeCN was performed as described for the preparation of **2** (1.5 h at 10°C or 2 h at 50°C). After work up **12** was recovered quantitatively.

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