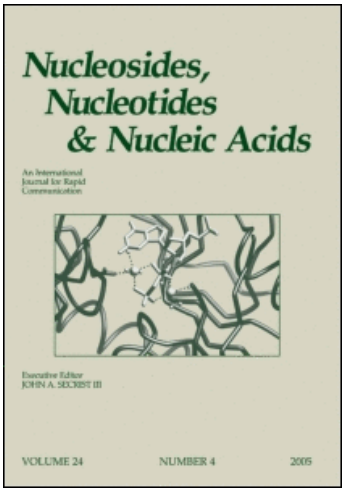

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Synthesis and Antiviral Studies of Unsaturated Analogues of Isomeric Dideoxynucleosides

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SYNTHESIS AND ANTIVIRAL STUDIES OF UNSATURATED ANALOGUES OF ISOMERIC DIDEOXYNUCLEOSIDES

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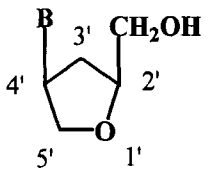
ABSTRACT: Novel isomeric dideoxynucleosides with unsaturation in the carbohydrate moiety have been synthesized. For example, isod4A was synthesized through a rearrangement reaction involving a cyclonucleoside. Support for the structures of both purine and pyrimidine d4 compounds came from UV, NMR, HRMS and single crystal X-ray data. Interestingly, the single crystal X-ray data for isod4C shows that the base is almost orthogonal to the carbon-carbon double bond of the sugar moiety. Consistent with this is the observation that the UV data of this compound does not show a bathochromic shift compared to the saturated compound implying that the π-bond is not in conjugation with the pyrimidine base.

Introduction

Isomeric dideoxynucleosides as antiviral agents have been the subject of intense investigation in our laboratory for a number of years. Included in this group are those compounds where the base is moved from the natural 1′-position to the isomeric 2′-position or the -CH_2OH is transposed from the 4′- to the 3′-position (also equivalent to the transposition of the endocyclic oxygen to the 3′- and 2′-positions, respectively, see **1** and **2** in Figure 1).[1-5] For example, 4(*S*)-(6-amino-9*H*-purin-9-yl)tetrahydro-2(*S*)-furanmethanol (**1**, B = adenine), an isomeric dideoxy-nucleoside synthesized by us, has potent anti-HIV activity against HIV-1, HIV-2, and HIV-resistant strains. Its triphosphate is a strong inhibitor of HIV reverse transcriptase (K_i 16 nM).[5] In the search for new isomeric dideoxynucleosides with anti-HIV activity, we have investigated a novel class of compounds within the family of isomeric nucleosides, *i.e.*, those that have unsaturation in the carbohydrate moiety and only one asymmetric center.



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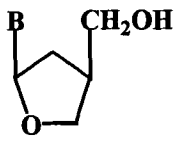

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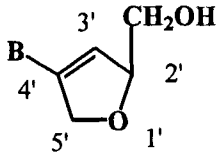

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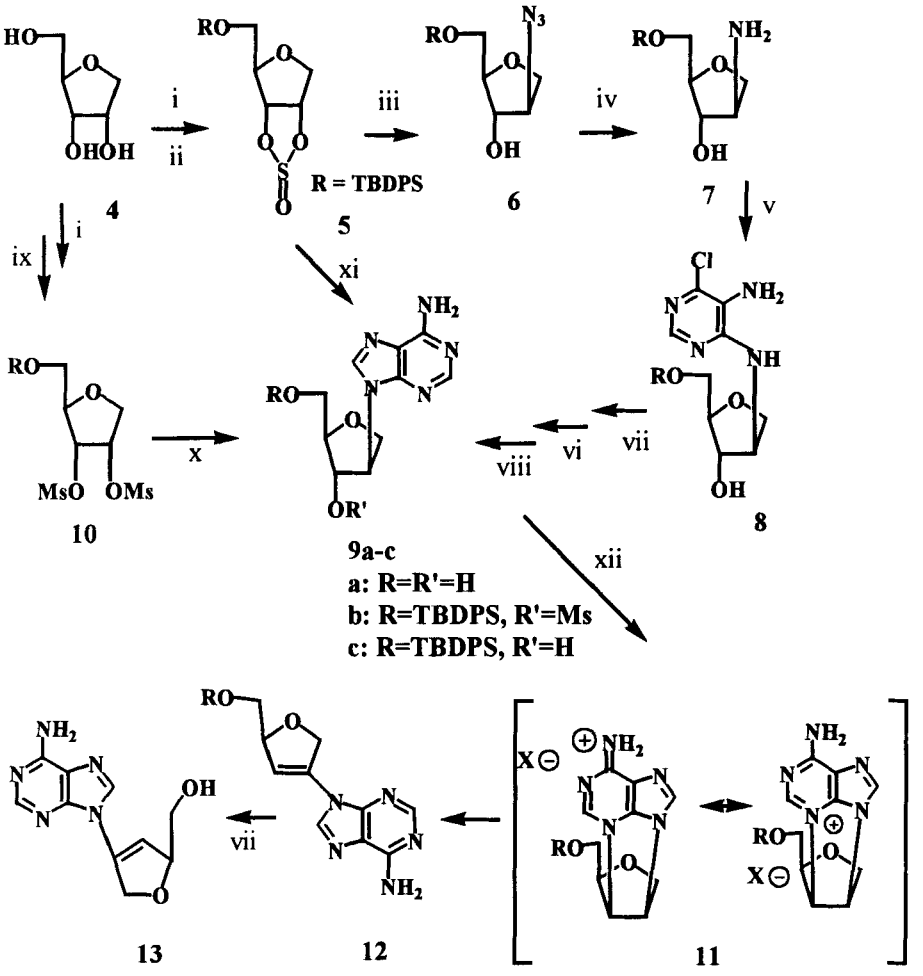
Figure 1

Results and discussion

These isodideoxydidehydronucleosides (isod4Ns) were synthesized through an interesting rearrangement reaction. The synthesis will be illustrated with the case of isodideoxy-didehydroadenosine (iso-d4A, **13**) (Scheme 1). The starting compound was 1,4-anhydro-D-ribitol, **4**, prepared as described previously by us.[6] Treatment of the 5'-*tert*-butyldiphenylsilyl protected derivative[7] of **4** with thionyl chloride in pyridine[8,9] at room temperature produced the cyclic sulfite **5** in almost quantitative yield. Coupling of **5** with adenine in the presence of potassium carbonate and 18-crown-6 gave IsodA, **9c**,[7,10] but in low yields (13%). The low yields in this reaction may be attributed to the large steric hindrance from the protected primary hydroxyl group. Consistent with this explanation was the observation that the reaction appeared to be regiospecific and only the less hindered isonucleoside **9c** was isolated. Isodeoxy-nucleoside **9a** (the deprotected form of **9c**) was also obtained by construction of the adenine base using the β-amino compound **7** as the precursor, utilizing a known methodology for adenine base synthesis.[10-13] Compound **7** was prepared in 91% yield by catalytic reduction of azide **6** which was stereospecifically and regiospecifically produced by reaction of the cyclic sulfite **5** with sodium azide in DMF at 80° C (78% yield).

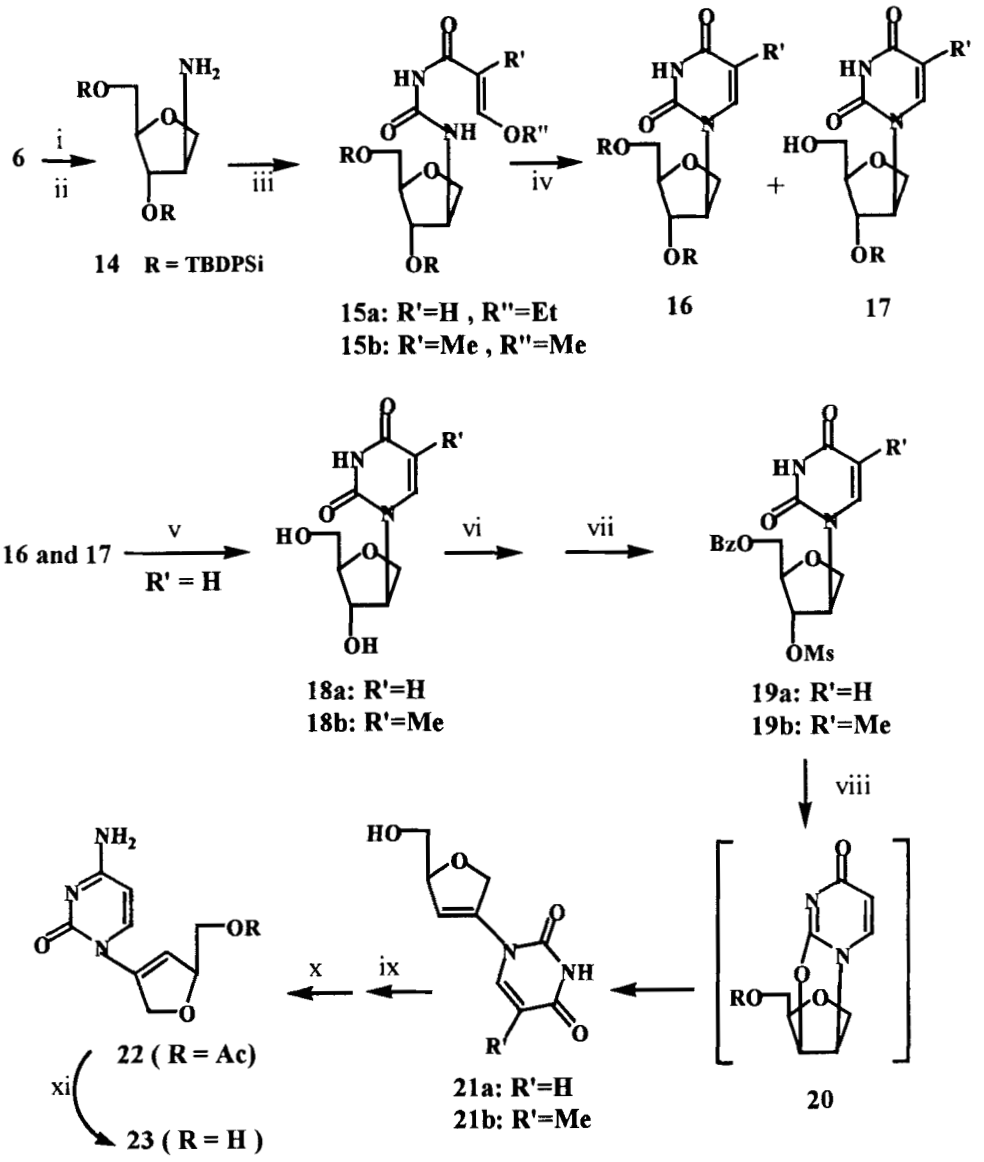
With the knowledge that bulky substituents at the primary hydroxyl group would dictate the regiochemistry of displacement reactions on the sugar ring, we prepared the bis-mesylate **10** from **4**. The intent of the synthetic approach was to produce the isodeoxynucleoside **9b** by coupling with adenine and then, through an elimination



Scheme 1. (i) TBDPSCl, pyridine, 0 °C, (ii) $SOCl_2$, pyridine, room temperature, (iii) NaN_3, DMF, 80 °C, (iv) Pd-C/H_2, (v) 5-amino-4,6-dichloro-pyrimidine, N-methyl-pyrrolidinone, 140 °C, (vi) $CH(OEt)_3$, Con. HCl, (vii) NH_4F, MeOH, reflux, (viii) NH_3-MeOH, (ix) MsCl, CH_2Cl_2, TEA, 0 °C, (x) Adenine, K_2CO_3, 18-crown-6, DMF, 105 °C, (xi) Adenine, K_2CO_3, 18-crown-6, DMF, 115 °C, (xii) DMF, K_2CO_3, 100°C.

reaction, generate the d4 compound. However, when compound **10** was heated with adenine and potassium carbonate in DMF in the presence of 18-crown-6, a mixture containing **9b** and the d4 nucleoside, **12**, was produced. The product distribution was dependent on reaction time and temperature. For example, when the reaction condition was 75 °C for 30 h, compounds **9b** and **12** were obtained in a ratio 2.2:1 (17% overall yield). When the reaction was carried out at 105 °C for 18 h, **9b** and **12** were obtained in a ratio of 1:2.7 (20% overall yield). Changing the reaction conditions to 120 °C for 40 h resulted in only one product, **12,** which was isolated after purification in 11% yield. The d4 product **12** appeared to be produced through the intermediacy of the cycloadenosine **11**. That compound **9b** was the intermediate for the formation of **12** was established by treatment of **9b** with potassium carbonate and 18-crown-6 which resulted in the formation of **12**. Support for the intermediacy of **11** comes from the observation that heating the N,N-dibenzoyl derivative of **9b** in the presence of potassium carbonate and 18-crown-6 did not produce the dibenzoyl derivative of **12**. Purine cyclonucleosides, such as 3,5′-anhydroadenosine and 3,3′-anhydroadenosine, have been invoked as intermediates in other studies.[14,15] Deprotection of **12** with ammonium fluoride gave the target molecule **13**. The quantitative UV data of **13** confirmed the extended conjugation and the ^{13}C NMR spectrum showed the presence of unsaturated carbons on the sugar moiety at 111.4 ppm and 131.9 ppm. A single crystal X-ray analysis of **13** confirmed its structure.

For the synthesis of the d4 pyrimidine nucleosides, compound **6** was chosen as the starting material. Protection of the secondary OH group with TBDPSCl (87%) and catalytic reduction of the azido group (93%) gave the β-amino compound **14** (Scheme 2). Treatment of **14** with 3-ethoxyacryloyl isocyanate, prepared *in situ* from 3-ethoxyacryloyl chloride and silver cyanate, afforded the acryloylurea derivative **15a**,[6,16-18] in 93% yield. Cyclization[6,16-18] of **15a** with 2N H_2SO_4 in dioxane at 100°C produced **16** and its partially deprotected derivative, **17**. That the primary hydroxyl group was deprotected in this reaction was confirmed by the observation that the O-mesyl derivative of **17** did not produce an anhydro compound when treated with DBU in THF.[6]



Scheme 2. (i) TBDPSCl, DMF, Imidazole, 70 °C, (ii) Pd-C, H_2, (iii) EtOCH=CHCONCO, toluene, -18 °C to r.t., or MeOCH=CH(Me)CONCO, toluene, DMF, 0 °C to r. t., (iv) 1M H_2SO_4, 100 °C, (v) NH_4F, MeOH, Reflux, (vi) BzCl, pyridine, -15 °C, (vii) MsCl, pyridine, 0 °C, (viii) $KOBu^t$, DMSO, 75 °C, (ix) Ac_2O, pyridine, r. t., (x) TIPSCl, CH_3CN, DMAP, 0 °C to r. t., then NH_4OH, (xi) NH_4OH, MeOH

For the synthesis of iso-d4 pyrimidine nucleosides, compounds **18** derived from **16** (**17**) by deprotection were chosen as the starting compounds. The primary hydroxyl groups of **18** were selectively protected by treatment with benzoyl chloride and pyridine to give the benzoylated derivatives, which on treatment with MsCl in pyridine, produced compounds **19** in high yields. Treatment of these compounds separately with $KOBu^t$ in DMSO[19] at 75 °C produced isod4U (**21a**) and isod4T (**21b**). Using known synthetic methods, the acetylated derivative of **21a** was converted to the cytosine derivative **23**.[17] The structures of these unsaturated nucleosides were confirmed by NMR, quantitative UV data, and mass spectrometry. The ortep plot of the single crystal X-ray structure of the acetate of compound **23** (i.e., compound **22**) is shown in Figure 2 and provides supportive confirmation of structure. Interestingly, the compound crystallizes out in two forms (A and B) and the crystal structure indicates that the nucleobase is almost orthogonal to the plane of the sugar ring. This is supported by the quantitative UV data. It is clear that in going to this unsaturated system, the distance between the base and the CH_2OH group has been increased which is expected to have an impact on the ability of these compounds to undergo initial phosphorylation by deoxycytidine kinase or other kinases. Consistent with this was the observation that our initial anti-HIV data indicated inactivity in infected CEM-SS cells.

Experimental

Melting points reported are uncorrected and were determined on an Electrothermal Engineering Ltd. melting point apparatus. Ultraviolet (UV) spectra were recorded on a Cary 3 UV-Visible spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument at 300 and 75 MHz, respectively. Chemical shifts are referenced to an internal TMS standard for ^1H NMR spectra and to solvent ($CDCl_3$, DMSO-d_6, or CD_3OD) for ^{13}C NMR spectra. Column chromatographic separations were carried out using 230-400 mesh silica gel. High resolution FAB mass spectral data were obtained on a VG ZAB-HF high resolution mass spectrometer.

2(*R*)-(*tert*-Butyldiphenylsilyloxymethyl)tetrahydrofuran-(3*R*, 4*S*)-disulfite (5). 2 (*R*)-(*tert*-Butyldiphenylsilyloxymethyl)tetrahydrofuran-(3*S*, 4*S*)-diol was synthesized from compound **4** following the method described previously by us.[6,7] To a solution of

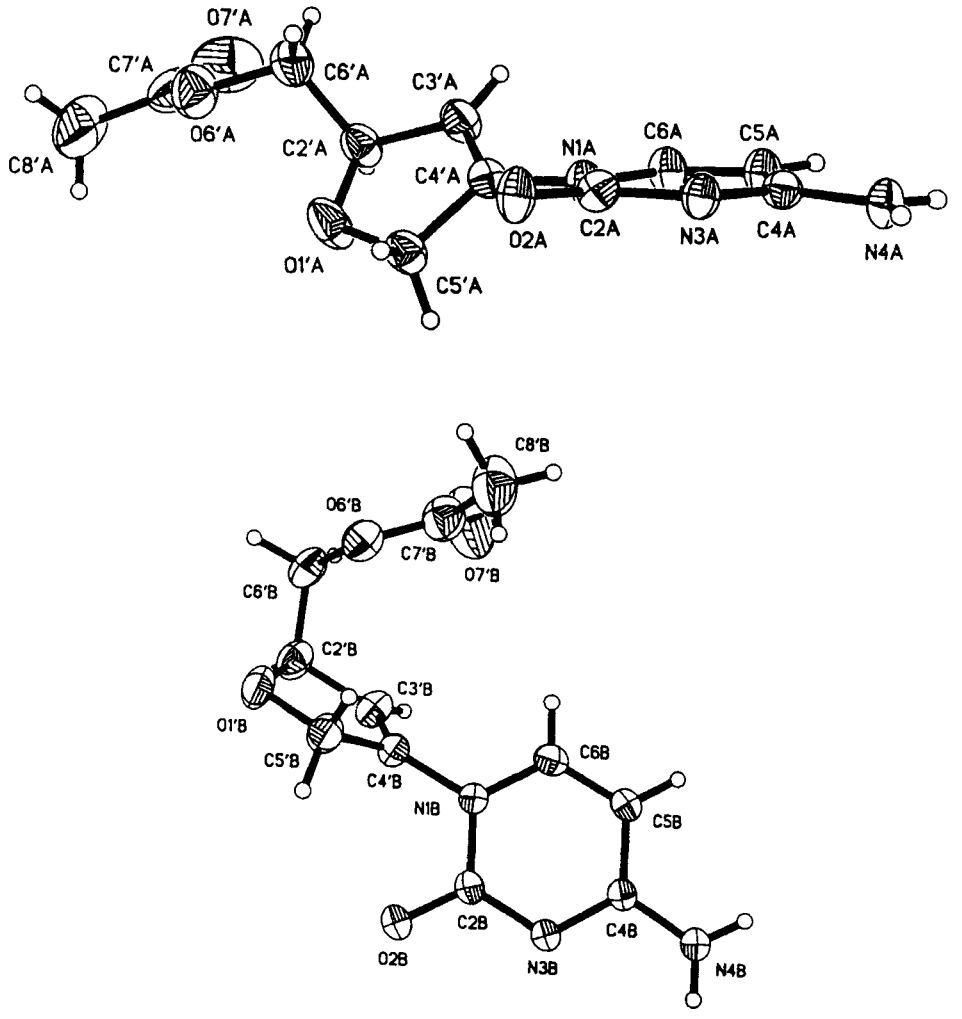


FIGURE 2

2(*R*)-(*tert*-butyldiphenylsilyloxymethyl)tetrahydrofuran-(3*S*, 4*S*)-diol[6,7] (1 g, 2.66 mmol) in pyridine (15 mL) was added $SOCl_2$ (0.97 mL, 13.4 mmol). The reaction mixture was stirred overnight at room temperature and quenched with water (2 mL). Pyridine was removed under reduced pressure and the residue was coevaporated with toluene. The gummy crude product was partitioned between EtOAc (75 mL) and water (75 mL). The EtOAc layer was dried over Na_2SO_4 and evaporated to dryness. The residue was purified over silica gel to give **5** as a colorless oil (1.04 g, 93%). ^{1}H-NMR($CDCl_3$) δ

7.65 (m, 4H), 7.44 (m, 6H), 5.62 (m, 2H), 4.4 (m, 1H), 4.23 (t, J = 3.2 Hz 1H), 4.10 (d, J = 11.1 Hz, 1H), 3.85 (m, 2H), 1.06 (s, 9H, *tert*-butyl); HRMS (FAB): $(M+Li)^+$ calcd for $C_{21}H_{26}LiO_5SSi$ 425.1430, found 425.1432.

2(*R*)-(*tert*-Butyldiphenylsilyloxymethyl)-4(*R*)-azidotetrahydrofuran-3(*S*)-ol (6). To a solution of compound **5** (1.20 g, 2.87 mmol) in DMF (40 mL) was added NaN_3 (1.30 g, 20 mmol) and the reaction mixture was heated at 80 °C for 3 days. DMF was removed under reduced pressure and the residue was partitioned between EtOAc (70 mL) and water (100 mL). The EtOAc layer was dried over Na_2SO_4 and evaporated to dryness. The gummy residue was purified on silica gel to give **6** as a colorless oil (0.89 g, 78%): ^{1}H-NMR($CDCl_3$) δ 7.68 (m, 4 H, phenyl), 7.40 (m, 6 H, phenyl), 4.26 (t, 1H, J = 4.0 Hz, H-3), 4.05 (dd, 1H, J = 6.0. 9.5 Hz, H-5a), 3.95 (dd, 1H, J = 4.1, 10.1 Hz, H-5b), 3.80 (m, 4H, H-2, H-4, -CH_2), 1.11 (s, 9H,*tert*-butyl); ^{13}C-NMR($CDCl_3$) δ 135.2, 132.8, 129.5, 127.5 (phenyl); 84.9 (C-2), 77.1 (C-3), 69.8 (C-5), 66.9 (C-4), 63.3 (-CH_2), 26.5 (*tert*-butyl), 18.9 (*tert*-butyl); HRMS (FAB): $(M+Na)^+$ calcd for $C_{21}H_{27}N_3NaO_3Si$ 420.1719, found 420.1716.

2(*R*)-(*tert*-Butyldiphenylsilyloxymethyl)-4(*R*)-aminotetrahydrofuran-3(*S*)-ol (7). To a solution of compound **6** (2 g, 5.03 mmol) in ethanol, Pd/C (0.40 g, 10% Pd) was added and the suspension was stirred under hydrogen pressure (25 psi) for 6 h. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was purified over silica gel to give compound **7** as a gum (1.70 g, 91%): ^{1}H-NMR($CDCl_3$) δ 7.68 (m, 4H, phenyl), 7.38 (m, 6 H, phenyl), 4.03 (m, 2H, H-5), 3.79 (m, 3H, H-3, -CH_2), 3.63 (m, 1H, H-2), 3.32 (m, 1H, H-4), 1.05 (s, 9H,*tert*-butyl); ^{13}C-NMR($CDCl_3$) δ 135.4, 132.9, 129.6, 127.6 (phenyl), 85.7 (C-2), 78.6 (C-3), 74.3 (C-5), 64.0 (-CH_2), 60.0 (C-4), 26.7 (*tert*-butyl), 19.1 (*tert*-butyl); HRMS (FAB): $(M+Na)^+$ calcd for $C_{21}H_{29}NNaO_3Si$ 394.1814, found 394.1824.

2(*R*)-(*tert*-butyldiphenylsilyloxymethyl)-4(*R*)-(5-amino-6-chloro-4-pyrimidyl-amino)tetrahydrofuran-3(*S*)-ol (8). A solution of **7** (0.37 g, 1 mmol), 5-amino-4,6-dichloropyrimidine (0.17 g, 1 mmol) and pyridine (0.08 g, 1 mmol) in N-methylpyrrolidinone (15 mL) was heated at 140 °C for 5 h. The solution was evaporated to dryness and the brown residue was dissolved in EtOAc (60 mL) and washed with saturated $NaHCO_3$ (30 mL) and water (30 mL). The EtOAc layer was dried over

Na_2SO_4 and evaporated to dryness. Purification of the residue on a silica gel column gave **8** (0.26 g, 52 %) as a crystalline solid: mp 78 °C; ^{1}H-NMR($CDCl_3$) δ 8.02 (s, 1H), 7.64 (m, 4H, phenyl), 7.37 (m, 6H, phenyl), 5.33 (d, 1H, *J* = 5.1Hz), 4.22 (m, 3H); 3.92 (m, 4H), 3.40 (m, 2H), 1.03 (s, 9H); ^{13}C-NMR($CDCl_3$) δ 153.6 (C-4), 147.8 (C-2), 141.2 (C-6), 135.4, 135.3, 133.2, 133.1, 129.7, 127.6 (phenyl), 122.9 (C-5), 85.7 (C-2'), 77.9 (C-3'), 70.8 (C-5'), 64.1 (-CH_2), 61.3 (C-4'), 28.8 (*tert*-butyl), 19.2 (*tert*-butyl); HRMS (FAB): $(M+Na)^+$ calcd for $C_{25}H_{31}N_4NaO_3SiCl$: 521.1751, found: 521.1740.

4(*R*)-(6-Amino-9H-purin-9-yl)–2(*R*)-(hydroxymethyl) tetrahydrofuran-3(*S*)-ol (9a). A solution of compound **8** (0.25 g, 0.5 mmol) in triethylorthoformate (3mL) containing conc. HCl (0.05 mL) was stirred at room temperature for 5h. The reaction mixture was diluted with EtOAc (60 mL) and the EtOAc layer was washed with saturated $NaHCO_3$ (2 x 25mL) and water (50 mL) and then dried over Na_2SO_4 and evaporated to dryness. The residue was purified over silica gel to give 4(*R*)-(6-chloro-9H-purin-9-yl)–2(*R*)-(tert-butyldiphenylsilyloxymethyl) tetrahydrofuran-3(*S*)-ol (0.23g, 90%) as a white solid: mp 64-65 °C; ^{1}H-NMR ($CDCl_3$) δ 8.72 (s, 1H, H-2), 8.16 (s, 1H, H-8), 7.62 (m, 4H, phenyl), 7.36 (m, 6H, phenyl), 5.00 (q, 1H, *J* = 6.1Hz, H-4'), 4.64 (t, 1H, *J* = 5.7Hz, H-3'), 4.46 (dd, 1H, *J* = 6.5, 9.8Hz, H-5'a), 4.37 (dd, 1H, *J* = 6.3, 9.8Hz, H-5'b), 4.01 (m, 1H, H-2'), 3.90 (m, 2H, -CH_2), 1.01 (s, 9H,*tert*-butyl); ^{13}C-NMR ($CDCl_3$) δ 152.0 (C-4), 151.5 (C-2), 151.0 (C-6), 143.9 (C-8), 135.2, 132.6, 131.0 (C-5), 129.6, 127.5 (phenyl), 85.4 (C-2'), 76.5 (C-3'), 69.5 (C-5'), 63.3 (-CH_2), 63.0 (C-4'), 26.6 (*tert*-butyl), 18.9 (*tert*-butyl); HRMS (FAB): $(M+Na)^+$ calcd for $C_{26}H_{29}ClN_4NaO_3Si$: 531.1595, found 531.1606.

4(*R*)-(6-Chloro-9H-purin-9-yl)–2(*R*)-(tert-butyldiphenylsilyloxymethyl)tetrahydrofuran-3(*S*)-ol (0.23 g, 0.45 mmol) was dissolved in MeOH (25 mL) and NH_4F (0.20 g) was added and the solution was heated under reflux. Methanol was removed under reduced pressure and the residue was purified on silica gel to give the title compound[10] in 82% yield. The deprotected compound was converted to the amino derivative **9a** following the method previously described.[2,10]

2(*R*)-(*tert*-Butyldiphenylsilyloxymethyl)-4(*R*)-(6-amino-9H-purin-9-yl)-3(*S*)-mesyloxytetrahydrofuran (9b) and 2(*S*)-(*tert*-Butyldiphenylsilyloxymethyl)-4-(6-amino-9H-purin-9-yl)-2,5-dihydrofuran (12). To a solution of 2(*R*)-(*tert*-butyl-

diphenylsilyloxymethyl)tetrahydro-furan-(3*S*, 4*S*)-diol (3.15 g, 8.4 mmol) in dichloromethane (80 ml), triethylamine (7.60 mL, 50 mmol) was added. To this solution mesyl chloride (2.60 mL, 34 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at the same temperature for 3h and then quenched by the addition of 5 mL of water. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (150 mL) and water (100 mL). Evaporation of the Na_2SO_4 dried EtOAc layer gave a residue which was purified on a silica gel column to give compound **10** as a viscous oil (99 % yield). ^{1}H-NMR ($CDCl_3$) δ 7.66 (m, 4H, phenyl), 7.42 (m, 6H, phenyl), 5.30 (m, 2H, H-3, H-4), 4.28 (dd, 1H, J = 4.8, 9.6Hz, H-5a), 4.19 (m, 1H, H-2), 4.08 (dd, 1H, J = 4.7, 9.6Hz, H-5b), 3.89 (dd, 1H, J = 2.5, 11.6Hz, one H of $-CH_2$), 3.78 (dd, 1H, J = 2.5, 11.6Hz, one H of $-CH_2$), 3.11 (s, 3H, SO_2CH_3), 3.08 (s, 3H, SO_2CH_3), 1.07 (s, 9H,*tert*-butyl); ^{13}C-NMR ($CDCl_3$) δ 135.5, 132.6, 132.5, 129.9, 127.8, 127.7 (phenyl), 81.6 (C-2), 76.5 (C-4 and C-3), 70.1 (C-5), 62.4 ($-CH_2$), 38.3 and 38.2 (2 x $-CH_3$), 26.7 (*tert*-butyl), 19.1 (*tert*-butyl).

A mixture of compound **10** (1.40 g, 2.65 mmol), adenine (0.72 g, 5.3 mmol), K_2CO_3 (0.73 g, 5.3 mmol) and 18-crown-6 (0.70 g, 2.65 mmol) in DMF (50 ml) was stirred at 105 °C for 18 h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (150 mL) and washed with water (3 x 60 mL). The EtOAc layer was dried over Na_2SO_4 and evaporated to dryness and that residue was purified on a silica gel column to give **9b** (5.3%) and **12** (14.4%). Compound **9b**: mp 174-176°C; ^{1}H-NMR (DMSO-d_6) δ 8.15 (s, 1H, H-8), 8.11 (s, 1H, H-2); 7.60 (m, 4H, phenyl), 7.45 (m, 6H, phenyl), 5.70 (t, J = 4.2 Hz, 1H, H-4'), 5.34 (m, 1H, H-3'), 4.53 (dd, J = 10, 4.8 Hz, 1H, H-5'a), 4.28-4.20 (m, 2H, H-2', H-5'b), 3.84 (m, 2H, $-CH_2$), 3.28 (s, 3H, SO_2CH_3), 0.92 (s, 9H,*tert*-butyl); ^{13}C-NMR ($CDCl_3$) δ 156.1 (C-6) 152.4 (C-2), 149.3 (C-4), 139.1 (C-8), 135.1, 132.4, 129.9, 127.5 (phenyl) 119.1 (C-5), 83.3 (C-2') 81.7 (C-3'), 68.9 (C-5'), 62.1 ($-CH_2$), 59.8 (C-4'), 37.8 (mesyl $-CH_3$), 26.5 (*tert*-butyl) 18.6 (*tert*-butyl); HRMS (FAB): $(M+H)^+$ calcd for $C_{27}H_{34}N_5O_5SiS$ 568.2049, found 568.2038

4-(6-Amino-9H-purin-9-yl)-2(*S*)-(hydroxymethyl)-2,5-dihydrofuran (13). To a solution of **12** (0.16 g, 0.34 mmol) in methanol (10 mL) was added NH_4F (0.05 g, 1.3 mmol). The reaction was heated under reflux for 18 h and then the solvent was evaporated under reduced pressure. The residue was purified over silica gel to give

compound **13** as a crystalline solid (0.06 g, 76%): mp 230 °C; ^{1}H-NMR (DMSO-d_6) δ 8.30 (s, 1H, H-2), 8.21 (s, 1H, H-8), 7.42 (bs, 2H, -NH_2), 6.58 (d, 1H, J = 3.6Hz, H-3'), 5.18-5.02 (m, 2H, H-5'a, H-5'b), 4.94 (m, 1H, H-2'), 4.85 (t, 1H, -OH), 3.52 (t, 2H, J = 5.4Hz, -CH_2); ^{13}C-NMR(DMSO-d_6) δ 156.2 (C-6), 153.4 (C-2), 148.9 (C-4), 138.5 (C-8), 131.9 (C-4'), 118.8 (C-5), 111.4 (C-3), 86.7 (C-2'), 71.5 (C-5'), 64.0 (-CH_2); UV (MeOH) λ_{max} 232 (ε 19950), 262 (sh) (ε 12960), 279 (sh) nm (ε 14100); HRMS (FAB): $(M+H)^+$ calcd for $C_{10}H_{12}N_5O_2$ 234.0991, found 234.1004.

2(*R*)-(*tert*-Butyldiphenylsilyloxymethyl)-3(*S*)-(*tert*-butyldiphenylsilyloxy)-4(*R*)-aminotetrahydrofuran (14). *2(R)-(*tert-*Butyldiphenylsilyloxymethyl)-3(S)-(*tert-*butyldiphenylsilyloxy)-4(R)-azidotetrahydro-furan* : To a solution of **6** (2.50 g, 6.3 mmol) and imidazole (0.90 g, 13.2 mmol) in DMF (60 mL), *tert*-butyldiphenylsilylchloride (2.40 mL, 9.4 mmol) was added and the reaction mixture was heated at 70 °C for 18 h. DMF was removed under reduced pressure and the residue was dissolved in EtOAc (120 mL) and washed with water (2 x 50mL). The EtOAc layer was dried over Na_2SO_4 and evaporated to dryness and the oily residue was purified on silica gel to give the azido derivative as a colorless oil (3.50 g, 87%): ^{1}H-NMR($CDCl_3$) δ 7.60 (m, 8H, phenyl), 7.40 (m, 12H, phenyl), 4.25 (s, 1H, H-3), 4.08 (m, 2H, H-5), 3.85-3.78 (m, 2H, H-2, H-4), 3.49 (d, J = 5.5Hz, 2H, -CH_2), 1.06 (s, 9H, *tert*-butyl), 0.96 (s, 9H, *tert*-butyl); ^{13}C-NMR ($CDCl_3$) δ 135.6, 135.5, 130.0, 129.9, 129.5, 127.9, 127.8, 127.5 (phenyl) 87.1 (C-2), 78.2 (C-3), 70.4 (C-5), 67.9 (-CH_2), 63.7 (C-4), 26.8 and 26.7 (2 x *tert*-butyl), 19.1 and 19.0 (*tert*-butyl); HRMS (FAB): $(M+Li)^+$ calcd for $C_{37}H_{45}LiN_3O_3Si_2$ 642.3159, found 642.3151.

To a solution of the azido alcohol (6.30 g, 9.9mmol) in EtOAc/EtOH (20 mL, 1:1), 10% Pd/C (1.20 g) was added and the suspension was stirred under hydrogen pressure (25 psi) for 6 h. The reaction mixture was filtered and then evaporated to dryness. The oily residue was purified on silica gel to produce compound **14** as a colorless oil (5.60 g, 93%): ^{1}H-NMR ($CDCl_3$) δ 7.68-7.51 (m, 8H, phenyl), 7.43-7.24 (m, 12H, phenyl), 4.08 (m, 2H, H-3, H-2), 3.86 (m, 2H, H-5), 3.60 (dd, 1H, one H of –CH_2), 3.37 (bs, 1H, H-4), 3.19 (dd, 1H, J = 3.0, 11.1 Hz, one H of –CH_2), 1.06 (s, 9H, *tert*-butyl), 0.95 (s, *tert*-butyl); ^{13}C-NMR ($CDCl_3$) δ 135.6, 135.5, 133.2, 133.1, 132.6, 129.9, 129.8, 129.6, 127.8, 127.7, 127.6, (phenyl) 87.5 (C-2), 80.7 (C-3), 73.1 (C-5), 63.6 (-CH_2), 59.9 (C-

4), 26.8 (*tert*-butyl), 18.9 (*tert*-butyl); HRMS (FAB): $(M+Na)^+$ calcd for $C_{37}H_{47}NNaO_3Si_2$ 632.2992, found 632.3011.

4(*R*)-[{(3-Ethoxy-1-oxo-2-propenyl)aminocarbonyl}amino]-2(*R*)-(*tert*-butyl-diphenylsilyloxymethyl)-3(*S*)-(*tert*-butyldiphenylsilyloxy)tetrahydrofuran (15a). A solution of 3-ethoxy-2-propenyl isocyanate [prepared from 3-ethoxy-2-propenoyl chloride (0.40 g, 2.9 mmol) and silver cyanate (0.90 g, 6 mmol) by heating under reflux in toluene for 30 min] was added dropwise to a solution of compound **14** (0.70 g, 1.14 mmol) in toluene (10 mL) at 0 °C. After the addition, the reaction mixture was stirred at 0 °C for 30 min, then at room temperature for 2h and the solution was poured into a saturated solution of $NaHCO_3$ and extracted with EtOAc (3 x 50 mL). The combined EtOAc layers were washed with water, dried over Na_2SO_4 and evaporated to dryness. The residue was purified on silica gel to give **15a** (0.8g, 93%) as a white solid: mp 62 °C; ^{1}H-NMR($CDCl_3$) δ 9.50 (bs, 1H, 1-NH), 8.71 (d, 1H, J = 7.8Hz, 3-NH), 7.64-7.51 (m, 9H, H-6 and phenyl), 7.40-7.25 (m, 12H, phenyl), 5.28 (d, 1H, J = 12.2Hz, H-5), 4.42 (m, 1H, H-4'), 4.16 (m, 2H); 4.01 (m, 1H), 3.95 (q, 2H, J = 7.1Hz, $-OCH_2$), 3.77 (dd, 1H, J = 3.8, 9.2Hz), 3.42 (m, 2H, $-CH_2$), 1.33 (t, 3H, J = 7.1Hz, $-CH_3$), 1.05 (s, 9H, *tert*-butyl), 0.94 (s, 9H, *tert*-butyl); ^{13}C-NMR ($CDCl_3$) δ 167.8 (C-4), 162.3 (C-6), 155.3 (C-2), 135.7, 135.5, 135.4, 133.2, 133.1, 133.0, 132.4, 129.7, 129.3, 127.6, 127.4 (phenyl), 97.9 (C-5), 86.5 (C-2'), 78.7 (C-3'), 71.5 (C-5'), 66.9 ($-OCH_2$), 64.0 ($-CH_2$), 58.3 (C-4'), 26.7 and 26.6 (*tert*-butyl), 19.0 and 18.9 (*tert*-butyl), 14.3 ($-CH_2CH_3$); HRMS (FAB): $(M+Na)^+$ calcd for $C_{43}H_{54}N_2NaO_6Si_2$ 773.3418, found 773.3434.

4(*R*)-[(3,4-Dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-2(*R*)-(*tert*-butyldiphenyl-silyl-oxymethyl)-3(*S*)-(*tert*-butyldiphenylsilyloxy)tetrahydrofuran (16) and 4(*R*)-[(3,4-Dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-2(*R*)-(hydroxymethyl)-3(*S*)-(*tert*-butyl-diphenylsilyloxy)tetrahydrofuran (17). To a solution of **15a** (2.50 g, 3.3 mmol) in dioxane (40 mL), 2N H_2SO_4 (12 mL) was added and the reaction mixture was heated at 100 °C for 2.5 h. After cooling, the reaction mixture was neutralized with 2N NaOH at 0 °C. The solvent was evaporated to dryness and the residue was purified over silica gel to give **16** (0.40 g, 17%) and **17** (0.81 g, 54%). Compound **17** (partly deprotected derivative of **16**): mp 78-79 °C; ^{1}H-NMR($CDCl_3$) δ 9.12 (bs, 1H, NH), 7.61 (m, 4H, phenyl), 7.44-7.32 (m, 6H, phenyl), 7.17 (d, 1H, J = 8.1Hz, H-6), 5.45 (d, 1H, J =

8.1Hz, H-5), 5.08 (m, 1H, H-2'), 4.42 (m, 1H), 4.22 (dd, 1H, J = 7.0, 10.5Hz), 3.87 (m, 2H), 3.68 (dd, J = 12.0Hz, 1H), 3.35 (dd, J = 12.3Hz, 3.4Hz, 1H); 1.07 (s, 9H, *tert*-butyl); ^{13}C-NMR($CDCl_3$) δ 163.8 (C-4), 150.4 (C-2); 141.8 (C-6), 135.5, 135.4, 132.6, 131.9, 129.9, 127.6, 127.5 (phenyl), 102.2 (C-5), 86.4 (C-2'), 77.4 (C-3'), 70.7 (C-5'), 64.2 (-CH_2), 60.3 (C-4'), 26.6 (*tert*-butyl), 18.8 (*tert*-butyl). Compound **16:** mp 77-79 °C; ^{1}H-NMR($CDCl_3$) δ 8.23 (bs, 1H, NH), 7.66-7.20 (m, 21H, H-6 and phenyl), 5.14 (m, 1H, H-4'), 5.07 (dd, 1H, J = 2.3, 8.1 Hz, H-5), 4.55 (dd, 1H, J = 2.3, 6.1Hz, H-3'), 4.18 (dd, 1H, J = 3.8, 10.3Hz, H-5'a), 3.96-3.70 (m, 4H, H-5'b, H-2', -CH_2), 1.06 (s, 9H, *tert*-butyl), 0.92 (s, 9H, *tert*-butyl); ^{13}C-NMR($CDCl_3$) δ 163.5 (C-4), 150.4 (C-2), 141.2 (C-6), 135.7, 135.4, 135.2, 132.8, 132.7, 132.4, 131.8, 130.1, 129.9, 129.7, 127.8, 127.6 (phenyl), 102.7 (C-5), 86.5 (C-2'), 77.9 (C-3'), 72.2 (C-5'), 63.2 (C-4'), 62.0 (-CH_2), 26.6 (2 x *tert*-butyl), 19.0, 18.9 (*tert*-butyl); HRMS (FAB): $(M+Na)^+$ calcd for $C_{41}H_{48}N_2NaO_5Si_2$ 727.2995, Found 727.2993.

4(*R*)-[(3,4-Dihydro-2,4-dioxo-5-methyl-1(2H)-pyrimidinyl]-2(*R*)-(hydroxymethyl)tetrahydrofuran-3(*S*)-ol (18b). To a solution of 3-methoxy-2-methyl-acryloyl chloride (5.54 g, 41.2 mmol) in anhydrous toluene (100 mL) was added silver cyanate (11.10 g, 74. 16 mmol). The suspension was heated under reflux and under a N_2 atmosphere for 30 min and the resulting isocyanate suspension was added dropwise to a solution of **14** (12.54 g, 20.6 mmol) in anhydrous DMF (100 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 18 h at which time it was filtered and the excess solvents were removed under reduced pressure. Purification of the resulting oil on silica gel gave **15b** (13.25 g, 17.7 mmol) as a white foam in 86% yield. This product was immediately cyclized without further characterization. To a solution of **15b** (13.25 g, 17.7 mmol) in dioxane (100 mL) was added 2N H_2SO_4 (100 mL) and the resulting solution was stirred at reflux for 4 h. It was allowed to cool to room temperature and neutralized using 2N NaOH. Excess solvent was removed under reduced pressure and the resulting residue was purified on silica gel to give **18b**[6] (4.28 g, 17.7 mmol, ~100%) as a white solid.

4(*R*)-[(3,4-Dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-2(*R*)-(hydroxymethyl)tetrahydrofuran-3(*S*)-ol (18a). Compound **17** (0.70 g, 1.5 mmol) in MeOH (30 mL) was treated with NH_4F (0.2 g) and the solution was refluxed for 8 h. Methanol was removed

under reduced pressure and the residue was purified over silica gel to give **18a**[6] (0.30 g, 87%).

2(*S*)-(Hydroxymethyl)-4-[(3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-2,5-dihydrofuran (21a): To a solution of **18a** (0.19 g, 0.83 mmol) in pyridine (10 mL), benzoyl chloride (0.12 mL, 1 mmol) in pyridine (5 mL) was added dropwise at −15 °C. After the addition, the reaction mixture was stirred at the same temperature for 2 h and then the reaction was quenched with MeOH (5 mL). The solution was evaporated under reduced pressure, coevaporated with toluene and the residue was purified over silica gel to give the 5-O-benzoylated product in 69% yield. The benzoylated derivative (0.47 g, 1.41 mmol) was dissolved in dry pyridine (25 mL) and mesyl chloride (0.54 mL, 7 mmol) was added dropwise to it at 0 °C. After the addition, the reaction mixture was kept at +4 °C overnight. The reaction was quenched with water (2 mL) and evaporated to dryness. The residue was taken up in EtOAc (100 mL) and washed with water (3 x 50 mL). The EtOAc layer was dried over Na_2SO_4 and evaporated to dryness to give the mesylated product **19a** as a light brown foam. The crude mesylated product was used for the next reaction. Mesylate **19a** was taken up in dry DMSO (10 mL) and KOBu^t (0.47 g, 4.2 mmol) was added to the solution. The reaction mixture was heated at 75 °C for 2 h. After cooling down to room temperature, the solution was neutralized with 10% aqueous acetic acid solution and evaporated to dryness under reduced pressure. The residue was purified on silica gel to give **21a** as a crystalline solid (0.12 g, 42% from benzoylated derivative): mp 174 °C; ^{1}H-NMR (DMSO-d_6) δ 11.49 (s, 1H, NH), 7.68 (d, J = 8.1 Hz, 1H, H-6), 6.12 (s, 1H, H-3'), 5.69 (d, J = 8.1 Hz, 1H, H-5), 4.83 (m, 4H, H-2', H-5', -OH), 3.44 (d, 2H, -CH_2); ^{13}C-NMR (DMSO-d_6) δ 162.9 (C-4), 149.3 (C-2), 143.2 (C-6), 136.4 (C-2'), 115.1 (C-3'), 102.5 (C-5), 85.6 (C-4), 72.2 (C-5'), 63.9 (-CH_2); UV (MeOH) λ_{max} 272 nm (ε 10900); HRMS (FAB): $(M+H)^+$ calcd for $C_9H_{11}N_2O_4$ 211.0718, found 211.0702.

2(*S*)-(Hydroxymethyl)-4-[(3,4-dihydro-2,4-dioxo-5-methyl-1(2H)-pyrimidin-yl]-2,5-dihydrofuran (21b). Following the same method as described above, compound **18b** was converted to its benzoyl derivative in 82% yield. The benzoylated product was converted to the mesylate derivative **19b.** The crude mesylated product was converted to **21b** (50% from the benzoylated derivative) following the same method as for **21a.**

Data for **21b**: mp 134-135 °C; ^{1}H-NMR (CD_3OD) δ 7.50 (d, 1.3Hz, 1H, H-6), 6.01 (t, 1.8Hz, 1H, H-3'), 4.97-4.89 (m, 3H, H-2', H-5'), 3.62 (m, 2H, -CH_2), 1.89 (s, 3H, -CH_3); ^{13}C-NMR (CD_3OD) δ 166.0 (C-4), 151.0 (C-2), 140.4 (C-6), 139.0 (C-4'), 115.8 (C-3'), 112.4 (C-5), 83.0 (C-2'), 73.9 (C-5') 65.4 (-CH_2), 12.2 (-CH_3); UV (MeOH) λ_{max} 276.9 nm (ε 10222); HRMS (FAB): $(M+H)^+$ calcd for $C_{10}H_{13}N_2O_4$ 225.0875, found 225.0886.

2(*S*)-(Acetyloxymethyl)-4-[(3,4-dihydro-2-oxo-4-amino-1(2H)-pyrimidinyl]-2,5-dihydrofuran (22). To a solution of compound **21a** (0.08 g, 0.38 mmol) in pyridine (10 mL), Ac_2O was added and the reaction mixture was stirred at room temperature overnight. Saturated $NaHCO_3$ solution (30 mL) was then added and the solution was extracted with $CHCl_3$ (3 x 20 mL). The combined $CHCl_3$ part was evaporated to dryness and the residual pyridine was coevaporated with toluene. The gummy residue was purified on a silica gel column.to give the acetyl derivative (0.09 g, 94%). Triethylamine (0.1 mL, 0.72 mmol) was added to a solution of the acetyl derivative (0.09 g, 0.35 mmol) in CH_3CN (10 mL) containing TPSCl (0.22 g, 0.72 mmol) and DMAP (0.90 g, 0.72 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3.5 h. Conc. NH_4OH solution (28% solution, 6 mL) was added and the solution was further stirred at room temperature for 2 h. The solvent was evaporated to dryness, the residue was purified on a silica gel column and crystallized from methanol to give **22** (0.048 g, 54%): mp 111 °C ^{1}H-NMR (DMSO-d_6) δ 7.56 (d, J = 7.5Hz, 1H, H-6), 7.40 (bd, 2H, NH_2), 6.05 (m, 1H, H-3'), 5.78 (d, J = 7.5Hz, 1H, H-5), 4.98 (m, 1H, H-2'), 4.87 (m, 2H, H-5'), 4.06 (m, 2H, -CH_2), 2.01 (s, 3H, acetyl –CH_3); ^{13}C-NMR (DMSO-d_6) δ 172.7 (ester CO), 167.6 (C-2), 157.0 (C-4), 145.1 (C-6), 141.4 (C-4'), 115.9 (C-3'), 97.1 (C-5), 84.3 (C-2') 74.1 (C-5') 67.1 (-CH_2), 20.7 (-CH_3); HRMS (FAB): $(M+H)^+$ calcd for $C_{11}H_{14}N_3O_4$ 252.0984, found 252.0979.

2(*S*)-(Hydroxymethyl)-4-[(3,4-dihydro-2-oxo-4-amino-1(2H)-pyrimidinyl]-2,5-dihydrofuran (23). For the synthesis of compound **23,** the acetylated derivative **22** was first synthesized from 2(*S*)-(acetyloxymethyl)-4-[(3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-2,5-dihydrofuran (0.04 g, 0.16 mmol). After the reaction was over, the CH_3CN and excess NH_4OH were evaporated under reduced pressure. The crude reaction mixture was then dissolved in methanol (10 mL) and aqueous ammonia (28%, 6

mL) was added. The reaction mixture was then stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was purified on a silica gel column and crystallized from methanol to give **23** (0.015 g, 45%): mp 218 °C; ^{1}H-NMR (CD_3OD) δ 7.61 (d, J = 7.6Hz, 1H, H-6), 6.03 (m, 1H, H-3'), 5.93 (d, J = 7.4Hz, 1H, H-5), 4.95 (m, 3H, H-2', H-5'), 3.63 (m, 2H,-CH_2); ^{13}C-NMR (CD_3OD) δ 167.6 (C-2), 157.2 (C-4), 145.3 (C-6), 140.9 (C-4'), 117.2 (C-3'), 96.9 (C-5), 87.2 (C-2') 74.1 (C-5'), 65.5 (-CH_2); UV (MeOH) λ_{max} 284.8 nm (ε 10738); HRMS (FAB): $(M+H)^+$ calcd for $C_9H_{12}N_3O_3$: 210.0878, found: 210.0897.

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