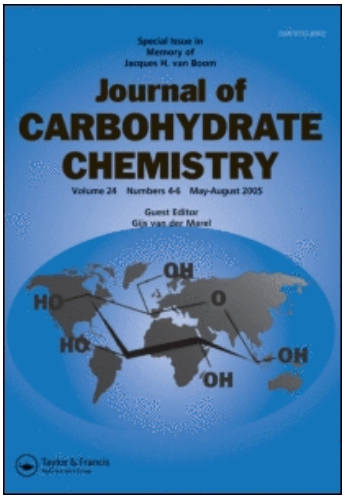

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SYNTHESIS AND CONFORMATIONAL STUDIES OF UNNATURAL PYRIMIDINE NUCLEOSIDES

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ABSTRACT

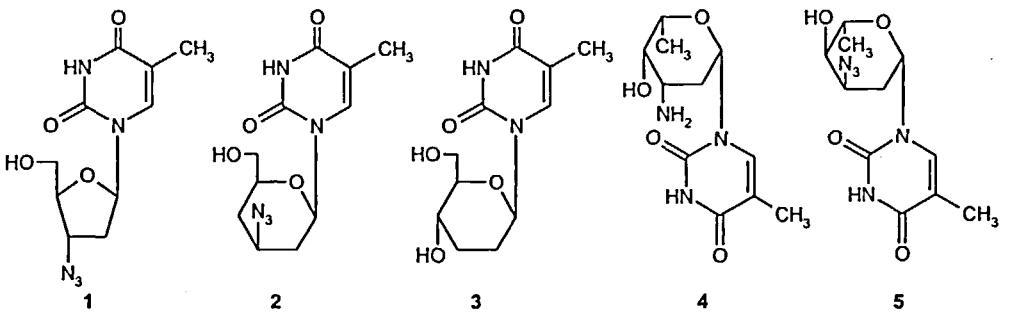
Starting from 3,4-di-*O*-acetyl-L-rhamnal (**6**) and thymine (**7**) the unsaturated nucleosides 1-(2',3',6'-trideoxy-4'-*O*-acetyl-α- and β-L-*erythro*-hex-2'-enopyranosyl)-thymine (**8a** and **8b**) were prepared in anomerically pure form. In solution **8a** was shown to be present in the $^5H_0$ and $^0H_5$ conformations, whereas the predominant conformation of **8b** was $^5H_0$. Chemical transformation of **8a** and **8b** led to the saturated nucleosides 1-(2',3',6'-trideoxy-α- and β-L-*erythro*-hexopyranosyl)thymine (**10a** and **10b**, respectively), which were converted into 1-(4'-azido-2',3',4',6'-tetradeoxy-α- and β-L-*threo*-hexopyranosyl)thymine (**12a** and **12b**). Preliminary biological studies showed that **9b** was inactive against the HIV-1 and HIV-2 viruses.

INTRODUCTION

During their studies on the synthesis of oligonucleotides containing a 2,3-dideoxy-D-glucopyranosyl unit, Eschenmoser and Dobler[1] found in the 1990's that the obtained *homo*-DNA is much more stable than the natural DNA. They also demonstrated

that these analogues possess a linear stucture, in contrast to the helical structural arrangement of the natural DNA. It is interesting to note that such a structural feature has been observed earlier for certain pyrimidine nucleoside-type antibiotics[2] (amicetins, blasticidins, gougerotin, mildiomycin, etc.) produced by microorganisms. In connection with structure-activity relationship studies of the anti-HIV AZT (**1**, azidothymidine) Pedersen et al.[3,4] synthesized several β-D-hexopyranosyl analogues (such as **2** and **3**) of thymidine.

The L-nucleosides are the unnatural enantiomers of the nucleic acid components occurring in nature. The synthetic production of the corresponding β-L-pentofuranosyl derivatives has been a long-lasting challenge for researchers,[5-8] and these studies have revealed that the transportation and metabolism of the L-nucleosides are different[9-11] from those of the β-D-nucleosides. At the same time, the synthesis and biological properties of the α- and β-L-hexopyranosyl nucleosides (e.g. **4**, **5**) have been relatively less-studied.[12,13]

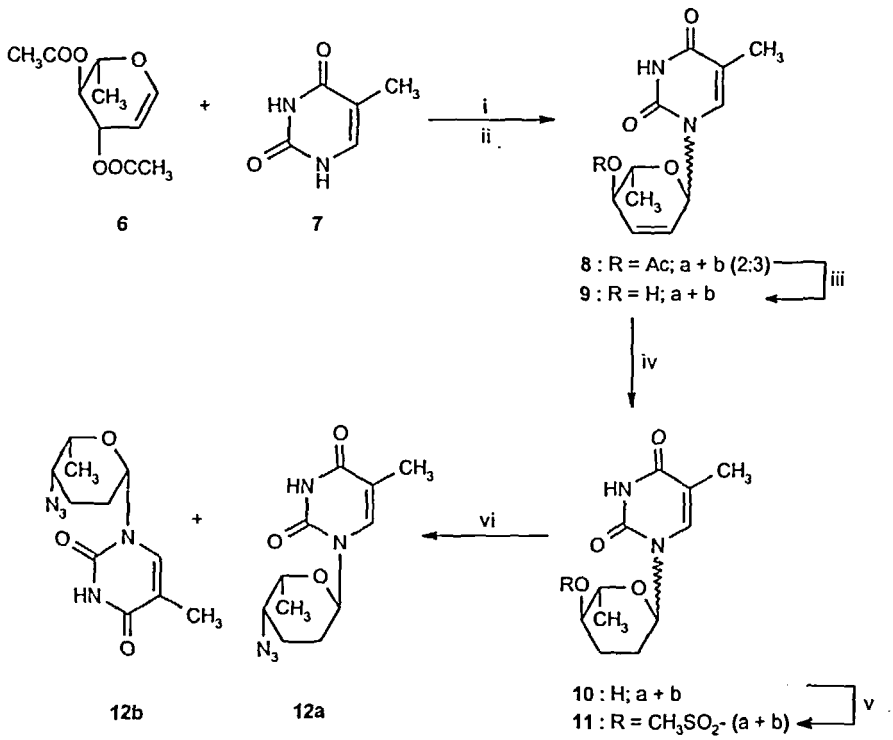


1 **2** **3** **4** **5**

The present paper deals with the synthesis and conformational investigation of unnatural L-hexopyranosyl thymine derivatives.

RESULTS AND DISCUSSION

Following silylation, thymine (**7**) was glycosylated with 3,4-di-*O*-acetyl-L-rhamnal (**6**) in acetonitrile in the presence of trimethylsilyl trifluoromethanesulphonate promoter (Scheme 1) to furnish a 2:3 mixture (52%) of 1-(2',3',6'-trideoxy-4'-*O*-acetyl-α- and β-L-*erythro*-hex-2'-enopyranosyl)thymine (**8a** and **8b**). Both products could be



Scheme 1. i: $((CH_3)_3Si)_2NH$, $(NH_4)_2SO_4$ 120 °C, 3 h; ii: $CF_3SO_3Si(CH_3)_3$, MeCN, 0 °C, column chromat (52%); iii : MeOH, NaOMe (93%); iv: H_2/Pd/C, MeOH (95%); v: CH_3SO_2Cl, pyridine, 20 °C, column chromat (83%); vi: NaN_3, DMF, 120 °C, 24 h, column chromat (76%)

isolated by column chromatography in anomerically pure form. The structure of the unsaturated nucleoside **8a** was substantiated by means of X-ray crystallography.[18]

The anomeric configurations and conformations of **8a** and **8b** were also established and verified by means of conventional NMR techniques (1D homonuclear NOE, HETCOR, long-range INEPT, and 2D J-resolved INEPT).

The value of the $^3J_{H\text{-}4',H\text{-}5'}$ homonuclear coupling constant (6 Hz), observed for **8a**, suggests an average of the ^5H_o (H-1' *pseudoequatorial*, H-4' and H-5' *trans-diaxial*) and $_5H^o$ (H-1 *pseudoaxial*, H-4' and H-5' *gauche*) conformations (Fig. 2) in $CDCl_3$ solution. However, the measured homonuclear NOE can only be explained by the occurrence of the ^5H_o conformer, as irradiation of H-6 caused an increase of the signal intensity of H-5' and

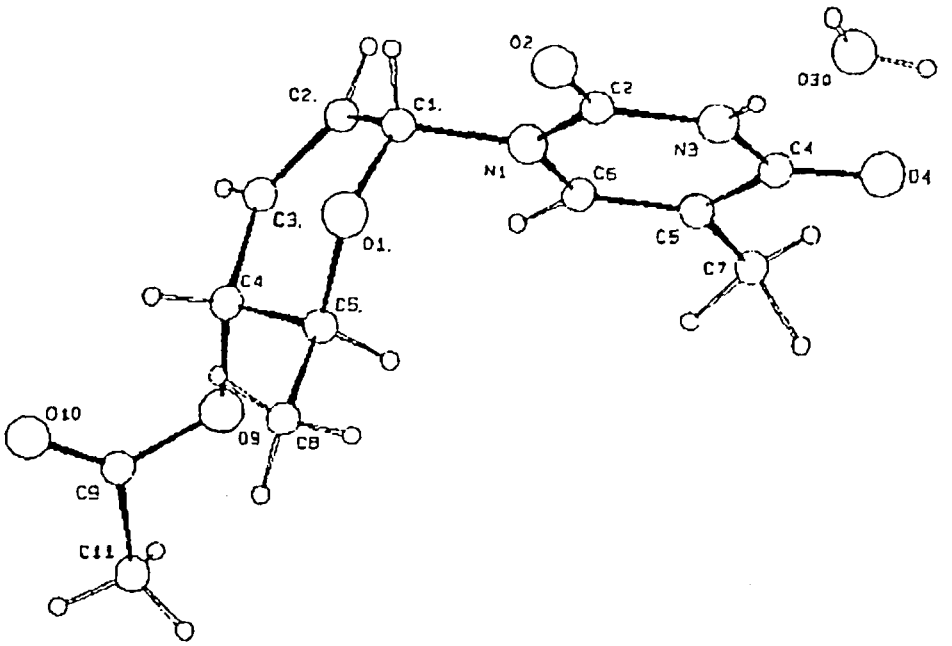


Fig. 1. X-Ray structure of **8a** crystallized with water

H-2' (+7.5% and +4.2%, respectively), indicating that H-6' is located above the plane of the unsaturated sugar-ring. On the basis of the observed values of the heteronuclear coupling constants ($^3J_{H\text{-}1',C\text{-}2}$ = 2.1 Hz and $^3J_{H\text{-}1',C\text{-}6}$ = 2.8 Hz) it is most probable that in the ^5H_o conformation, C-6 and H-1' are rather *trans*-oriented compared to atoms C-2 and H-1'. In the case of the other conformation ($_5H^o$), irradiation of H-6 cannot cause NOE effects with the protons of the sugar ring, and the plane of the aglycone ring is parallel with that of the sugar skeleton. In this conformation the *pseudo-axial* position of H-1' is also demonstrated by the +2.9% homonuclear NOE enhancement of H-1' when 5'-CH_3 is irradiated. Consequently, the occurrence of both conformers should be considered in solution.

The large value (8.9 Hz) of the $^3J_{H\text{-}4',H\text{-}5'}$ homonuclear coupling constant, measured for **8b** indicates the *pseudo trans-diaxial* arrangement of the protons H-4' and H-5', and thus the preponderance of the ^5H_o conformation (Fig. 2). In the homonuclear NOE experiment irradiation of H-1' resulted in a 12% intensity enhancement of H-5'

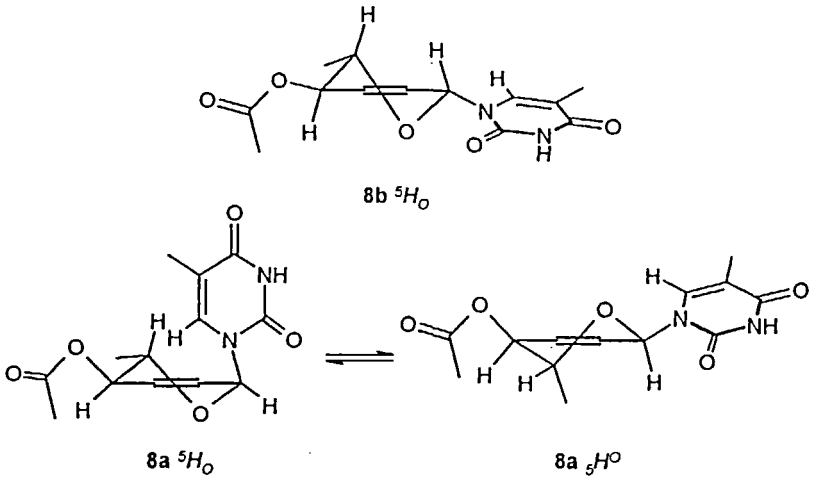


Fig. 2. Possible conformers of **8a** and **8b**

demonstrating that these protons are close to each other. This means a *cis*-arrangement, when both protons are *pseudo-axial* (which is also proved by the $^3J_{H\text{-}4',H\text{-}5'}$ coupling constant). The H-6 proton of the thymine aglycone does not show a NOE with the protons of the sugar skeleton, and thus the H-2' and C-2 atoms of the two rings are in a *cis* steric relation. The small, and very close values (2.8 Hz and 2.3 Hz, respectively) of the $^3J_{H\text{-}1',C\text{-}2}$ and $^3J_{H\text{-}1',C\text{-}6}$ heteronuclear coupling constants demonstrate that the H-1' C-2 and H-1' C-6 planar angles are identical in average, permitting a relatively free rotation around the C-1' N-1 bond. However, a stable conformer in which the plane of the thymine ring is perpendicular to the plane constituted by the C-1', C-2', C-3' and C-4' atoms is most unlikely. Consequently, the measured experimental data strongly suggest that C-1', C-2', C-3' and C-4' atoms are in the same plane, the C-5' carbon is located above this plane, and the oxygen atom of the cyclohemiacetal ring is placed below this plane (^5H_o conformation).

Further chemical transformations of the anomerically pure nucleosides **8a** and **8b** were then accomplished separately, but essentially in the same fashion. Thus, Zemplén *O*-deacetylation[14] of **8a** and **8b** afforded **9a** and **9b**, respectively, which were hydrogenated over palladium-on-carbon catalyst in methanol to furnish 1-(2',3',6'-trideoxy-α- and β-L-*erythro*-hexopyranosyl)thymine (**10a** and **10b**, respectively) (Scheme 1).

Table. Anti-HIV-1 and HIV-2 activity and cytotoxic properties of the compound **9b** compared with AZT in human T-lymphocyte (CEM/0) cells.[15]

Compound	EC_{50}[a] (μg/mL)		CC_{50}[b] (μg/mL)
	HIV-1	HIV-2	
9b	> 200	> 200	> 200
AZT	0.36 μM	1.3 μM	> 500 μM

a. 50% Effective concentration or concentration required to protect CEM cells against the cytopathogenicity of HIV by 50%. b. 50% Cytotoxic concentration or concentration required to reduce CEM cells viability by 50%.

Mesylation of **10a** and **10b** at the C-4' hydroxyl group with methanesulphonyl chloride led to the 4'-*O*-methanesulphonates **11a** and **11b**. Bimolecular nucleophilic replacement of the sulphonate esters with sodium azide afforded 1-(4'-azido-2',3',4',6'-tetradeoxy-α- and β-L-*threo*-hexopyranosyl)thymine (**12a** and **12b**).

Investigation of the anti-HIV properties of the new nucleoside (**9b**) is shown in the Table.

EXPERIMENTAL

General methods. Melting points were determined on a Kofler hot-stage apparatus and in capillary tubes, and the data are uncorrected. ^1H (200 MHz) and ^{13}C NMR spectra (50.3 MHz) were obtained with a Bruker WP 200 SY spectrometer (internal standard: tetramethylsilane). IR spectra were recorded in KBr pellets with a Perkin-Elmer 16 PC FT spectrophotometer. Mass spectra were recorded with a VG-7035 instrument (EI, 70 eV) and with a VG TRIO-2 instrument by applying the plasma spray (PSP) technique. Specific rotations were measured with a Perkin-Elmer 141 MC polarimeter. Thin-layer chromatography was carried out on Kieselgel 60 F_{254} (Merck) precoated plates, and column chromatography was performed on Kieselgel 60 (Merck, 0.063-0.2) adsorbent with the following eluent systems: *A*: 7:3 hexane-acetone, *B*: 6:5 hexane-acetone, *C*: 9:1 ethyl acetate-dichloromethane. Visualization of the chromatograms was effected in UV light (254 nm). For drying of the organic solutions of the preparations anhydrous magnesium sulphate was applied. Evaporations were carried out under diminished pressure (ca. 20 mmHg, bath temperature below 40 °C).

1-(2',3',6'-Trideoxy-4'-*O*-acetyl-α- and β-L-*erythro*-hex-2'-enopyranosyl)thymine (8a and 8b). A solution of thymine (7; 945 mg, 7.5 mmol), ammonium sulphate (25 mg) and hexamethyldisilazane (10 mL) was stirred at 120 °C for 3 h, and then concentrated. The residue and 3,4-di-*O*-acetyl-L-rhamnal (6; 1.07 g, 5 mmol) were dissolved in acetonitrile (20 mL), and to the cooled (0 °C) solution trimethylsilyl trifluoromethanesulphonate (1.36 mL) was added and the reaction mixture was stirred for 90 min.[16,17] Then saturated aqueous sodium hydrogencarbonate solution (10 mL) was added, and the mixture was extracted with dichloromethane (5x50 mL). The organic layer was washed with water, dried and concentrated to give 680 mg (52%) of a 2:3 mixture of **8a** and **8b**, which was separated by column chromatography (*A*).

8a: $[\alpha]_D^{25}$ -84.19 (*c* 0.62, MeOH), mp 76-78 °C; IR 3160 (ν_{NH}), 2978 (ν_s CH_3), 2930 (ν_{as} CH_2), 1700-1658 (thymine $\nu_{C=O}$ and ester $\nu_{C=O}$) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.57 (1H, s, NH), 6.41 (1H, dd, H-1', $J_{1',2'}$ = 4 Hz), 6.29 (1H, dq, H-3', $J_{2',3'}$ = 10 Hz), 5.84 (1H, dq, H-2'), 5.00 (1H, m, H-4'), 3.97 (1H, m, H-5', $J_{5',6'}$ = 6.5 Hz), 2.15 (3H, s, Ac), 1.94 (3H, d, thymine Me, $J_{CHT,CH3}$ = 1 Hz), 1.32 (3H, d, Me-5'); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.2 (C-7'), 164.0 (C-4), 150.9 (C-2), 136.4 (C-6), 130.7 (C-3'), 126.7 (C-2'), 110.6 (C-5), 75.3 (C-1'), 68.8 (C-5'), 68.5 (C-4'), 20.8 (C-8'), 17.0 (C-6'), 12.3 (C-7); *m/z* (PSP) 281 $(M+H)^+$, 298 $(M+NH_4)^+$.

Anal. Calcd for $C_{13}H_{16}N_2O_5$ (280.28): C, 55.72; H, 5.75; N, 10.00. Found: C, 55.60; H, 6.26; N, 9.94.

8b: $[\alpha]_D^{25}$ -106.67 (*c* 0.54, MeOH), mp 205-206 °C; IR 3170 (ν_{NH}), 2936 (ν_{as} CH_2), 1710-1740 (thymine $\nu_{C=O}$ and ester $\nu_{C=O}$) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.39 (1H, s, NH), 7.00 (1H, d, -C=, $J_{CHT,CH3}$ = 1.2 Hz), 6.46 (1H, dq, H-1', $J_{1',2'}$ = 1.8 Hz), 6.08 (1H, dt, H-3', $J_{2',3'}$ = 10.2 Hz, $J_{1',3'}$ = 1.9 Hz, $J_{3',4'}$ = 1.9 Hz), 5.70 (1H, dt, H-2', $J_{2',4'}$ = 1.9 Hz), 5.12 (1H, dq, H-4', $J_{4',5'}$ = 8.9 Hz, $J_{1',4'}$ = 2 Hz), 3.82 (1H, dq, H-5'), 2.12 (3H, s, Ac), 1.94 (3H, s, thymine Me, $J_{5',6'}$ = 6.1 Hz), 1.30 (3H, d, Me-5'); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.2 (C-7'), 163.8 (C-4), 150.7 (C-2), 135.6 (C-6), 132.5 (C-3'), 127.4 (C-2'), 111.6 (C-5), 78.0 (C-1'), 72.9 (C-5'), 69.3 (C-4'), 20.7 (C-8'), 17.7 (C-6'), 12.2 (C-7); *m/z* (PSP) 281 $(M+H)^+$, 298 $(M+NH_4)^+$.

Anal. Calcd for $C_{13}H_{16}N_2O_5$ (280.28): C, 55.72; H, 5.75; N, 10.00. Found: C, 55.86; H, 5.88; N, 10.36.

1-(2',3',6'-Trideoxy-α-L-*erythro*-hex-2'-enopyranosyl)thymine (9a). The pH of a solution of **8a** (100 mg, 0.36 mmol) in dry methanol (5.0 mL) was adjusted to 8.5 by the addition of 0.1 M sodium methoxide (0.25 mL), and then heated under reflux for 12 h. The reaction mixture was acidified to pH=6.0 by the addition of methanol containing 10% of acetic acid, concentrated, and the residue was chromatographed (*B*) to give 85 mg (93%) of pure **9a**: $[\alpha]_D^{25}$ -36.33 (*c* 0.30, MeOH), mp 179-180 °C; IR 3426 (ν_{OH}), 3054 (ν_{NH}), 1700 ($\nu_{C=O}$) cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 7.60 (1H, d, -CH=, $J_{CHT,CH3}$ = 1 Hz), 6.31 (1H, dq, H-3', $J_{2',3'}$ = 9.5 Hz, $J_{1',3'}$ = 2 Hz), 6.24 (1H, dd, H-1', $J_{1',2'}$ = 4.5 Hz), 5.79 (1H, dq, H-2', $J_{2',4'}$ = 2 Hz), 3.82 (1H, dt, H-4', $J_{4',5'}$ = 8.0 Hz), 3.55 (1H, dq, H-5', $J_{5',6'}$ = 6 Hz), 1.88 (3H, d, thymine Me), 1.26 (3H, d, Me-5'); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 166.4 (C-4), 152.8 (C-2), 139.2 (C-6), 138.0 (C-3'), 124.4 (C-2'), 110.5 (C-5), 77.8 (C-1'), 70.9 (C-5'), 68.9 (C-4'), 18.1 (C-6'), 12.2 (C-7); *m/z* (EI) 239 $(M+H)^+$.

Anal. Calcd for $C_{11}H_{14}N_2O_4$ (238.24): C, 55.46; H, 5.92; N, 11.76. Found: C, 54.90; H, 6.60; N, 11.42.

1-(2',3',6'-Trideoxy-β-L-*erythro*-hex-2'-enopyranosyl)thymine (9b). Zemplén O-deacetylation[14] of **8b** was accomplished as described for the preparation of **9a**. Yield of **9b**: 93%, $[\alpha]_D^{25}$ -91.83 (*c* 0.71, MeOH), mp 165-166 °C; IR 3428 (ν_{OH}), 3060 (ν_{NH}), 1690 ($\nu_{C=O}$) cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 7.23 (1H, d, -CH=, $J_{CHT,CH3}$ = 1 Hz), 6.36 (1H, dq, H-1', $J_{1',2'}$ = 1.8 Hz, $J_{1',3'}$ = 1.9 Hz $J_{1',4'}$ = 2 Hz), 6.19 (1H, dt, H-3', $J_{2',3'}$ = 10.2 Hz, $J_{3',4'}$ = 1.9 Hz), 5.69 (1H, dt, H-2', $J_{2',4'}$ = 1.9 Hz), 3.94 (1H, dq, H-4', $J_{4',5'}$ = 8.9 Hz), 3.63 (1H, dq, H-5', $J_{5',6'}$ = 6 Hz), 1.87 (3H, d, thymine Me), 1.33 (3H, d, Me-5'); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 166.2 (C-4), 152.4 (C-2), 138.1 (C-6), 136.0 (C-3'), 126.4 (C-2'), 112.0 (C-5), 79.9 (C-1'), 77.4 (C-5'), 69.0 (C-4'), 18.3 (C-6'), 12.2 (C-7); *m/z* (EI) 239 $(M+H)^+$.

Anal. Calcd for $C_{11}H_{14}N_2O_4$ (238.24): C, 55.46; H, 5.92; N, 11.76. Found: C, 54.90; H, 6.60; N, 11.42.

1-(2',3',6'-Trideoxy-α-L-*erythro*-hexopyranosyl)thymine (10a). A solution of **9a** (50 mg, 0.21 mmol) in dry methanol (5.0 mL) was hydrogenated at atmospheric pressure in the presence of 10% palladium-on-carbon catalyst (Merck). The filtered solution was concentrated and the residue submitted to column chromatography (*C*) to yield 48 mg (95%) of pure **10a**: $[\alpha]_D^{25}$ -4.31 (*c* 0.51, MeOH), mp 142-143 °C; IR 3408 (ν_{OH}), 3064

(ν_{NH}), 1682 ($\nu_{C=O}$) cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 7.72 (1H, d, -CH=, $J_{CHT,CH3}$ = 1 Hz), 5.90 (1H, dd, H-1', $J_{1',2'a}$ = 10 Hz, $J_{1',2'e}$ = 2.5 Hz), 4.23-4.06 (1H, m, H-5'), 3.70-3.63 (1H, m, H-4'), 2.15-1.65 (4H, m, H-2'a, H-2'e, H-3'a, H-3'e), 1.89 (3H, d, thymine Me), 1.34 (3H, d, Me-5', $J_{5',6'}$ = 7 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) 166.2 (C-4), 152.1 (C-2), 138.3 (C-6), 111.4 (C-5), 77.9 (C-1'), 77.1 (C-5'), 67.4 (C-4'), 26.1 (C-2'), 25.5 (C-3'), 16.0 (C-6'), 12.3 (C-7); *m/z* (EI) 241 $(M+H)^+$.

Anal. Calcd for $C_{11}H_{16}N_2O_4$ (240.26): C, 54.99; H, 6.71; N, 11.66. Found: C, 54.16; H, 7.18; N, 11.18.

1-(2',3',6'-Trideoxy-β-L-*erythro*-hexopyranosyl)thymine (10b). The synthesis was carried out as described for the preparation of **10a**, to obtain 50 mg (99%) of pure **10b**: $[\alpha]_D^{25}$ -22.09 (*c* 0.48, MeOH), mp 207-208 °C; IR 3412 (ν_{OH}), 3044 (ν_{NH}), 1698 ($\nu_{C=O}$) cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 7.50 (1H, d, -CH=, $J_{CHT,CH3}$ = 1 Hz), 5.62 (1H, dd, H-1'), 3.52-3.33 (1H, m, H-5'), 3.29-3.15 (1H, m, H-4'), 2.22-1.5 (5H, m, H-2'a, H-2'e, H-3'a, H-3'e, thymine Me), 1.29 (3H, d, Me-5', $J_{5',6'}$ = 5.8 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 166.1 (C-4), 152.0 (C-2), 137.8 (C-6), 111.5 (C-5), 82.7 (C-1'), 80.1 (C-5'), 71.5 (C-4'), 32.4 (C-2'), 30.5 (C-3'), 18.5 (C-6'), 12.3 (C-7); *m/z* (EI) 241 $(M+H)^+$.

Anal. Calcd for $C_{11}H_{16}N_2O_4$ (240.26): C, 54.99; H, 6.71; N, 11.66. Found: C, 54.68; H, 6.74; N, 11.41.

1-(2',3',6'-Trideoxy-4'-*O*-methanesulphonyl-α-L-*erythro*-hexopyranosyl)thymine (11a). To a solution of **10a** (50 mg, 0.208 mol) in dry pyridine (2 mL) methanesulphonyl chloride (0.018 mL, 0.229 mmol) was added, and the mixture was kept at rt for 3h. It was then poured into ice-water and extracted with dichloromethane (3x30 mL). The organic layer was washed several times with water to free it of pyridine and dried. The residue obtained after evaporation of the solvent was submitted to column chromatography (*C*) to furnish 31.3 mg (48%) of pure crystalline **11a**: $[\alpha]_D^{25}$ -0.41 (*c* 1.0, $CHCl_3$), mp 82-84 °C; IR 3032 (ν_{NH}), 1694 ($\nu_{C=O}$), 1350 and 1176 (ν_{SO2O}) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.32 (1H, s, NH), 7.29 (1H, d, -CH=, $J_{CHT,CH3}$ = 1,5 Hz), 5,95 (1H, dd, H-1' $J_{1',2'a}$ = 10.5 Hz, $J_{1',2'e}$ = 3 Hz), 4.64-4.58 (1H, m, H-4'), 4.53-4.41 (1H, m, H-5', $J_{5',6'}$ = 7 Hz), 3.12 (3H, s, SMe), 2.29-1.76 (4H, m, H-3'a, H-3'e, H-2'a, H-2'e), 1.96 (3H, d, thymine Me), 1.42 (3H, d, Me-5'); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 163.7 (C-4), 150.2 (C-2), 135.1 (C-6), 111.2 (C-5), 76.1 (C-1'), 75.1 (C-4'), 74.4 (C-5'), 38.7 (C-7'), 24.6 (C-2'), 23.8 (C-3'), 15.3 (C-6'), 12.4 (C-7); *m/z* (EI) 319 $(M+H)^+$.

Anal. Calcd for $C_{12}H_{18}N_2O_6S$ (318.35): C, 45.27; H, 5.69; N, 8.79; S, 10.07. Found: C, 44.89; H, 5.57; N, 8.41; S, 10.35.

1-(2',3',6'-Trideoxy-4'-*O*-methanesulphonyl-β-L-*erythro*-hexopyranosyl)thymine (11b). Mesylation of **10b** was carried out as described for the preparation of **11a**. Yield of **11b**: 83%, $[\alpha]_D^{25}$ -43.75 (*c* 1.02, $CHCl_3$), mp 72-74 °C; IR 3036 (ν_{NH}), 1698 ($\nu_{C=O}$), 1352 and 1176 (ν_{SO2O}) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.63 (1H, s, NH), 7.19 (1H, d, -CH=, $J_{CHT,CH3}$ = 1,5 Hz), 5,74 (1H, dd, H-1', $J_{1',2'a}$ = 10.5 Hz, $J_{1',2'e}$ = 2.5 Hz), 4.40-4.25 (1H, m, H-4'), 3.80-3.64 (1H, m, H-5', $J_{5',6'}$ = 6 Hz), 3.07 (3H, s, SMe), 2.52-2.40 (1H, m, H-2'e), 2.11-1.96 (2H, m, H-3'e, H-3'a), 1.94 (3H, d, thymine Me), 1.90-1.72 (1H, m, H-2'a), 1.35 (3H, d, Me-5', $J_{5',6'}$ = 6 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 163.7 (C-4), 150.2 (C-2), 134.8 (C-6), 111.3 (C-5), 80.7 (C-1'), 78.2 (C-4'), 75.6 (C-5'), 38.7 (C-7'), 29.5 (C-2'), 29.2 (C-3'), 17.9 (C-6'), 12.4 (C-7); *m/z* (EI) 319 $(M+H)^+$.

Anal. Calcd for $C_{12}H_{18}N_2O_6S$ (318.35): C, 45.27; H, 5.69; N, 8.79; S, 10.07. Found: C, 45.74; H, 5.66; N, 8.95; S, 9.99.

1-(4'-Azido-2',3',6'-trideoxy-α-L-*threo*-hexopyranosyl)thymine (12a). To a solution of **11a** (31 mg, 0.108 mmol) in dry *N,N*-dimethylformamide (3.0 mL) sodium azide (26 mg, 0.39 mmol) was added and the reaction mixture was stirred at 120 °C for 24 h. The cooled mixture was diluted with ice-water, extracted with chloroform (3x30 mL), the combined organic layer was dried and concentrated. Column chromatography of the residue (*C*) gave 21.8 mg (76%) of pure **12a**: $[\alpha]_D^{25}$ +25.69 (*c* 1.00, $CHCl_3$), mp 48-49 °C; IR 3044 (ν_{NH}), 2102 (ν_{N3}), 1686 ($\nu_{C=O}$) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.53 (1H, s, NH), 7.23 (1H, d, -CH=, $J_{CHT,CH3}$ = 1.3 Hz), 5.89 (1H, dd, H-1', $J_{1',2'a}$ = 10.5 Hz, $J_{1',2'e}$ = 2.5 Hz), 4.36 (1H, m, H-5', $J_{5',6'}$ = 6.5 Hz), 3.87-3.72 (1H, m, H-4'), 2.38-1.58 (4H, m, H-3'a, H-3'e, H-2'a, H-2'e), 1.94 (3H, d, thymine Me), 1.35 (3H, d, Me-5'); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 163.7 (C-4), 150.2 (C-2), 135.0 (C-6), 111.1 (C-5), 75.2 (C-1'), 72.5 (C-5'), 57.9 (C-4'), 29.4 (C-2'), 22.6 (C-3'), 12.5 (C-6'), 11.8 (C-7); *m/z* (EI) 266 $(M+H)^+$.

1-(4'-Azido-2',3',6'-trideoxy-β-L-*threo*-hexopyranosyl)thymine (12b). The title compound was prepared from **11b** as described for **12a** to obtain 73% of the β-anomer **12b**: $[\alpha]_D^{25}$ +41.81 (*c* 1.04, $CHCl_3$), mp 119-121 °C; IR 3050 (ν_{NH}), 2098 (ν_{N3}), 1702 ($\nu_{C=O}$) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.14 (1H, s, NH), 7.26 (1H, d, -CH=, $J_{CHT,CH3}$ = 1.2 Hz), 5.73 (1H, dd, H-1', $J_{1',2'a}$ = 10.5 Hz, $J_{1',2'e}$ = 3.5 Hz), 3.89 (1H, m, H-5', $J_{5',6'}$ =

6.5 Hz, $J_{4',5'}$ = 2 Hz), 3.51-3.43 (1H, m, H-4'), 2.37-1.71 (4H, m, H-3'a, H-3'e, H-2'a, H-2'e), 1.96 (3H, d, thymine Me), 1.32 (3H, d, Me-5'); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 163.7 (C-4), 150.2 (C-2), 135.3 (C-6), 111.3 (C-5), 81.2 (C-1'), 75.6 (C-5'), 58.4 (C-4'), 27.6 (C-2'), 24.8 (C-3'), 18.0 (C-6'), 12.4 (C-7); *m/z* (EI) 266 $(M+H)^+$.

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