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Synthesis and Conformational Behavior of Purine and Pyrimidine β-D-*threo*-Hex-3'-enopyranosyl Nucleosides

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Abstract : Based on the previous observation that anhydrohexitol nucleosides may exert antiviral activity, we have synthesized a series of β-D-*threo*-hex-3'-enopyranosyl nucleosides starting from 1,5-anhydro-4,6-O-benzylidene-2-O-p-toluoyl-D-glucitol. These nucleosides adopt a predominant $^{0}H_{1}$ conformation with a pseudo axially oriented base moiety. This conformational behaviour can be explained by favorable π-σ* interactions, a gauche effect and hydrogen bond interactions. The alternative $^{1}H_{0}$ conformation is disfavored due to pseudo-1,3-diaxial interactions.

INTRODUCTION

The discovery of the potent anti-HIV activity of AZT (3'-azido-3'-deoxythymidine), ddI (2',3'-dideoxyinosine) and d4T (2',3'-dideoxy-2',3'-didehydrothymidine) has led to the synthesis of a great number of 2',3'-dideoxy- and 2',3'-dideoxy-2',3'-didehydropentofuranosyl nucleosides.[1] In order to interact with the reverse transcriptase, the dideoxynucleosides must be phosphorylated in the target cell to yield the 2',3'-dideoxynucleoside-5'-triphosphates. The difference in the antiviral activity of different 2',3'-dideoxynucleosides may be due to either differences in the inhibitory effect of their 5'-triphosphates on the reverse transcriptase or differences in the efficiency by which the 2',3'-dideoxynucleosides are metabolised intracellularly to their 5'-triphosphates. In the past some effort has already been directed towards the synthesis of hex-3'-enopyranosyl **1** and hex-2'-enopyranosyl analogues **2**. These compounds are devoid of antiviral activity[2]. Considering the resemblance of the 2'-deoxyfuranose ring and the 1',5'-anhydrohexitol moiety in the hexitol nucleosides[3] of formula **3**, which exert antiviral activity, we became interested in the synthesis of a series of 3',4'-dideoxy-1',5'-anhydrohexitol nucleosides **4** (figure 1). These compounds can be considered as analogues of the well known 2',3'-dideoxynucleosides and thus, as potential anti-HIV agents. Recently, the synthesis of the carbocyclic congeners of **4c** and **4d** has been reported.[4]

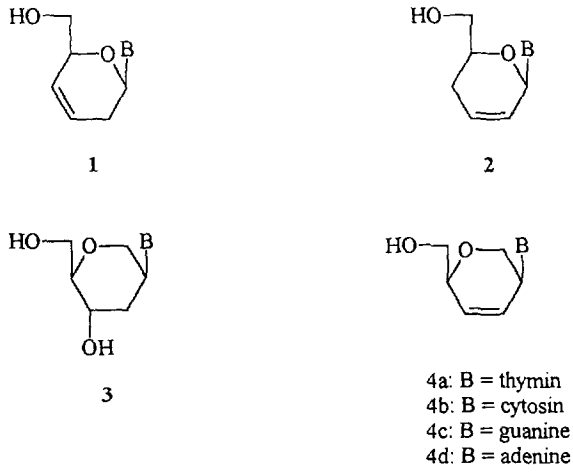
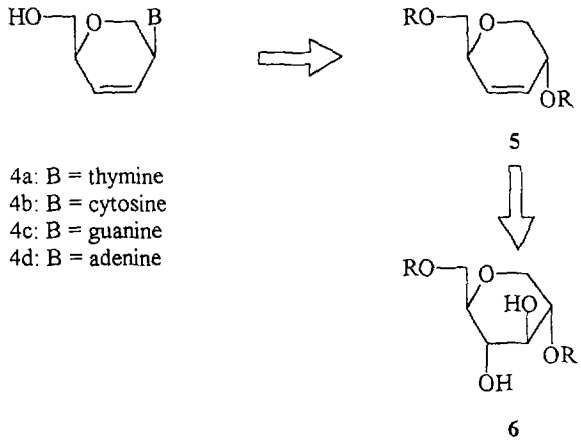


Figure 1

RESULTS AND DISCUSSION

The synthetic strategy used to synthesize the unsaturated hexitols **4** is based on a Mitsunobu type condensation of an appropriately protected unsaturated alcohol **5** with both purine and pyrimidine bases.[5] Introduction of the double bond between the 3' and 4' position was carried out on **6** using the chlorodiphenylphosphine/ iodine/imidazole system[6] (scheme 1).

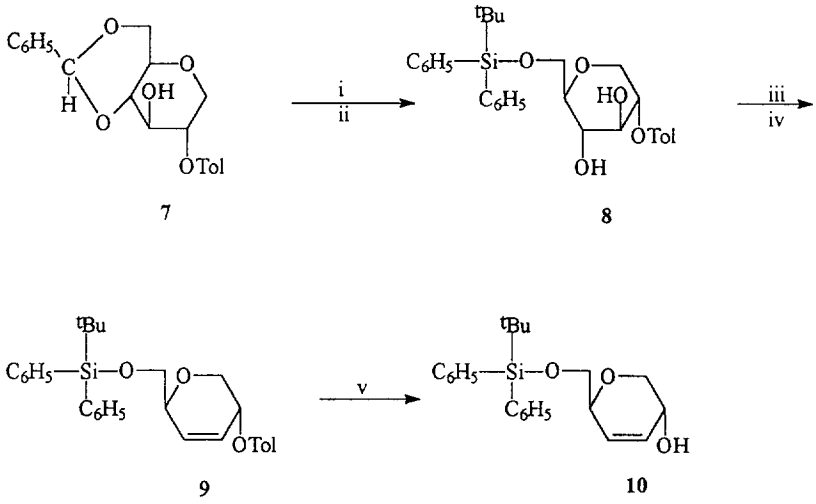


Scheme 1

(A) Preparation of the common synthon 10

The starting material used for the synthesis of the 2',3'-dideoxynucleoside mimics **4**, 1,5-anhydro-4,6-*O*-benzylidene-2-*O*-p-toluoyl-D-glucitol 7 was obtained from acetobromoglucose following a described procedure[3]. After the benzylidene moiety of 7 was hydrolyzed with 80% acetic acid at 80°C, the 6-OH was selectively protected with a t-butyldiphenylsilyl group which is stable under basic and acid conditions[7] to obtain **8** in 92% overall yield. The vicinal diol was subjected to an olefination reaction[6]. Heating of the diol **8** (1 eq) at 80°C in acetonitrile-toluene in the presence of chlorodiphenylphosphine (2.2 eq) and imidazole (4 eq) and portionwise addition of iodine (2.2 eq), followed by reaction "*in situ*" with Zn led to the unsaturated nucleoside **9** (78 % yield). The addition of Zn was necessary for the complete transformation of the intermediate iodo diphenylphosphinate to the final product. The toluoyl group was removed with sodium in methanol at 0°C to obtain the common synthon **10** in 80 % yield (scheme 2).

Scheme 2



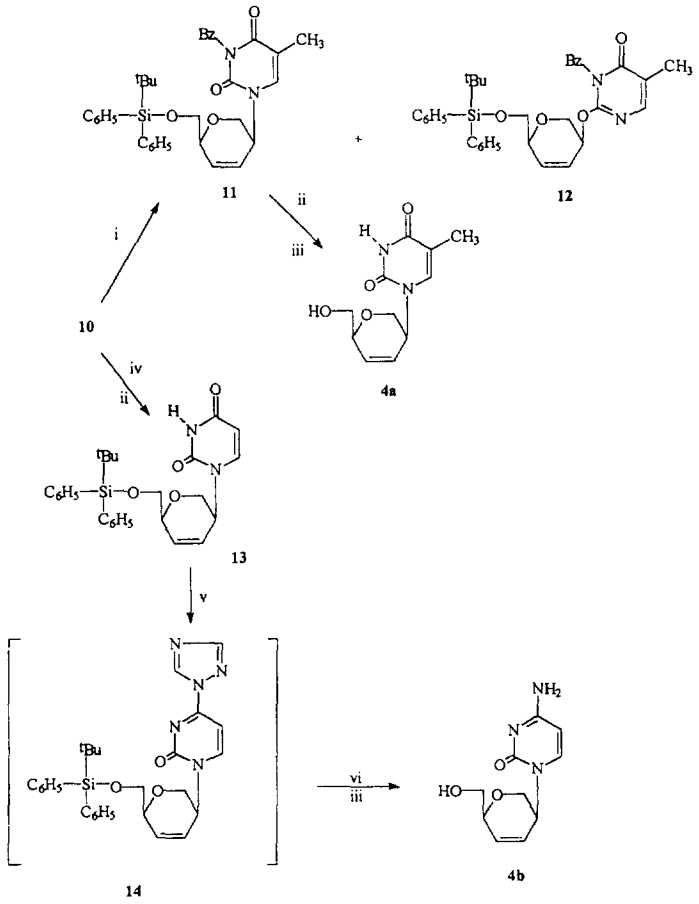
i) 80% HOAC ii) t-butyldiphenylsilyl chloride, imidazole, dry CH_2Cl_2 iii) Ph_2PCl, I_2, imidazole, CH_3CN-toluene, 80°C iv) Zn dust v) Na/MeOH, O°C

(B) Preparation of the β-D-*threo*-hex-3'-enopyranosylpurines and -pyrimidines 4

Condensation of **10** (1 equivalent) with N^3-benzoylthymine[8] (2 equivalents) in the presence of triphenylphosphine (Ph_3P, 2 equivalents) and DEAD (2 eq) in dry dioxane at room temperature afforded the N-1 alkylated derivative **11** in 43% yield, together with 20% of the less polar O-2 isomer **12**. The structure determination of both isomers was based on their NMR spectra (^1H and ^{13}C). For the O-2 isomer **12**, the signals corresponding to H-2' and C-

2' (sugar moiety) and the signals corresponding to C-2 and C-5 (pyrimidine base moiety) are shifted downfield relative to the same signals in the N-1 isomer. These data agree with those reported in the literature.[9] Debenzoylation of **11** with methanolic ammonia and subsequent fluoride ion desilylation led to the desired N-1 isomer **4a** (36%).

Scheme 3



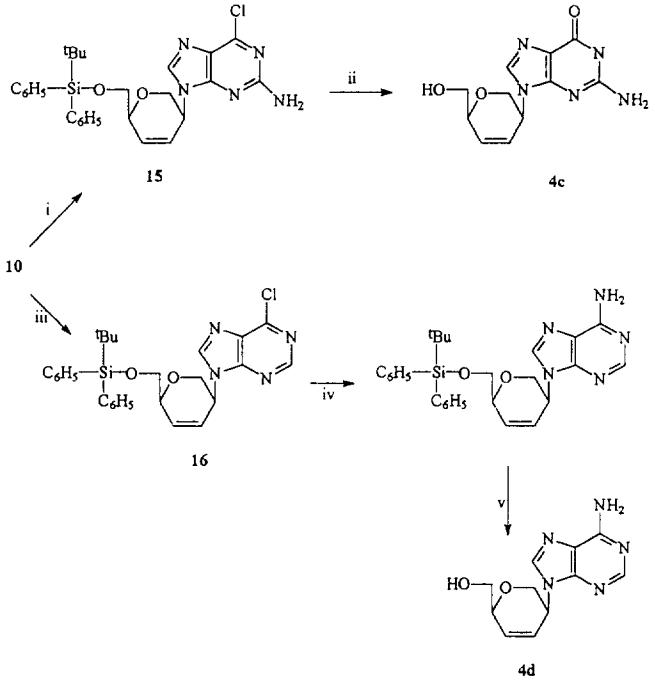
i) N^3-benzoylthymine, Ph_3P, DEAD, dioxane, rt ii) MeOH/NH_3 iii) Bu_4NF in THF (1M solution), rt iv) N^3-benzoyluracil, Ph_3P, DEAD, dioxane, rt v) $POCl_3$, 1,2,4-triazole, pyridine vi) NH_4OH

The cytosine derivative **4b** was obtained through transformation of the uracil analogue **13** via the 4-triazolyl-pyrimidinone intermediate **14** according to published methods[10]. When the condensation was performed with N^3-benzoyluracil[8] (1.2 equivalents) there was no O-alkylation probably due to the use of minor amounts of Ph_3P (1.2 eq) and DEAD (1.2eq). Debenzoylation with methanolic ammonia afforded **13** in 38 % overall yield (scheme 3).

For the synthesis of the guanine analogue **4c** by Mitsunobu reaction (Ph_3P (1.7 eq); DEAD (1.7 eq)), we used the commercially available 2-amino-6-chloropurine (1.7 eq) instead of N^2-isobutyryl-O^6-[p-nitrophenylethyl] guanine[11]. Reaction of **4c** with 2-amino-6-chloropurine (1.7 eq) under the above mentioned conditions (Ph_3P, 1.7 eq; DEAD, 1.7 eq in dry dioxane) afforded **15**, which is still contaminated with hydrazide. Therefore a mixture has been treated with trifluoroacetic:H_2O (1:1)[12] for three days at room temperature to furnish the unprotected **4c** in 18 % overall yield.

In a first effort we tried to synthesize the adenine derivative **4d** by performing the condensation reaction with N^6-benzoyladenine[13]. However this reaction was not successful and in a more general way we obtained **4d** from the 6-chloropurine analogue **16**[11]. Reaction of **10** with 6-chloropurine under Mitsunobu conditions (Ph_3P, 2 eq; DEAD, 2 eq in dry dioxane) afforded **16** in 26% yield. It is noteworthy that only the N-9 regioisomer has been formed in this condensation which generally gives a mixture of N-9/N-7 and N-3 isomers[5,11]. Treatment of **16** with methanol saturated with ammonia in a Parr Pressure reactor at 65°C[14] during two days gave, after removal of the t-butyldiphenylsilyl group, the desired adenine derivative **4d**. This compound was contaminated with tetrabutylammonium fluoride and was subjected to a reverse phase Rogel HPLC purification to afford **4d** in 33% yield (scheme 4).

Scheme 4



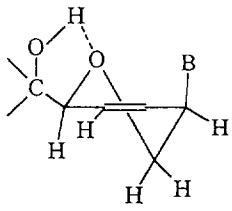
i) 6-chloro-2-aminopurine, Ph_3P, DEAD, dioxane, rt ii)CF_3COOH:H_2O (1:1), rt iii) 6-chloropurine, Ph_3P, DEAD, dioxane, rt iv) NH_3/MeOH v) Bu_4NF in THF (1 M solution)

(C) Conformational behavior of the β-D-*threo*-hex-3'-enopyranosylpurines and -pyrimidines 4

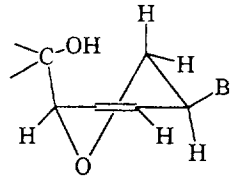
The assignment of the resonances of the protons of **4a,b,c,d** was made from a DQF-COSY of **4b** at 48°C and their 1D ^{1}H NMR spectra at 48°C at 500 MHz. The ^{1}H chemical shifts are given in table 1. The couplings constants $J_{H1'-H2'}$, $J_{H1''-H2'}$, $J_{H2'-H3'}$ and $J_{H4'-H5'}$ observed in the 1D ^{1}H NMR spectra enabled evaluation of their preferred conformations in solution (table 2, figure 2). These coupling constants were further refined by simulation with the xsimula program.[15] The chemical shifts of H-1' and H-1" of the thymine analogue **4a** are the same and gives a doublet as couplings pattern. Therefore, their $J_{H1'-H2'}$, $J_{H1''-H2'}$ coupling constants could be deduced from the multiplet of H-2' using the simulation program. Inspection of these coupling constants, which are more or less the same for all the bases, reveals the following conclusions. (i) The small values found for the vicinal couplings constants $^3J_{H1'-H2'} \approx 1$ - 1.5 Hz and $^3J_{H1''-H2'} \approx 2.5$ - 3 Hz excludes that H-1' and H-2' are diaxially disposed as in ^1H_O. (ii) The coupling $^3J_{H2'-H3'} \approx 5$ Hz is significantly higher than $^3J_{H4'-H5'} \approx 1$ - 1.5 Hz . This coupling pattern corresponds with conformation $^OH_1$ where H-4' and H-5' are more or less perpendicularly orientated (a torsional angle close to 90°) with a small couplings constant as result. Conformation ^1H_O, in contrast, would imply a smaller value of $^3J_{H2'-H3'}$ as for $^3J_{H4'-H5'}$ indicating a torsional angle close to 90° between H-2' and H-3'. These observations clearly indicates that the bases are oriented pseudoaxially via the predominant conformation $^OH_1$. In these 3',4'-unsaturated nucleosides **4a,b,c,d** the resonance between the π electron cloud and the antibonding orbital of the C-2'-N-9/N1 bond is responsible for the stabilizing effect . This resonance is only possible when the bases are oriented pseudoaxially . Such π-σ* interactions have been introduced to rationalize preferential axial orientations of electronegative substituents on allylic position in cyclic systems.[16-21] When examining the structures **4a,b,c,d**, the influence of the O-5'-C-1'-C-2'-N-9/N-1 gauche effect and the formation of a hydrogen bond between 6'-OH and 5'-O also might contribute to the driving force for this conformational preference. Moreover, conformation ^1H_O is disfavored by a sterical interaction between 1'-CH_2 and 6'-CH_2OH. [When the NMR spectra were recorded at different temperature (301 K, 311 K, 321 K, 331 K, 341 K and 351 K), there was no change in chemical shifts or couplings constants which means there exist no equilibrium]. The observed data are in agreement with those published[21] for pent-2'-enopyranosyl nucleosides[21,22]. Here, β-purine nucleosides[21] adopt a $^5H_0$ conformation due to π-σ* interactions, a favorable gauche effect and the anomeric effect. β-Pyrimidine nucleosides[21], however, adopt the $^0H_5$ conformation due to unfavorable sterical interactions between the base moiety and the 5'-CH_2 group in the $^5H_0$ conformation.

Table 1. ^1H chemical shifts of the 3'4'-unsaturated hexopyranosyl nucleosides.

	H2/H6	H8/H5/CH3	H1',H1"	H2'	H3'	H4'	H5'	H6',H6"
4a	7.65	1.64	3.82; 3.82	4.86	5.86	6.24	4.09	3.59
4b	6.25	5.64	3.75; 3.80	4.94	5.83	6.23	4.06	3.57; 3.53
4c	7.68		3.87; 3.90	4.72	6.04	6.21	4.15	3.61; 3.56
4d	8.19	8.24	3.92; 3.97	5.01	6.10	6.25	4.20	3.63; 3.60



$^OH_1$



^1H_O

Figure 2. Conformational forms of the 3'4'-unsaturated hexopyranosyl nucleosides.

Table 2. Selected NMR parameters and conformational features of the 3'4'-unsaturated hexopyranosyl nucleosides **4**.

	4a	**4b**	**4c**	**4d**	RMS
$^3J_{H1'-H2'}$	1.603 ± 0.086	1.205 ± 0.045	0.961 ± 0.044	1.075 ± 0.052	0.064
$^3J_{H1"-H2'}$	3.211 ± 0.046	2.585 ± 0.038	2.385 ± 0.052	2.498 ± 0.067	0.049
$^3J_{H2'-H3'}$	5.081 ± 0.018	4.925 ± 0.039	4.778 ± 0.066	4.816 ± 0.086	0.059
$^3J_{H4'-H5'}$	1.422 ± 0.044	1.467 ± 0.018	1.269± 0.019	1.213 ± 0.034	0.040
preferred conformation	$^OH_1$	$^OH_1$	$^OH_1$	$^OH_1$	

See experimental section for all coupling constants.

EXPERIMENTAL SECTION

Ultraviolet spectra were recorded with a Philips PU 8700 UV/vis spectrophotometer. The ^1H NMR and ^{13}C NMR spectra were determined with a Varian gemini 200 Mhz spectrometer with tetramethylsilane as internal

standard for the 1H NMR spectra and $DMSO_{d6}$ (39.6 ppm) or $CDCl_3$ (76.6 ppm) for the 13C NMR spectra (=singulet, d=doublet, dd=double doublet, t=triplet, dt=double triplet, br s=broad signal, m=multiplet). Liquid secondary ion mass spectra (LSIMS) and accurate mass measurements (HRMS) were obtained using KRATOS Concept 1H mass spectrometer (Kratos Manchester, UK). Precoated Machery-Nagel Alugram Sil G) UV254 plates were used for TLC, and the spots were examined with UV light and sulfuric acid-anisaldehyde spray. Column chromatography was performed on Janssen Chimica silica gel (0.060-0.200 nm and 0.030-0.750)

The ^1H and ^{13}C NMR spectra of **4** have been recorded on a Varian Unity+ 500 Mhz spectrometer. These compounds were dissolved in $DMSO_{d6}$ and these spectra were recorded at different temperatures (301 K, 311 K, 321 K, 331 K, 341 K and 351 K). The DQF-COSY spectrum of **4b** was recorded at 321 K using 400 experiments of 2K complex data points each with a relaxation delay of 2 s. $\pi/4$ shifted $sine^2$ windows were applied in both dimensions before Fourier transformation.

1,5-anhydro-6-*O*-t-butyldiphenylsilyl-2-*O*-(*p*-toluoyl)-D-glucitol 8

1,5-anhydro-4,6-*O*-benzylidene-2-*O*-(p-toluoyl)-D-glucitol 7 (5.5g; 13.5 mmol) was treated with 100 mL of 80% acetic acid at 80°C for two hours. After evaporation and coevaporation with toluene, the residue was dissolved in dry dichloromethane. To this solution was added imidazole (1.3g; 19.1 mmol) and tert.-butyldiphenylsilyl chloride (4.9 g; 16.2 mmol) at 0°C. After 24 h. stirring at room temperature, the reaction mixture was poured into water and extracted with dichloromethane (2 x 50 mL). The organic layer was concentrated and purified by column chromatography on silicagel (CH_2Cl_2:MeOH; (99:1)) to afford 6.5 g (92% yield) of **8**. HRMS calc. for $C_{30}H_{36}O_6Si$ + H 521.23592; found 521.23480. UV (MeOH) λ_{max} = 240 nm. ^1H NMR ($CDCl_3$, δ): 7.90 -7.20 (m, aromatic H, 14H); 5.15 - 4.95 (m, 2'-H, 1H); 4.24 - 4.12 (dd, 1'eq-H, $^1J_{1',1''}$=12Hz; $^3J_{1',2'}$=5.5Hz, 1H); 4.02 - 3.70 (m, 3'-H, 4'-H, 6'-H, 6"-H, 4H); 3.45 - 3.29 (m, 1"-H, 5'-H, 2H); 3.18 (br s, 4'-OH, 1H); 2.90 (br s, 3'-OH, 1H); 2.50 (s, $\underline{CH_3}$-toluoyl, 3H), 1.10 (s, $\underline{Me_3}C$, 9H) ppm. ^{13}C NMR ($CDCl_3$, δ) 166.45 (CO); 144.15, 135.6, 132.8, 129.8, 129.1, 127.9, 126.7 (aromatic C); 78.8 (C-5'); 77.01 (C-4'); 72.7 (C-3'); 71.9 (C-2'); 66.8 (C-1'); 64.7 (C-6'); 26.9 (C-$\underline{Me_3}$); 21.7 ($\underline{CH_3}$-Tol); 19.2 ($\underline{C}$-Me_3) ppm.

1,5-anhydro-6-*O*-t-butyldiphenylsilyl-3,4-dideoxy-2-*O*-(p-tolylsulfonyl)-D-*erythro*-hex-3-enose 9 and 1,5-anhydro-6-*O*-t-butyldiphenylsilyl-3,4-dideoxy-D-*erythro*-hex-3-enopyranose 10

To a solution of **8** (15g; 28.8 mmol) in toluene:acetonitrile (2:1; 50 mL) chlorodiphenylphosphine (11.3 mL, 63.4 mmol) and imidazole (7.8 g; 115.2 mmol) were added and the mixture was heated at 80 °C. Iodine (16.3 g; 63.4 mmol) was added portionwise during one hour. Two hours after the addition was finished, Zinc powder (15g) was added and the reaction was kept at 80°C for 12 hours more. The mixture was cooled to room temperature, filtered and evaporated. The residue was taken up in dichloromethane (100 mL) and washed twice with water (50 mL). The aqueous phase was further extracted with dichloromethane (2x50 mL). The organic phase was dried, concentrated and subjected to silicagel column chromatography (CH_2Cl_2:n-hexane; 3:2) to

afford 11 g (78% yield) of the title compound **9**. LSIMS (THGLY) 509 $(M+Na)^+$. HRMS calc. for $C_{30}H_{34}O_4Si$ +Na 509.21242; found 509.21260. ^1H NMR ($CDCl_3$, δ): 7.95 (d, aromatic H, 2H) ; 7.25 -7.70 (m, aromatic H, 12H); 6.05 (br s, H-3' and H-4', 2H); 5.45 (m, H-2', 1H); 3.60 - 4.35 (m, H-5'; H-1'; H-1", H-6' and H-6"); 2.40 (s, $\underline{CH_3}$-toluoyl, 3H), 1.10 (s, $\underline{Me_3}C$, 9H) ppm. ^{13}C NMR ($CDCl_3$, δ) 166.2 (CO); 143.7, 135.6, 133.4, 129.7, 129.0, 127.2 (aromatic C); 131.6 (C-4'); 125.4 (C-3'); 74.2 (C-5'); 65.3 and 65.1 (C-1', C-2', C-6'); 26.8 (C-$\underline{Me_3}$); 21.7 ($\underline{CH_3}$-Tol); 19.2 ($\underline{C}$-Me_3) ppm.

Removal of the toluoyl group of **9** (11g; 22.6 mmol) was accomplished by treatment with 150 mL of 0.1 M NaOMe for two hours at room temperature. After neutralization and evaporation of the volatiles, the residue was purified by column chromatography ((1) CH_2Cl_2; (2) CH_2Cl_2:MeOH (98:2)) to yield 6.7 g (80% yield) of **10**. This compound is not stable and decompose easily. ^1H NMR ($CDCl_3$, δ): 7.20 -7.90 (m, aromatic H, 10H); 6.01 - 5.80 (m, H-3' and H-4', 2H); 3.30 - 4.40 (m, H-5'; H-2'; H-1'; H-1", H-6' and H-6"); 1.10 (s, $\underline{Me_3}C$, 9H) ppm. ^{13}C NMR ($CDCl_3$, δ) 135.5, 133.4, 129.7, 129.0, 127.6 (aromatic C); (C-4'); (C-3'); 74.2 (C-5'); 68.6 (C-1'); 65.2 (C-6'); 62.5 (C-2'); 26.8 (C-$\underline{Me_3}$); 19.2 ($\underline{C}$-Me_3) ppm.

1',5'-anhydro-6'-*O*-t-butyldiphenylsilyl-2',3',4'-trideoxy-2'-(N^3-benzoylthymin-1-yl)-D-*threo*-hex-3'-enopyranose 11 and its 2-*O*-isomer 12

To a suspension containing the alcohol **10** (1 g, 2.7 mmol), Ph_3P (1.42 g; 5.4 mmol) and N^3-benzoylthymine (1.25 g; 5.4 mmol) in dry dioxane (40 mL) was slowly added a solution of DEAD (5.4 mmol, 0.841 mL) in dry dioxane (10 mL). The mixture was stirred at room temperature for one night. Evaporation of the volatiles and purification by column chromatography on silicagel [(1)CH_2Cl_2 (2) CH_2Cl_2:MeOH (99:1)] yielded 670 mg (43 %) of the N-1 isomer **11** and 300 mg (20%) of the O-2 isomer **12**.

For **11**: UV (MeOH) λ_{max} = 264,5 nm. ^1H NMR ($CDCl_3$, δ): 8.10 -7.30 (m, aromatic H, 14H); 6.44 (d, H-4', $^3J_{3',4'}$=10 Hz, 1H); 5.95 (dd, H-3', $^3J_{3',4'}$=10 Hz $^3J_{2',3'}$=5 Hz, 1H) 5.10 - 4.95 (m, H-2', 1H); 4.30 - 3.60 (m, , H-6', H-6'', H-1' H-1" and H-5', 5H); 1.70 (d, CH_3-C-5, $^4J_{H\text{-}6,CH3}$, 3H) 1.10 (s, $\underline{Me_3}C$, 9H) ppm. ^{13}C NMR ($CDCl_3$, δ) 168.7 (CO); 162.4 (C-4); 150.15 (C-2); 135.7 (C-4'); 137.9, 135.4, 134.9, 133.0, 131.6, 130.4, 129.8, 129.0, 127.7, (aromatic C); 122.4 (C-3') 110.2 (C-5) 75.2 (C-5'); 68.8 (C-1'); 65.7 (C-6'); 47.8 (C-2') 26.9 (C-$\underline{Me_3}$); 19.4 ($\underline{C}$-Me_3); 12.3 (5-CH_3) ppm.

For **12**: UV (MeOH) λ_{max} = 264,5 nm. ^1H NMR ($CDCl_3$, δ): 7.80 -7.30 (m, aromatic H, 14H); 6.20 (d, H-4', $^3J_{3',4'}$=10 Hz, 1H); 6.10 (dd, H-3', $^3J_{3',4'}$=10 Hz $^3J_{2',3'}$=5 Hz, 1H) 5.25 - 5.35 (m, H-2', 1H); 4.20 - 3.60 (m, , H-6', H-6'', H-1' H-1" and H-5', 5H); 1.95 (d, CH_3-C-5, $^4J_{H\text{-}6,CH3}$=1.1 Hz, 3H) 1.10 (s, $\underline{Me_3}C$, 9H) ppm. ^{13}C NMR ($CDCl_3$, δ) 163.8 (CO); 154.50 (C-4); 150.69 (C-2); 135.6, 134.6, 129.7, 127.6, (aromatic C); 122.4 (C-3') 118.2 (C-5) 74.6 (C-5'); 68.2 (C-1'); 66.9 (C-2') 65.7 (C-6'); 26.9 (C-$\underline{Me_3}$); 19.3 ($\underline{C}$-Me_3); 12.4 (5-CH_3) ppm.

1',5'-anhydro-2',3',4'-trideoxy-2'-(thymin-1-yl)-β-D-*threo*-hex-3'-enopyranose 4a

The compound **11** (670 mg; 1.15 mmol) was debenzoylated by treatment with methanolic ammonia (24 h). After evaporation of the volatiles the residue was directly desilylated with Bu_4NF in THF (1 M solution, 1.2 mmol, 1.2 mL) during two hours. the solvent was evaporated to furnish a brown oil. Column chromatography (CH_2Cl_2 to CH_2Cl_2:MeOH (90:10) afforded the title product **4a** (100 mg, 36%). This compound was further purified by HPLC on a Rogel Column (H_2O:MeOH; 70:30). HRMS (THGLY) calc. for $C_{11}H_{15}O_4N_2$ 239.1031; found 239.1040. UV (MeOH) λ_{max} = 272 nm (ε=8800). ^1H NMR ($CDCl_3$, δ): 7.65 (d, H-6, 1H); 6.24 (dt, H-4', $^3J_{3',4'}$=10 Hz, $^3J_{4',5'}$=1.42 Hz , $^3J_{2',4'}$=1,34 Hz 1H); 5.86 (qq, H-3', $^3J_{3',4'}$=10 Hz $^3J_{2',3'}$=5,08 Hz, $^3J_{3',5'}$=2.21Hz, $^3J_{1',3'}$=1.60 Hz ,1H) 4.92 (t, ^3J=5 Hz, OH, 1H) 4.86 (m, H-2', 1H); 4.09 (m, H-5', 1H); 3.82 (d, H-1' and H-1", 2H); 3.59 (m, H-6' and H-6", 2H); 1.64 (d, CH_3-C-5, 3H) ppm. ^{13}C NMR ($DMSO_{d6}$, δ) 164.0 (C-4); 151.1 (C-2); 139.1 (C-6); 135.7 (C-4'); 122.9 (C-3') 108.0 (C-5) 75.2 (C-5'); 67.8 (C-1'); 62.9 (C-6'); 46.8 (C-2') ; 12.3 (5-CH_3) ppm.

1',5'-anhydro-6'-*O*-t-butyldiphenylsilyl-2',3',4'-trideoxy-2'-(uracil-1-yl)-D-*threo*-hex-3'-enopyranose 13

To a mixture of the alcohol **10** (1.8 g, 5.2 mmol)with N^3-benzoyluracil (1.4g; 6.3 mmol) and Ph_3P (1.6g; 6.3 mmol) in dry dioxane (50 mL) was slowly added a solution of DEAD (0.97 mL, 6.3 mmol) in dry dioxane (5 mL). The mixture was stirred at room temperature for two hours. After evaporation of the solvent and purification by flash column chromatography [(1) CH_2Cl_2 (2) CH_2Cl_2:MeOH (98:2)], the residue was debenzoylated by treatment with methanolic ammonia during one night. Purification by flash column chromatography [CH_2Cl_2:MeOH (98:2)] afforded 900 mg (1.94 mmol, 38 %) of **13**. HRMS (THGLY) calc. for $C_{26}H_{31}O_4N_2Si$ 463.2053; found 463.2055. UV (MeOH) λ_{max} = 267 nm. ^1H NMR ($CDCl_3$, δ): 9.35 (br s, NH, 1H); 7.85 (d, $^3J_{5,6}$=8Hz; H-6, 1H) 7.70-7.30 (m, aromatic H, 10H); 6.45 (dt, H-4', $^3J_{3',4'}$=10 Hz, 1H); 5.90 (m, H-3', 1H) 5.35 (d, $^3J_{5,6}$=8Hz; H-5, 1H); 5.10 - 4.95 (m, H-2', 1H); 4.35 -4.20 (m, H-5', 1H); 4.10- 3.75 (m, , H-6', H-6'', H-1' H-1", 4H); 1.10 (s, $\underline{Me_3}C$, 9H) ppm. ^{13}C NMR ($DMSO_{d6}$, δ) 163.7 (C-4); 151.3 (C-2); 143.0 (C-6); 135.8 (C-4'); 135.6, 135.4, 133.0, 132.7, 129.9 and 127.8 (aromatic H); 122.6 (C-3') 101.8 (C-5) 75.2 (C-5'); 68.8 (C-1'); 65.6 (C-6'); 47.4 (C-2') ; 26.9 (C-$\underline{Me_3}$); 19.3 (C-Me_3)12.3 (5-CH_3) ppm.

1',5'-anhydro-2',3',4'-trideoxy-2'-(cytosin-1-yl)-β-D-*threo*-hex-3'-enopyranose 4b

Compound **13** (400 mg, 0.86 mmol) was coevaporated with anhydrous pyridine. A premixed solution of 133 μL (1.49 mmol) of phosphorous oxychloride and 1,2,4-triazole (400 mg, 5.79 mmol) in 30 mL of anhydrous pyridine was added. This mixture was stirred for 5 h. at room temperature, after which 10 mL of concentrated ammonia was added on a ice bath. After 10 min stirring at room temperature, the volatiles were removed in vacuo, coevaporated with toluene and the residue was suspended in 100 mL of CH_2Cl_2-MeOH (1:1) and filtered over a small layer of Celite to remove most of the inorganic salts. The filtrate was evaporated, coevaporated with

toluene and roughly purified by flash column chromatography (CH_2Cl_2:MeOH (95:5)). The residue was desilylated with Bu_4NF in THF (1M solution, 0.76 mL) during three hours. The solvent was evaporated to furnish a brown oil. Column chromatography [(1) CH_2Cl_2:MeOH (90:10), (2) CH_2Cl_2:MeOH (85:15), (3) CH_2Cl_2:MeOH (80:20)] afforded 170 mg of **4b** (0.75 mmol; 87%). Further purification was carried out by HPLC on a Rogel Column (H2O:MeOH (70:30)) to afford after lyophilisation 100 mg of the tittle compound as a hygroscopic powder. HRMS (TDG) calc. for $C_{10}H_{14}O_3N_3$ 224.1035; found 224.1052. UV (MeOH) λ_{max} = 276nm (ε=11436). ^{1}H NMR ($DMSO_{d6}$, δ): 6.25 (d, H-6, 1H); 6.23 (dt, H-4', $^3J_{3',4'}$=10 Hz, $^3J_{4',5'}$=1.47 Hz $^3J_{2',4'}$=1,46 Hz 1H); 5.83 (qq, H-3', $^3J_{3',4'}$=10 Hz $^3J_{2',3'}$=4.92 Hz, $^3J_{3',5'}$=1.82 Hz, $^4J_{1',3'}$=1.40 Hz ,1H); 5.64 (d, H-5, 1H); 4.77 (t, ^{3}J=5 Hz, OH, 1H) 4.94 (m, H-2', 1H); 4.06 (m, H-5', 1H); 3.80 (dd, $^3J_{1'',2'}$=2.58 Hz, $^2J_{1',1''}$, = -12 Hz, H-1", 1H); 3.75 (dt, $^3J_{1',2'}$=1.20 Hz , H-1', 1H) 3.59 (m, H-6' and H-6", 2H); ppm. ^{13}C NMR ($DMSO_{d6}$, δ) 165.6 (C-4); 155.7 (C-2); 143.5 (C-6); 134.9 (C-4'); 123.3 (C-3') 93.0 (C-5) 75.3 (C-5'); 67.9 (C-1'); 63.0 (C-6'); 47.7 (C-2') ppm.

1',5'-anhydro-2',3',4'-trideoxy-2'-(guanin-9-yl)-β-D-*threo*-hex-3'-enopyranose 4c

The alcohol **10** (1.60 g, 4.3 mmol) reacted with 2-amino-6-chloropurine (1.24 g, 7.33 mmol) under Mitsunobu conditions [Ph_3P (1.92 g, 7.33 mmol) and DEAD (1.13 mL, 7.33 mmol) in 70 mL dry dioxane]. After two hours stirring, the reaction mixture was concentrated and flash column chromatography (CH_2Cl_2:MeOH (98:2) afforded **15** which was still contaminated with hydrazide. The obtained mixture was dissolved in 50 mL of CF_3COOH:H_2O (1:1) and stirred for 3 days at room temperature. Solvents were evaporated and coevaporated with H_2O. The residue was cooled and treated with MeOH:NH_4OH (10:1) (20 mL). Volatiles were removed and the residue was purified by column chromatography [CH_2Cl_2:MeOH (80:20)] to afford **4c** which was still contaminated with salts. The residue was dissolved in MeOH and partial evaporation of the solvent gave a white precipitate (200 mg, 18 % overall yield) which was identified as **4c**. Further purification by HPLC on a Rogel Column (H_2O:MeOH, (70:30)) afforded after lyophilisation 130 mg of the tittle compound **4c**. HRMS (THGLY) calc. for $C_{11}H_{13}O_3N_5$ 264.1097; found 264.1090. UV (MeOH) λ_{max} = 254 nm (ε=9190). ^{1}H NMR ($DMSO_{d6}$, δ): 7.68 (s, H-2, 1H); 6.21 (dt, H-4', $^3J_{3',4'}$=10 Hz, $^3J_{4',5'}$=1.27 Hz $^3J_{2',4'}$=1.30 Hz 1H); 6.03 (qq, H-3', $^3J_{3',4'}$=10 Hz $^3J_{2',3'}$=4.78 Hz, $^3J_{3',5'}$=2.06Hz, $^4J_{1',3'}$=1.47 Hz ,1H); 4.87 (t, ^{3}J=5 Hz, OH, 1H) 4.72 (m, H-2', 1H); 4.15 (m, H-5', 1H); 3.90 (dd, $^3J_{1'',2'}$=2.38 Hz, $^2J_{1',1''}$, = -12 Hz, H-1", 1H); 3.87 (dt, $^3J_{1',2'}$=0.96 Hz, H-1', 1H) 3.59 (m, H-6' and H-6", 2H); ppm. ^{13}C NMR ($DMSO_{d6}$, δ) 156.9 (C-6); 153.6 (C-2); 150.5 (C-4); 136.5 (C-8);134.0 (C-4'); 122.8 (C-3') 116.6 (C-5); 109.0; 75.3 (C-5'); 67.5 (C-1'); 63.1 (C-6'); 46.1 (C-2') ppm.

1',5'-anhydro-6'-*O*-t-butyldiphenylsilyl-2',3',4'-trideoxy-2'-(6-chloropurin-9-yl)-β-D-*threo*-hex-3'-enopyranose 16

Following the previous procedure, **10** (1.4 g, 3.8 mmol) reacted with 6-chloropurine (1.28 g, 7.6 mmol) for one night at room temperature. The solution became completely black. Volatiles were removed and the residue was purified with column chromatography [CH_2Cl_2 to CH_2Cl_2:MeOH (95:5)]. The first fraction afforded **16,** the second fraction was still contaminated with hydrazide and triphenylphosphine and this fraction was subjected to a second purification on silicagel using n-hexane-EtOAc (80:20) as eluens. We obtained the title compound **16** in 26% yield. UV (MeOH) λ_{max} = 264.5 nm. ^{1}H NMR ($CDCl_3$, δ): 8.71 (s, , 1H); 8.37 (s, , 1H), 7.80 -7.30 (m, aromatic H, 10H); 6.45 (d, H-4', $^3J_{3',4'}$=9.8 Hz, 1H); 6.10 (dd, H-3', $^3J_{3',4'}$=9.8 Hz $^3J_{2',3'}$=4.3 Hz, 1H) 5.30 -5.10 (m, H-2', 1H); 4.40 - 3.80 (m, , H-6', H-6'', H-1' H-1" and H-5', 5H); 1.10 (s, $\underline{Me_3}$C, 9H) ppm. ^{13}C NMR ($DMSO_{d6}$, δ) 156.7 (C-6); 151.6 (C-2); 145.1 (C-4); 135.5, 132.8, 129.9 and 127.8 (aromatic C); 135.1 (C-4'); 121.9 (C-3') 75.3 (C-5'); 68.2 (C-1'); 65.6 (C-6'); 47.4 (C-2') ppm.

1',5'-anhydro-6'-*O*-t-butyldiphenylsilyl-2',3',4'-trideoxy-2'-(adenin-9-yl)-β-D-*threo*-hex-3'-enopyranose 17 and 1',5'-anhydro-2',3',4'-trideoxy-2'-(adenin-9-yl)-β-D-*threo*-hex-3'-enopyranose 4d

A solution of **16** (400 mg, 0.8 mmol) in 100 mL of methanol saturated with ammonia is heated in a Parr Pressure reactor for two days at 65°C. After evaporation, the obtained residue was purified by flash column chromatography [CH_2Cl_2:MeOH (95:5)] to afford 300 mg of **17** (78% yield). HRMS (THGLY) calc. for $C_{27}H_{32}O_2N_5Si$ 486.2325; found 486.2308. UV (MeOH) λ_{max} = 259 nm. ^{1}H NMR ($DMSO_{d6}$, δ): 8.05 (s, , 1H); 8.15 (s, , 1H), 7.80 -7.20 (m, aromatic H, 10H); 6.45-6.10 (m, H-3' and H-4', 2H); 5.50 (br s , NH_2, 2H); 5.10 -4.95 (m, H-2', 1H); 4.40 - 4.30 (m, H-5', 1H) 4.15-3.70 (m, H-6', H-6'', H-1' and H-1", 4H); 1.10 (s, $\underline{Me_3}$C, 9H) ppm. ^{13}C NMR ($DMSO_{d6}$, δ) 156.2 (C-6); 152.6 (C-2); 148.8 (C-4); 139.5 (C-8); 135.3, 133.5, 130.1 and 128.1 (aromatic C); 135.2 (C-4'); 123.5 (C-3') 118.7 (C-5); 74.9 (C-5'); 67.9 (C-1'); 65.7 (C-6'); 46.2 (C-2') ppm.

Compound **17** (300 mg; 0.62 mmol) was desilylated with a solution of Bu_4NF in THF (1 M solution, 0.68 mL). After one night stirring, the precipitate was separated and washed with water yielding 145 mg of the title compound **4d**, which was contaminated with Bu_4NF. Further purification was carried out with HPLC on a Rogel Column (H_20:MeOH, 60:40) which afford 50 mg (32.6 % yield) after lyofilisation. HRMS (THGLY) calc. for $C_{11}H_{14}O_2N_5$ 248.1147; found 248.1131. UV (MeOH) λ_{max} = 261 nm (ε=12609). ^{1}H NMR ($DMSO_{d6}$, δ): 8.19, 8.24 (2s, H-2, H-8, 2H); 6.25 (dt, H-4', $^3J_{3',4'}$=10 Hz, $^3J_{4',5'}$=1.21 Hz $^3J_{2',4'}$=1.23 Hz 1H); 6.10 (qq, H-3', $^3J_{3',4'}$=10 Hz $^3J_{2',3'}$=4.81 Hz, $^3J_{3',5'}$=2.14 Hz, $^4J_{1',3'}$=1.14 Hz ,1H); 5.01 (m, H-2', 1H); 4.20 (m, H-5', 1H); 3.97 (dd, $^3J_{1",2'}$=2.50 Hz, $^2J_{1',1"}$ = -12 Hz, H-1", 1H); 3.92 (dt, $3J_{1',2'}$=1.08 Hz, H-1', 1H) 3.61 (m, H-6' and H-6",

2H); ppm. ^{13}C NMR ($DMSO_{d6}$, δ) 155.5 (C-6); 151.6 (C-2); 148.9 (C-4); 140.3 (C-8); 134.3 (C-4'); 122.8 (C-3') 75.4 (C-5'); 67.5 (C-1'); 63.0 (C-6'); 46.4 (C-2') ppm.

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