Isonucleosides with Exocyclic Methylene Groups

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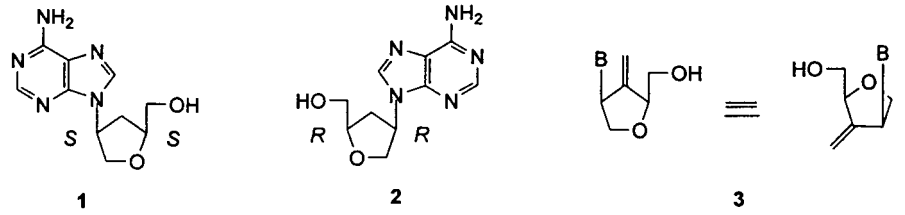
Dedicated to Prof. Dr. *Frank Seela* on the occasion of his 60th birthday

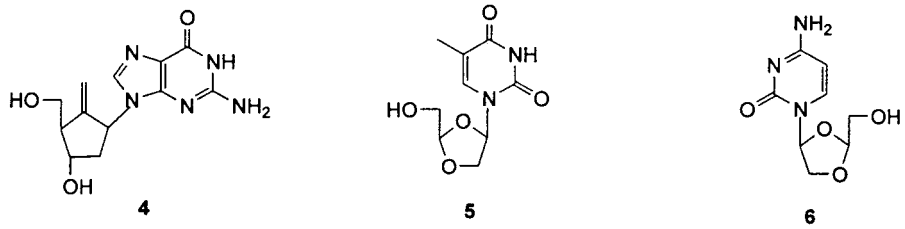
Synthesis of isonucleosides **13**, **14**, **16**, and **17**, bearing an exocyclic methylidene group at the sugar moiety, starting from a 3-keto sugar is described. The keto compound was converted to the methylene-sugar **10b** (*Scheme 1*), which was coupled with nucleobases by means of the *Mitsunobu* reaction. The coupling reaction with adenine and 8-azaadenine produced both the N^9- and N^3-nucleosides (see **13** and **14**, resp.; *Scheme 2*). The structures of **13a** and **14a** were confirmed by single-crystal X-ray data. Synthesis of the pyrimidine compounds was also approached from the β-amino sugar **20** that was prepared using a *Gabriel*-synthesis methodology (*Scheme 3*).

Introduction. – For a number of years, we have been investigating the synthesis, enzymology, and antiviral studies of various isomeric nucleosides in our laboratory [1]. For example, (2*S*,4*S*)-4-(6-amino-9*H*-purin-9-yl)tetrahydrofuran-2-methanol ((*S*,*S*)-isoddA; **1**), an isomeric dideoxynucleoside synthesized by us, exhibits activity against HIV-1 and HIV-2 [2]. Our interest in synthesizing analogs of (*S*,*S*)-isoddA (**1**) led us to the design of isomeric dideoxynucleosides **3** with an exocyclic methylene group. This synthetic design was supported by the observation of the *anti*-HIV and *anti*-HBV activity of carbocyclic nucleoside **4** [3] and the *anti*-HIV activity of the dioxolanyl compounds **5** and **6** [4]. It is likely that the antiviral activity of **4** is associated with its ability to function as a structural analog of 2′-deoxyguanosine. The exocyclic C=C bond appears to act as a functional replacement for the O-atom at that position. If this is so then our target molecules **3** (and mirror images) are related to both **4**, in which the endocyclic O-atom has replaced the exocyclic OH, and to compounds **5** and **6**. This paper reports the synthesis and antiviral studies of novel isonucleosides with exocyclic methylene groups.

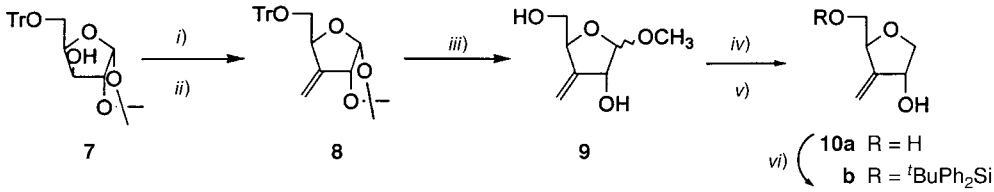
Results and Discussion. – Synthesis of the methylene-isonucleosides was approached from the corresponding carbohydrate precursor bearing the exocyclic methylene group. The synthesis commenced with the protected D-xylose **7** [5]. Oxidation of the 3-OH group with DMSO and P_2O_5 [6] and subsequent *Wittig* reaction [7][8] on the resulting ketone with NaH and (Ph_3PMe)Br in DMSO produced the alkene **8**. Acid-catalyzed methanolysis [9] of the acetonide group afforded the α- and β-D-glycosides **9**. Reductive demethoxylation was carried out by refluxing **9** with hexamethyldisilazane (HMDS) followed by treatment with Et_3SiH and $Me_3SiOSO_2CF_3$ [9–11] in MeCN at room temperature to give **10a**. The primary OH group of **10a** was selectively protected [12] with the (*tert*-butyl)diphenylsilyl group to yield **10b**, which was the key starting material for the synthesis of both isodideoxypurine and pyrimidine nucleosides (*Scheme 1*).



Enantiomeric IsoddAs



Scheme 1

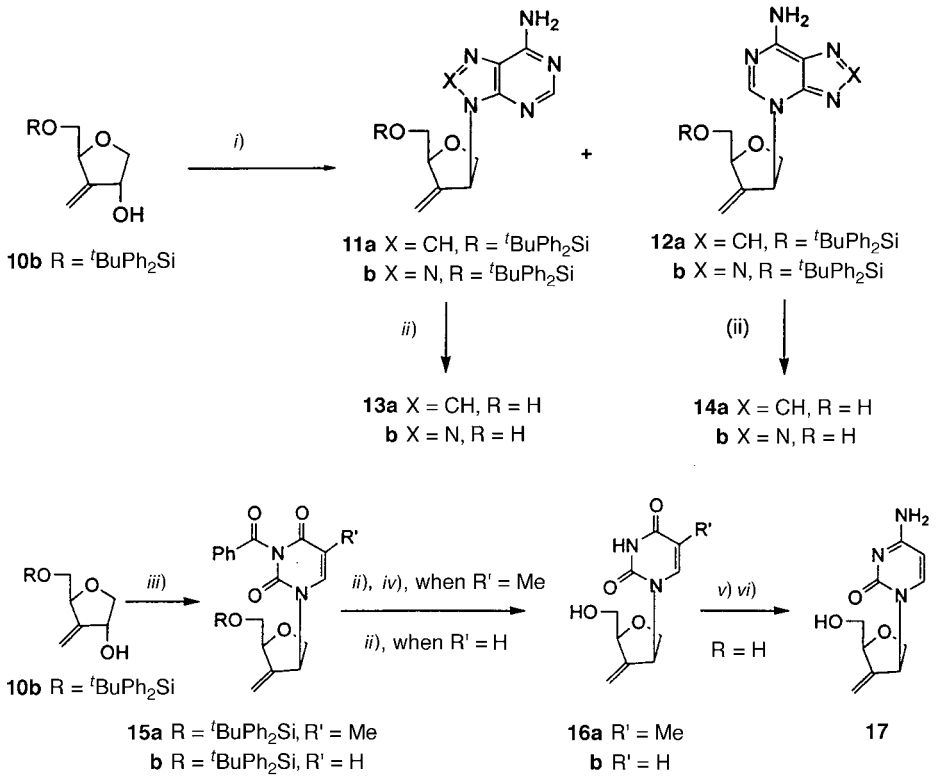


i) DMSO, P_2O_5, r.t. *ii*) NaH, DMSO, $(Ph_3PMe)Br$. *iii*) HCl, MeOH. *iv*) Me_3SiCl, HMDS. *v*) Et_3SiH, $Me_3SiOSO_2CF_3$, MeCN, r.t. *vi*) $^t BuPh_2SiCl$, pyridine, 4°.

Purine isonucleosides having adenine or 8-azaadenine bases were synthesized *via* the *Mitsunobu* reaction [13–15]. Interestingly, treatment of **10b** with adenine in the presence of DEAD (diethyl diazenedicarboxylate) and Ph_3P in dioxane at room temperature produced the N^9-isomer **11a** and its N^3 isomer **12a** (*Scheme 2*). Similarly, compounds **11b** and **12b** were obtained when **10b** was treated with 8-azaadenine under *Mitsunobu* conditions. Desilylation of compounds **11** and **12** with NH_4F in MeOH afforded compounds **13** and **14**, respectively. The structures of both the N^9- and N^3-isomers of the coupling products were confirmed by their multinuclear NMR and HR-MS data and particularly by their UV spectra and single-crystal X-ray data. For example, the UV spectrum of compound **13a** showed a λ_{max} at 261 nm (ε 14000), whereas compound **14a** exhibited a λ_{max} at 275 nm (ε 13300). The X-ray structure of **13a** (*Fig. 1*) confirmed unequivocally its structure and absolute configuration and showed the glycosidic bond attachment of N(9) of the base, the presence of the exocyclic methylene group, the *anti*-conformation about the glycosidic bond, and the *endo* puckering of the sugar ring at the O-atom. The X-ray structure of compound **14a** also confirmed its structure and absolute configuration but showed the attachment of the base at N(3) (*Fig. 2*). Interestingly, the crystal structure of compound **14a** showed the presence of two independent molecules in an asymmetric unit. Each formed a dimer *via*

two H-bonds with a symmetry equivalent molecule of the other (*i.e.*, molecule A was dimerized with molecule B, and *vice versa*). The two molecules differ in conformation mainly at the primary OH group of the sugar moiety.

Scheme 2



i) Ph_3P, DEAD, purine base, dioxane. *ii*) NH_4F, MeOH. *iii*) 3-benzoylthymine or uracil, Ph_3P, DEAD, THF. *iv*) MeONa, MeOH. *v*) Ac_2O, pyridine. *vi*) $^iPr_3SiCl$, 4-(dimethylamino)pyridine, Et_3N, MeCN, then NH_4OH

Isodideoxypyrimidine nucleosides having an exocyclic methylene group were also synthesized by the *Mitsunobu* reaction. Thus, compound **10b**, on treatment with 3-benzoyluracil or 3-benzoylthymine under *Mitsunobu* conditions gave the desired products **15a**,**b** (*Scheme 2*). The protecting groups of **15a**,**b** were removed by treatment with NH_4F or by successive treatment with NH_4F and NaOMe to produce **16a**,**b**. It is interesting to note that in the case of the uracil derivative **15b**, only NH_4F treatment was required to completely deprotect to product **16b**. Compound **16b** was converted to the corresponding cytosine derivative **17** according to a previously reported procedure [16].

Because of the relatively low yields obtained in the *Mitsunobu* coupling procedure with pyrimidine nucleosides, we also developed an approach to these compounds from the appropriate amino sugar **20** which was prepared from **10b** (*Scheme 3*). When compound **10b** was treated with phthalimide under *Mitsunobu*-reaction conditions, no

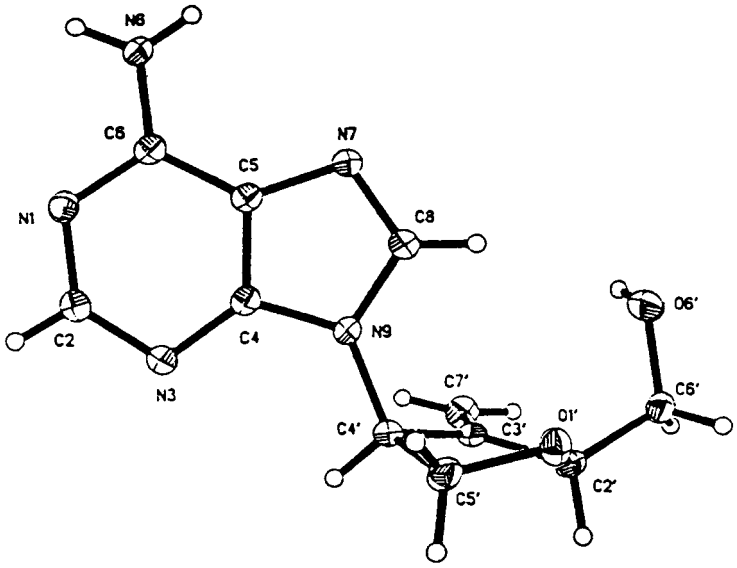


Fig. 1. *ORTEP Plot of single-crystal X-ray structure of* **13a**

phthalimido derivative **19** was obtained. However, the reaction of mesylate **18**, prepared from **10b**, with potassium phthalimide in DMF produced stereospecifically the substituted product **19**. It should be mentioned that treatment of mesylate **18** with NaN_3 did not give the S_N2 product but compound **22** resulting from the S_N2'

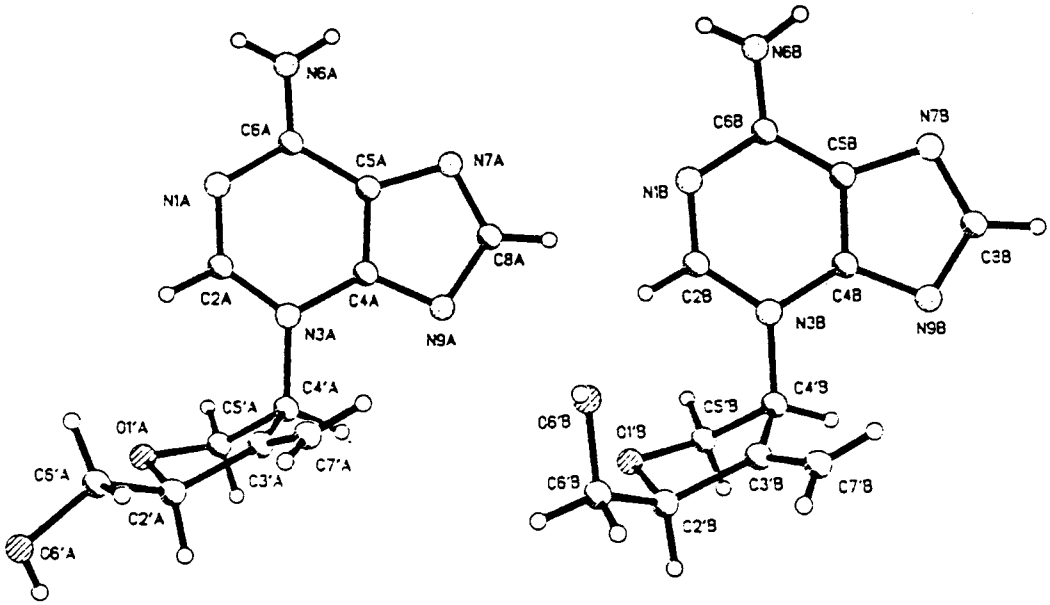
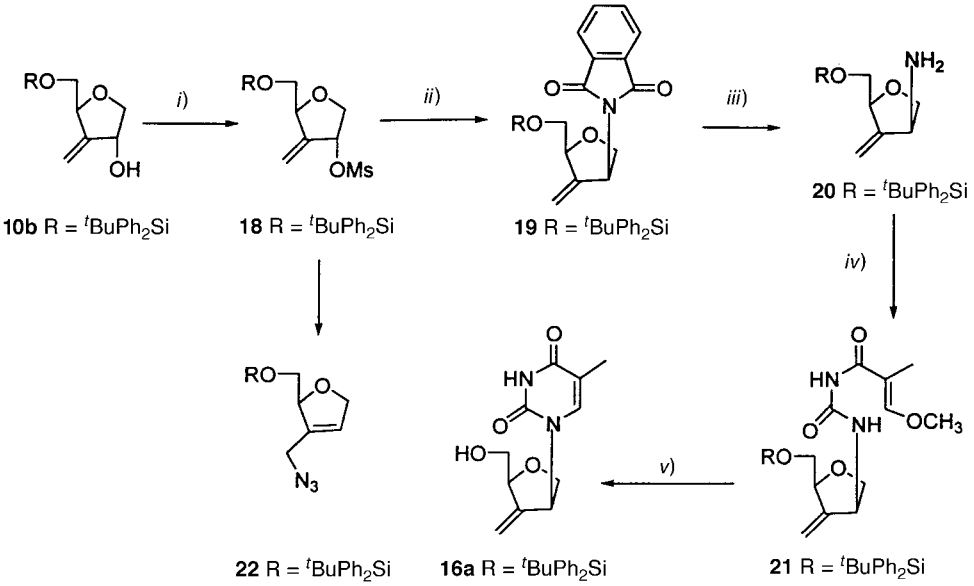


Fig. 2. *ORTEP Plot of single-crystal X-ray structure of* **14a**

displacement reaction by the azido group. The amino derivative **20** was obtained by the deprotection of **19** with hydrazine [17]. Treatment of **20** with 3-methoxy-2-methylprop-2-enoyl isocyanate [10][18][19] produced **21**, which, on acid-catalyzed cyclization, produced the thymine derivative **16a**.

Scheme 3



10b R = ^{t}BuPh$_2$Si **18** R = ^{t}BuPh$_2$Si **19** R = ^{t}BuPh$_2$Si **20** R = ^{t}BuPh$_2$Si

22 R = ^{t}BuPh$_2$Si **16a** R = ^{t}BuPh$_2$Si **21** R = ^{t}BuPh$_2$Si

i) MsCl, Et_3N, CH_2Cl_2, 0°. *ii*) Potassium phthalimide, DMF, 110°. *iii*) NH_2NH_2, EtOH, reflux. *iv*) 3-Methoxy-2-methylprop-2-enoyl isocyanate, DMF, Et_2O, 0° to r.t. *v*) 2N H_2SO_4, dioxane, 100°. *vi*) NaN_3, DMF, 90°.

In summary, synthesis of the methylene-isonucleosides **13**, **14**, **16**, and **17** was achieved starting from a 3-keto sugar prepared from inexpensive D-xylose. The keto sugar was converted to an appropriate methylene-bearing carbohydrate precursor that was coupled, *via* the *Mitsunobu* reaction, with nucleobases. Synthesis of the pyrimidine compound **16a** was also approached from the β-amino sugar **20** which was prepared by means of a *Gabriel*-synthesis methodology. In the case of the direct coupling reaction with adenine and 8-azaadenine, both the N^9- and N^3-nucleosides (see **13** and **14**) were produced. The structure of **13a** and **14a** was unequivocally confirmed by single-crystal X-ray data. Preliminary antiviral evaluations suggested that the target compounds did not show significant *anti*-HIV activity *in vitro* in infected CEM-SS cells. Further biological studies are in progress.

We are grateful to Dr. *Dale Swenson* for the single-crystal X-ray structure determinations and Dr. *Lynn Teesch* and Ms. *Diane Herschberger* for the HR-MS data. This research work was supported by the *N.I.H.* (*National Institute of Allergy and Infectious Diseases*). We thank the *National Cancer Institute* for the *anti*-HIV evaluations.

Experimental Part

General. M.p.s.: uncorrected. *Electrothermal-Engineering-Ltd.* melting-point apparatus. UV Spectra: *Cary-3* UV-Visible spectrophotometer. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-AC-300* instrument at 300 and 75 MHz, resp., δ in ppm referenced to internal $SiMe_4$ for ^{1}H and to solvent $CDCl_3$, (D_6)DMSO, (D_6)acetone, or CD_3OD) for ^{13}C. Column chromatography (CC): 230–400 mesh silica gel. High-resolution FAB-MS: *VG-ZAB-HF* high-resolution mass spectrometer.

*3-Deoxy-1,2-*O*-isopropylidene-3-methylidene-5-*O*-trityl-α-*D*-ribofuranose* (**8**). To a soln. of **7** [5] (4.3 g, 10 mmol) in DMSO (30 ml), P_2O_5 (2.6 g, 18.3 mmol) was carefully added while maintaining the temp. at 20–30°. The mixture was stirred at 30° for 20 h. The brown soln. was diluted with $CHCl_3$ (120 ml) and washed with ice-cold H_2O until the washings were neutral. The org. phase was dried (Na_2SO_4) and evaporated and the residue purified by CC: keto compound as white solid foam (2.9 g, 67%).

NaH (0.72 g, 15.1 mmol) was suspended in DMSO (30 ml) and the mixture heated at 75° for 45 min under N_2. After the soln. was cooled to r.t., methyltriphenylphosphonium bromide (5.8 g, 16.3 mmol) was added, and the soln. was stirred at r.t. for 30 min. To this mixture a soln. of the keto compound in DMSO (20 ml) was added dropwise. After the addition, the mixture was stirred for an additional 2 h and then poured into H_2O (100 ml). The aq. soln. was extracted with Et_2O (3 × 60 ml), the combined org. phase washed with H_2O (2 × 75 ml), dried (Na_2SO_4), and evaporated, and the gummy residue purified by CC: **8** (2.3 g, 89%). White solid. M.p. 159–160°. ^{1}H-NMR ($CDCl_3$): 7.46–7.17 (*m*, 3 Ph); 5.95 (*d*, *J* = 4.1, H–C(1)); 5.34 (*t*, *J* = 1.1, 1 H, =CH_2); 5.04 (*t*, *J* = 1.4, 1 H, =CH_2); 4.94–4.87 (*m*, H–C(2), H–C(4)); 3.28 (*dd*, *J* = 9.9, 4.0, H_a–C(5)); 3.19 (*dd*, *J* = 9.9, 4.5, H_b–C(5)); 1.52 (*s*, 3 H, Me_2C); 1.39 (*s*, 3 H, Me_2C). ^{13}C-NMR ($CDCl_3$): 147.0 (C(3)); 143.7 (Ph); 128.6, 127.7, 127.0 (Ph); 112.4 (Me_2*C*); 111.8 (=CH_2); 104.8 (C(1)); 86.6 (Ph_3*C*); 81.8 (C(2)); 79.1 (C(4)); 65.8 (C(5)); 27.4, 27.1 (*Me*$_2$C). HR-FAB-MS: 451.1885 ($C_{28}H_{28}NaO_4Si^+$, $[M+Na]^+$; calc. 451.1885).

*(3*R*,5*S*)-5-{[[(*tert*-Butyl)diphenylsilyl]oxy}methyl]tetrahydro-4-methylidenefuran-3-ol* (**10b**). To a soln. of **8** (5.7 g, 13.3 mmol) in MeOH (150 ml) 4N HCl in dioxane (0.27 ml) was added, and the mixture was heated under reflux for 2 h. The acid was neutralized with K_2CO_3, the suspension adsorbed on silica gel, and the mixture purified by CC: **9** (1.66 g, 78%). Oil.

A mixture of **9** (0.54 g, 3.4 mmol) and Me_3SiCl (0.25 ml) in hexamethyldisilazane (HMDS; 25 ml) was heated under reflux for 17 h. Unreacted HMDS was evaporated to afford a pale yellow liquid. Dry MeCN was added to the residue followed by the addition of Et_3SiH (1.6 ml, 10.2 mmol) and $Me_3SiOSO_2CF_3$ (1.8 ml, 10.2 mmol), and the mixture was stirred overnight at r.t. It was then quenched with H_2O (5 ml), stirred for 1 h, and then neutralized with *Dowex* resin (OH^- form). The soln. was filtered, the filtrate evaporated, and the residue purified by CC: *(2*S*,4*R*)-tetrahydro-4-hydroxy-3-methylidenefuran-2-methanol* (**10a**; 78%). Oil. ^{1}H-NMR (CD_3OD): 5.29 (*t*, *J* = 2.2, 1 H, =CH_2); 5.11 (*t*, *J* = 2.0, 1 H, =CH_2); 4.55–4.48 (*m*, H–C(2), H–C(4)); 4.04 (*dd*, *J* = 9.0, 6.1, H_a–C(5)); 3.61 (*dd*, *J* = 11.8, 3.5, 1 H, CH_2); 3.50 (*m*, 2 H, H_b–C(5), CH_2). ^{13}C-NMR (CD_3OD): 152.2 (C(3)); 108.6 (=CH_2); 82.2 (C(2)); 74.2 (C(4)); 73.5 (C(5)); 65.4 (CH_2).

^{t}BuPh$_2$SiCl (0.57 ml, 2.2 mmol) was added to a soln. of **10a** (0.26 g, 2 mmol) in pyridine (20 ml) at 0°. After the addition, the mixture was stirred at 0° for 6 h and at 4° overnight. The reaction mixture was quenched with H_2O (2 ml). Pyridine was evaporated and the conc. soln. co-evaporated with toluene. The residue was purified by CC: **10b** (0.62 g, 84%). Gum. ^{1}H-NMR ($CDCl_3$): 7.68–7.38 (*m*, 2 Ph); 5.34 (*s*, 1 H, =CH_2); 5.08 (*s*, 1 H, =CH_2); 4.60 (*m*, H–C(3), H–C(5)); 4.1 (*dd*, *J* = 9.3, 5.6, H_a–C(2)); 3.68 (*m*, H_b–C(2), CH_2); 1.04 (*s*, Me_3C). ^{13}C-NMR ($CDCl_3$): 151.3 (C(4)); 135.5, 135.4, 133.2, 133.1, 129.6, 129.5, 127.5 (Ph); 108.6 (=CH_2); 80.6 (C(3)); 73.9, 72.9 (C(2), C(5)); 66.4 (CH_2); 26.6 (Me_3*C*); 19.1 (*Me*$_3$C). HR-FAB-MS: 391.1695 ($C_{22}H_{28}NaO_3Si^+$, $[M+Na]^+$; calc. 391.1705).

*(2*S*,4*S*)-4-(6-Amino-9*H*-purin-9-yl)tetrahydro-3-methylidenefuran-2-methanol* (**13a**) *and (2*S*,4*S*)-4-(6-Amino-3*H*-purin-3-yl)tetrahydro-3-methylidenefuran-2-methanol* (**14a**). To a suspension of **10b** (0.61 g, 1.66 mmol), Ph_3P (0.65 g, 2.5 mmol), and adenine in dioxane (80 ml) at r.t., DEAD (0.4 ml, 2.6 mmol) was added dropwise. After the addition, the mixture was stirred at r.t. for 22 h. The solvent was then evaporated and the residue purified by CC: **11a** (0.34 g, 42%) and **12a** (0.15 g, 19%).

Data of **11a**: M.p. 170°. ^{1}H-NMR ($CDCl_3$): 8.33 (*s*, H–C(8)); 7.90 (*s*, H–C(2)); 7.69–7.35 (*m*, 2 Ph); 5.87 (*s*, NH_2); 5.64 (br. *s*, H–C(4′)); 5.27 (*m*, =CH_2); 4.20 (*dd*, *J* = 10.0, 6.0, H_a–C(5′)); 4.14 (*dd*, *J* = 10.0, 4.0, H_b–C(5′)); 3.93 (*d*, *J* = 4.7, CH_2). ^{13}C-NMR ($CDCl_3$): 155.5 (C(6)); 152.9 (C(2)); 150.0 (C(4)); 146.9 (C(3′)); 138.9 (C(8)); 135.6, 132.9, 129.8, 127.8 (2 Ph); 119.3 (C(5)); 112.1 (=CH_2); 81.3 (C(2′)); 72.1 (C(5′)); 65.6 (CH_2); 56.6 (C(4′)); 26.8 (Me_3*C*); 19.2 (*Me*$_3$C).

Data of **12a**: M.p. 160–161°. ^{1}H-NMR ($CDCl_3$); 8.36 (*s*, H–C(8)); 8.02 (*s*, H–C(2)); 7.70–7.26 (*m*, 2 Ph); 6.05 (br. *s*, H–C(4′)); 5.50 (br. *s*, 1 H, =CH_2); 5.40 (br. *s*, 1 H, =CH_2); 4.50 (*m*, H–C(2′)); 4.25 (*d*, *J* = 4.0,

2 H–C(5′)); 4.02 (*dd*, *J* = 11.5, 3.9, 1 H, CH_2); 3.97 (*dd*, *J* = 11.4, 4.4, 1 H, CH_2); 1.07 (*s*, Me_3C). ^{13}C-NMR ($CDCl_3$): 154.4 (C(6)); 153.7 (C(2)); 150.6 (C(4)); 145.8 (C(3′)); 140.8 (C(8)); 135.5, 132.8, 129.9, 127.8 (Ph); 120.5 (C(5)); 113.9 (=CH_2); 81.5 (C(2′)); 72.5 (C(5′)); 64.9 (CH_2); 61.3 (C(4′)); 26.8 (Me_3C); 19.1 (*Me*$_3$C).

To a soln. of **11a** (0.32 g, 0.66 mmol) in MeOH (30 ml), NH_4F (0.4 g) was added and the soln. heated under reflux for 3 h. The soln. was then adsorbed on silica gel and purified by CC: **13a** (0.14 g, 85%). White solid. M.p. 190°. UV (MeOH): 260.6 (14000). ^{1}H-NMR ((D$_6$)DMSO): 8.15 (2*s*, H–C(2), H–C(8)); 7.25 (br. *s*, NH_2); 5.56 (*t*, H–C(4′)); 5.30 (br. *s*, 1 H, =CH_2); 5.15 (*t*, *J* = 2.0, 1 H, =CH_2); 5.06 (*t*, *J* = 5.6, OH); 4.44 (br. *s*, H–C(2′)); 3.73 (*m*, 2 H–C(5′)); 3.31 (*t*, *J* = 6.7, CH_2). ^{13}C-NMR (CD_3OD): 157.3 (C(6)); 153.7 (C(2)); 150.5 (C(4)); 148.6 (C(3′)); 141.4 (C(8)); 119.9 (C(5)); 112.7 (=CH_2); 83.1 (C(2′)); 72.9 (C(5′)); 64.2 (CH_2); 58.7 (C(4′)). HR-FAB-MS: 270.0959 ($C_{11}H_{13}N_5NaO_2^+$, $[M+Na]^+$; calc. 270.0966).

Compound **12a** was similarly deprotected to give **14a** (86%). White solid. M.p. 256°. UV (MeOH): 274.5 (13300). ^{1}H-NMR (CD_3OD): 8.62 (*s*, H–C(8)); 7.90 (*s*, H–C(2)); 5.85 (*m*, H–C(4′)); 5.49 (*m*, CH_2); 4.52 (br. *s*, H–C(2′)); 4.29 (*dd*, *J* = 10.6, 2.7, H_a–C(5′)); 4.22 (*dd*, *J* = 10.6, 5.9, H_b–C(5′)); 4.00 (*dd*, *J* = 12.5, 2.9, 1 H, CH_2); 3.90 (*dd*, *J* = 12.4, 3.3, 1 H, CH_2). ^{13}C-NMR (CD_3OD): 156.6 (C(6)); 152.9 (C(2)); 150.5 (C(4)); 147.4 (C(3′)); 144.3 (C(8)); 120.8 (C(5)); 114.4 (=CH_2); 83.3 (C(2′)); 73.1 (C(5′)); 63.7 (CH_2); 63.6 (C(4′)). HR-FAB-MS: 270.0954 ($C_{11}H_{13}N_5NaO_2^+$, $[M+Na]^+$; calc. 270.0966).

*(2*S*,4*S*)-4-(7-Amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)tetrahydro-3-methylidenefuran-2-methanol* (**13b**) *and (2*S*,4*S*)-4-(7-Amino-4*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-4-yl)tetrahydro-3-methylidenefuran-2-methanol* (**14b**). Compounds **11b** and **12b** were synthesized as described for **13a** and **13b** in 50 and 23% yield, resp.

Data of **11b**: M.p. 168°. ^{1}H-NMR ($CDCl_3$): 8.37 (*s*, H–C(5)); 7.73–7.34 (*m*, 2 Ph); 7.06 (br. *s*, NH_2); 5.93 (*t*, *J* = 6.3, H–C(4′)); 5.25 (*s*, 1 H, =CH_2); 5.04 (*s*, 1 H, =CH_2); 4.74 (*t*, *J* = 5.4, H–C(2′)); 4.50 (*dd*, *J* = 9.4, 6.0, H_a–C(5′)); 4.33 (*dd*, *J* = 9.4, 7.2, H_b–C(5′)); 4.10 (*dd*, *J* = 10.8, 6.6, 1 H, CH_2); 3.91 (*dd*, *J* = 10.8, 5.1, 1 H, CH_2); 1.07 (*s*, Me_3C). ^{13}C-NMR ($CDCl_3$): 156.5 (C(7)); 156.1 (C(5)); 149.1 (C(3a)); 146.2 (C(3′)); 135.6, 133.4, 133.2, 129.6, 127.6 (2 Ph); 124.4 (C(7a)); 111.4 (=CH_2); 81.5 (C(2′)); 69.6 (C(5′)); 65.8 (CH_2); 60.0 (C(4′)); 26.7 (Me_3C); 19.1 (*Me*$_3$C).

Data of **12b**: M.p. 74–75°. ^{1}H-NMR ($CDCl_3$): 8.49 (*s*, H–C(5)); 7.70–7.32 (*m*, 2 Ph); 5.81 (*m*, H–C(4′)); 5.39 (*s*, 1 H, =CH_2); 5.36 (*s*, 1 H, =CH_2); 4.68 (*m*, H–C(2′)); 4.68 (*dd*, *J* = 10.1, 4.0, H_a–C(5′)); 4.35 (*dd*, *J* = 10.1, 6.5, H_b–C(5′)); 3.97 (*dd*, *J* = 10.8, 6.3, 1 H, CH_2); 3.85 (*dd*, *J* = 15.1, 5.1, 1 H, CH_2). ^{13}C-NMR ($CDCl_3$): 157.8 (C(7)); 156.6 (C(3a)); 156.4 (C(5)); 145.5 (C(3′)); 135.5, 135.4, 133.2, 133.0, 129.6, 127.5 (2 Ph); 126.0 (C(7a)); 113.3 (=CH_2); 81.4 (C(2′)); 70.9 (C(5′)); 68.9 (C(4′)); 65.9 (CH_2), 26.6 (Me_3C); 19.0 (*Me*$_3$C).

Compounds **11b** and **12b** were deprotected as described for **11a** to give **13b** and **14b** in 81 and 88% yield, resp.

Data of **13b**: White solid powder. M.p. 243°. UV (MeOH): 279.5 (12400). ^{1}H-NMR ((D$_6$)DMSO): 8.45 (br. *s*, 1 H, NH_2); 8.29 (*s*, H–C(5)); 8.11 (br. *s*, 1 H, NH_2); 5.93 (*m*, H–C(4′)); 5.26 (*s*, 1 H, =CH_2); 4.95 (*m*, 2 H, =CH_2, –OH); 4.51 (br. *s*, H–C(2′)); 4.38 (*dd*, *J* = 9.4, 5.4, H_a–C(5′)); 4.25 (*dd*, *J* = 9.4, 8.2, H_b–C(5′)); 3.74 (*m*, 1 H, CH_2); 3.59 (*m*, 1 H, CH_2). ^{13}C-NMR ((D$_6$)DMSO): 156.7 (C(7)); 156.2 (C(5)); 148.6 (C(3a)); 147.1 (C(3′)); 123.9 (C(7a)); 110.4 (=CH_2); 81.5 (C(2′)); 68.9 (C(5′)); 63.4 (CH_2); 59.6 (C(4′)). HR-FAB-MS: 271.0902 ($C_{10}H_{12}N_6NaO_2^+$, $[M+Na]^+$; calc. 271.0919).

Data of **14b**: White powder. M.p. 201°. UV (MeOH): 295.3 (10900). ^{1}H-NMR (CD_3OD): 8.28 (*s*, H–C(5)); 5.93 (*m*, H–C(4′)); 5.41 (*d*, *J* = 4.5, =CH_2); 4.65 (*dd*, *J* = 10.3, 3.3, H_a–C(5′)); 4.58 (*m*, H–C(2′)); 4.33 (*dd*, *J* = 10.3, 6.3, H_b–C(5′)); 3.82 (*dd*, *J* = 11.7, 6.7, 1 H, CH_2); 3.73 (*dd*, *J* = 11.7, 4.1, CH_2). ^{13}C-NMR (CD_3OD): 158.7 (C(7)); 158.6 (C(3a)); 157.7 (C(5)); 147.6 (C(3′)); 127.1 (C(7a)); 113.6 (=CH_2); 83.2 (C(2′)); 72.1 (C(5′)); 70.6 (C(4′)); 65.1 (CH_2). HR-FAB-MS: 271.0919 ($C_{10}H_{12}N_6NaO_2^+$, $[M+Na]^+$, calc. 271.0919).

*3-Benzoyl-1-{(3*S*,5*S*)-5-{[[(*tert*-butyl)diphenylsilyl]oxy}methyl}tetrahydro-4-methylidenefuran-3-yl}-5-methylpyrimidine-2,4(1*H*,3*H*)-dione* (**15a**). To a soln. of Ph_3P (0.3 g, 0.92 mmol) in anh. THF (10 ml), DEAD (0.17 ml, 1.1 mmol) was added. The mixture was stirred at 0° for 30 min and then cooled to –45°. To this soln., N^3-benzoylthymine (0.21 g, 0.92 mmol) and **10b** (0.17 g, 0.46 mmol) in THF (10 ml) were added within 1 h. The mixture was stirred overnight at –45°. The soln. was directly adsorbed on silica gel and purified by CC: **15a** (0.08 g, 30%). Low-melting solid. ^{1}H-NMR (CD_3OD): 7.92–7.25 (*m*, H–C(6), 3 Ph); 5.66 (br. *s*, H–C(3′)); 5.34 (*d*, *J* = 13.6, =CH_2); 4.47 (br. *s*, H–C(5′)); 4.14 (*dd*, *J* = 10.2, 6.8, 1 H); 4.04 (*dd*, *J* = 11.0, 3.7, 2 H); 3.94 (*dd*, *J* = 11.3, 4.5, 1 H); 1.64 (*s*, Me); 1.10 (*s*, Me_3C). ^{13}C-NMR ($CDCl_3$): 168.9 (C=O); 162.5 (C(4)); 150.3 (C(2)); 146.3 (C(4′)); 136.8 (C(6)); 112.1 (=CH_2); 111.6 (C(5)); 81.1 (C(5′)); 71.1 (C(2′)); 65.4 (CH_2); 57.3 (C(3′)); 26.9 (Me_3C); 19.3 (*Me*$_3$C); 12.2 (Me). HR-FAB-MS: 603.2305 ($C_{34}H_{36}N_2NaO_5Si^+$, $[M+Na]^+$; calc. 603.2291).

*5-Methyl-1-[(3*S*,5*S*)-tetrahydro-5-(hydroxymethyl)-4-methylidenefuran-3-yl]pyrimidine-2,4(1*H*,3*H*)-dione* (**16a**). To a soln. of **15a** (0.07 g, 0.13 mmol) in MeOH (10 ml), NH_4F (0.065 g, 2 mmol) was added, and the soln. was

heated under reflux for 3 h. The soln. was cooled to r.t., adsorbed on silica gel, and purified by CC to give the *N*(3)-benzoylated derivative, which was dissolved in MeOH (5 ml) and treated with NaOMe (0.03 g). The mixture was stirred at r.t. for 8 h, neutralized with 10% AcOH/H_2O, and evaporated. The residue was taken up in MeOH, adsorbed on silica gel, and purified by CC: **16a** (0.018 g, 62% for two steps). Hygroscopic foam. UV (MeOH): 270.9 (9400). ^{1}H-NMR ((D$_6$)acetone): 10.14 (br. *s*, NH); 7.62 (*s*, H–C(6)); 5.56 (*m*, H–C(3′)); 5.36 (*t*, *J* = 2.1, 1 H, =CH$_2$); 5.30 (*t*, *J* = 2.3, 1 H, =CH$_2$); 4.40 (br. *s*, H–C(5′)); 4.18–3.84 (*m*, H–C(2′), H–C(3), CH$_2$); 1.76 (*s*, Me). ^{13}C-NMR (CD$_3$OD): 166.3 (C(4)); 153.2 (C(2)); 148.5 (C(4′)); 140.3 (C(6)); 112.2 (=CH$_2$); 111.6 (C(5)); 82.8 (C(5′)); 72.2 (C(2′)); 638 (CH$_2$); 58.9 (C(3′)); 12.3 (Me). HR-FAB-MS: 261.0855 ($C_{11}H_{14}N_2NaO_4^+$, $[M+Na]^+$; calc. 261.0851).

*1-[(3*S*,5*S*)-Tetrahydro-5-(hydroxymethyl)-4-methylidenefuran-3-yl]pyrimidine-2,4(1*H*,3*H*)-dione* (**16b**). To a soln. of Ph_3P (0.84 g, 3.18 mmol) in anh. THF, DEAD (0.49 ml, 3.12 mmol) was added. The mixture was then stirred at 0° for 30 min and cooled to −70°. A suspension of 3-benzoyluracil (0.54 g, 3.12 mmol) and **10b** (0.46 g, 1.25 mmol) was added to the soln. within 30 min. The mixture was stirred overnight at −40° and then quenched with H_2O (1 ml) and evaporated. The gummy residue was purified by CC. The product was dissolved in MeOH (40 ml), NH_4F (0.5 g) added, and the resulting soln. heated under reflux for 3 h. The soln. was directly adsorbed on silica gel and purified by CC: **16b** (0.16 g, 57%). White solid. M.p. 178°. UV (MeOH): 266.6 (11800). ^{1}H-NMR (CD$_3$OD): 7.80 (*d*, *J* = 8.1, H–C(6)); 5.64 (*d*, *J* = 8.1, H–C(5)); 5.57 (*m*, H–C(3′)); 5.35 (*m*, =CH$_2$); 4.82 (br. *s*, H–C(5′)); 4.07 (*dd*, *J* = 10.3, 6.5, H$_a$–C(2′)); 4.00 (*dd*, *J* = 10.2, 3.6, H$_b$–C(2′)); 3.90 (*dd*, *J* = 12.3, 2.9, 1 H, CH$_2$); 3.80 (*dd*, *J* = 12.3, 4.2, 1 H, CH$_2$). ^{13}C-NMR (CD$_3$OD): 166.2 (C(4)); 153.2 (C(2)); 148.5 (C(4′)); 144.6 (H–C(6)); 112.5 (=CH$_2$); 102.7 (C(5)); 82.9 (C(5′)); 72.3 (C(2′)); 63.9 (CH$_2$); 59.3 (C(3′)). HR-FAB-MS: 247.0703 ($C_{10}H_{12}N_2NaO_4^+$, $[M+Na]^+$; calc. 247.0694).

*4-Amino-1-[(3*S*,5*S*)-tetrahydro-5-(hydroxymethyl)-4-methylidenefuran-3-yl]pyrimidin-2(1*H*)-one* (**17**). Ac_2O (0.25 ml, 2.65 mmol) was added to a soln. of **16b** (0.12 g, 0.53 mmol) in pyridine (10 ml) at r.t. After the addition, the mixture was stirred at r.t. overnight and then quenched with H_2O (1 ml). The solvent was evaporated and the conc. soln. co-evaporated with toluene. The residue was purified by CC to give the acetylated derivative (0.13 g, 92%) as pale yellow foamy solid. Et_3N (0.1 ml) was added to a soln. of the acetylated derivative (0.09 g, 0.33 mmol) in MeCN (10 ml) containing 2,4,6-^{i}Pr$_3$C$_6$H$_2$SO$_2$Cl (0.23 g, 0.75 mmol) and 4-(dimethylamino)pyridine (0.092 g, 0.75 mmol) at 0°. The mixture was stirred at r.t. for 4 h. NH_4OH soln. (28%, 6 ml) was added, and the soln. was stirred at r.t. for 24 h. After evaporation, the residue was purified by CC: **17** (0.035 g, 47% in two steps). Hygroscopic solid. UV (MeOH): 276.4 (8650). ^{1}H-NMR (CD$_3$OD): 7.80 (*d*, *J* = 7.4, H–C(6)); 5.83 (*d*, *J* = 7.5, H–C(5)); 5.63 (*m*, H–C(3′)); 5.35 (*t*, *J* = 2.1, 1 H, =CH$_2$); 5.30 (*t*, *J* = 2.2, 1 H, =CH$_2$); 4.40 (br. *s*, H–C(5′)); 4.08 (*dd*, *J* = 10.1, 6.5, H$_a$–C(2′)); 3.96 (*dd*, *J* = 10.1, 3.6, H$_b$–C(2′)); 3.90 (*dd*, *J* = 12.3, 3.0, 1 H, CH$_2$); 3.81 (*dd*, *J* = 12.3, 4.2, 1 H, CH$_2$). ^{13}C-NMR (CD$_3$OD): 167.4 (C(2)); 159.2 (C(4)); 149.0 (C(4′)); 144.8 (C(6)); 112.2 (=CH$_2$); 96.1 (C(5)); 83.1 (C(5′)); 72.9 (C(2′)); 63.9 (CH$_2$); 60.3 (C(3′)). HR-FAB-MS: 224.1040 ($C_{10}H_{14}N_3O_3^+$, $[M+H]^+$; calc. 224.1035).

*2-[(3*S*,5*S*)-5-{[[(*tert*-Butyl)diphenylsilyl]oxy}methyl]tetrahydro-4-methylidenefuran-3-yl]-1*H*-isoindol-1,3(2*H*)-dione* (**19**). To a soln. of **10b** (1.1 g, 3 mmol) in CH_2Cl_2 (30 ml), Et_3N (1.7 ml, 12 mmol) and MsCl (0.7 ml, 9 mmol) were added at 0°. After the addition, the mixture was stirred at 0° for 3 h. H_2O (75 ml) was added and extracted with CH_2Cl_2 (3 × 30 ml). The combined CH_2Cl_2 part was washed with H_2O, dried (Na_2SO_4), and evaporated. The oily residue was purified by CC: **18** (1.11 g, 83%). Pale yellow low-melting solid. ^{1}H-NMR ($CDCl_3$): 7.70 (*m*, 4 H, Ph); 7.42 (*m*, 6 H, Ph); 5.64 (*s*, 1 H, =CH$_2$); 5.51 (*m*, H–C(3)); 5.33 (*s*, 1 H, =CH$_2$); 4.65 (br. *s*, H–C(5)); 4.18 (*dd*, *J* = 10.6, 4.8, H$_a$–C(2)); 4.06 (*dd*, *J* = 10.6, 2.8, H$_b$–C(2)); 3.82 (*dd*, *J* = 11.0, 3.7, 1 H, CH$_2$); 3.71 (*dd*, *J* = 11.0, 4.6, 1 H, CH$_2$); 3.04 (*s*, Me); 1.06 (*s*, Me$_3$C). ^{13}C-NMR ($CDCl_3$): 145.4 (C(4)); 114.3 (=CH$_2$); 80.9, 80.2 (C(3), C(5)); 72.1 (C(2)); 66.3 (CH$_2$); 39.2 (Me); 26.9 (Me$_3$*C*); 19.3 (*Me*$_3$C).

To a soln. of **18** (0.3 g, 0.67 mmol) in DMF (30 ml), potassium phthalimide (0.74 g, 4 mmol) was added, and the mixture was heated at 110° overnight. The soln. was cooled and filtered, and the filtrate was evaporated. The residue was taken up in AcOEt (80 ml) and washed with H_2O (2 × 50 ml). The AcOEt part was dried (Na_2SO_4), evaporated, and purified by CC: **19** (0.17 g, 51%). Low-melting solid. ^{1}H-NMR ($CDCl_3$): 7.84–7.30 (*m*, 14 arom. H); 5.34 (*m*, H–C(3′)); 5.03 (*t*, *J* = 2.2, 1 H, =CH$_2$); 4.87 (*t*, *J* = 2.4, 1 H, =CH$_2$); 4.70 (*m*, H–C(5′)); 4.15 (*dd*, *J* = 11, 7.8, 1 H, CH$_2$); 4.04 (*d*, *J* = 8.7, 2 H–C(2′)); 3.86 (*dd*, *J* = 11.1, 4.6, 1 H, CH$_2$); 1.11 (*s*, Me$_3$C). ^{13}C-NMR ($CDCl_3$): 167.1 (C=O); 145.8 (C(4′)); 135.7, 135.6, 134.1, 133.8, 133.5, 131.7, 129.5, 127.6, 123.3 (arom. C); 107.0 (=CH$_2$); 81.8 (C(5′)); 66.0, 65.9 (C(2′), CH$_2$); 51.9 (C(3′)); 26.8 (Me$_3$*C*); 19.2 (*Me*$_3$C). HR-FAB-MS: 520.1930 ($C_{30}H_{31}NNaO_4Si^+$, $[M+Na]^+$; calc. 520.1920).

*(3*S*,5*S*)-5-{[[(*tert*-Butyl)diphenylsilyl]oxy}methyl]tetrahydro-4-methylidenefuran-3-amine* (**20**). To a soln. of **19** (0.16 g, 0.32 mmol) in EtOH (20 ml), hydrazine hydrate (0.12 g) was added, and the mixture was heated under reflux for 3 h and then allowed to cool to r.t. The white precipitate was filtered and washed with EtOH.

The combined EtOH part was evaporated and the residue purified by CC: **20** (0.09 g, 77%). ^{1}H-NMR ($CDCl_3$): 7.71–7.25 (*m*, 2 Ph); 5.29 (br. *s*, 1 H, $=CH_2$); 4.48 (*m*, H–C(5)); 3.99–3.64 (*m*, 2 H–C(2), H–C(3), CH_2); 1.06 (*s*, Me_3C). ^{13}C-NMR ($CDCl_3$): 153.3 (C(4)); 135.6, 133.3, 133.2, 129.6, 127.6 (Ph); 106.2 ($=CH_2$); 81.0 (C(5)); 74.4 (C(2)); 66.4 (CH_2); 55.5 (C(3)); 26.8 (Me_3C); 19.1 (Me_3C). HR-FAB-MS: 390.1870 ($C_{22}H_{29}NNaO_2Si^+$, $[M+Na]^+$; calc. 390.1865).

*5-Methyl-1-[(3*S*,5*S*)-tetrahydro-5-(hydroxymethyl)-4-methylidenefuran-3-yl]pyrimidine-2,4(1*H*,3*H*)-dione* (**16a**). A soln. of 3-methoxy-2-methylprop-2-enoyl isocyanate (prepared by heating the corresponding acid chloride (0.11 g, 0.8 mmol) and silver cyanate (0.22 g) in toluene for 0.5 h) was added dropwise to a soln. of **20** (0.09 g, 0.25 mmol) in DMF (10 ml) and Et_2O (5 ml) at $-10°$. After the addition, the mixture was allowed to warm to r.t. and stirred for 16 h. The volatile materials were evaporated. EtOH was added to the residue with stirring and then evaporated. The gummy residue was purified by CC to give the acryloylurea derivative **21**. This compound was dissolved in dioxane (5 ml) and heated at 100° for 4 h with 2N H_2SO_4 (1.0 ml). The mixture was allowed to cool to r.t. and then neutralized with 2N aq. NaOH and evaporated. The residue was purified by CC: **16a** (0.04 g, 50% in two steps), identical to the compound prepared by direct coupling and deprotection (see above).

Single-Crystal X-Ray Structure Determination of Compounds **13a** *and* **14a**. A colorless prismatic crystal ($0.21 \times 0.24 \times 0.36$ mm and $0.25 \times 0.25 \times 0.31$ mm, resp.) was isolated from the sample and mounted with grease on the tip of a glass capillary epoxied to a brass pin and placed on the diffractometer with the long crystal dimension (*a*-axis and *AB* dimension, resp.) approximately parallel to the diffractometer ϕ-axis. Data were collected on an *Enraf-Nonius-CAD4* diffractometer (MoK_α radiation, graphite monochromator) at 200 K (cold N_2 gas cooling) using θ-2θ scans. Intensity standards were measured at 2 h intervals. Net intensities were obtained by profile analysis of the 4469 and 5428 data, resp. *Lorentz* and polarization corrections were applied. No change in the intensity standards was detected. Absorption was minimal and no correction was applied. Equivalent data were averaged yielding 2018 unique data (R-int = 0.023, $1926 > 4\,\sigma(F)$) in the case of **13a** and 3817 unique data (R-int = 0.072, $3042 > 4\sigma(F)$) in the case of **14a**. Based on preliminary examination of the data, the space group $P2(1)2(1)2(1)$ was assigned to **13a** and $P2(1)$ to **14a**. The computer programs from the MoLEN package were used for data reduction. The preliminary model of the structure was obtained with XS, a direct-methods program. Least-squares refining of the model *vs.* the data was performed with the XL computer program. Illustrations were made with the XP program, and tables were made with the XCIF program. All are in the SHELXTL v5.0 package. Thermal ellipsoids are drawn at the 35% level unless otherwise noted. All non-H-atoms were refined with anisotropic thermal parameters. All H-atoms were included with a riding model based on default values. In the case of **14a**, there are two independent molecules in the asymmetric unit. Each forms a dimer *via* two H-bonds with a symmetry-equivalent molecule of the other (*i.e.*, molecule A dimerizes with molecule B, and *vice versa*). The two molecules differ in conformation mainly at the sugar CH_2OH group.

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