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New Synthesis of 3'-C-substituted-3'-Nitromethyl-*ribo*-Thymidines

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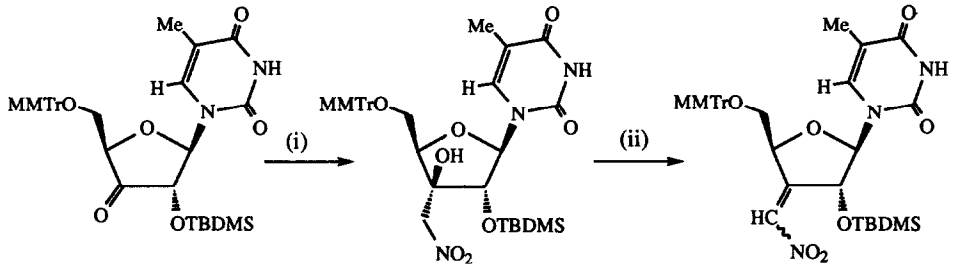
Summary: The 3'-exo-nitromethylene function in ribo-thymidine, as in 3, has been used for the first time as a general intermediate in the Michael addition reaction to give varieties of 3'-C-substituted nucleosides (12 - 21). The reaction of the conjugate base of acetylacetone with 3 however gave cis-fused furanose[3.2.1]hexopyranose nucleoside 24 as a major product due to the base catalyzed rearrangement of the initially formed Michael adduct 17. Detailed NMR spectroscopic data have been presented in support of the structural integrity of all reaction products.

Several 2',3' dideoxy 3'-substituted nucleoside analogues (AZT, ddI and ddC) are now FDA approved as anti-AIDS drugs targeted as effective inhibitors of HIV-reverse transcriptase (RT). In our efforts to design suitable candidate drugs against HIV-RT through modification of either 2' or 3'-position of the sugar moiety of nucleosides, we have developed procedures[1a-r] for the introduction of the C-substituent at C2' or C3' in the stereoselective manner. Different chemical methodologies that have been developed in different laboratories for the chemoselective introduction of the C-substituent *at the nucleoside level* may be grouped as follows: (1) addition to 2'- and 3'-keto function,[1f-h,2a-q] (2) nucleophilic opening of 2',3'-epoxides,[3a-d] (3) intramolecular free-radical addition reaction,[1i-k,2l] (4) intermolecular free-radical addition reaction,[4a-c] (5) Michael addition reaction to 2',3'-unsaturated nucleosides,[1a-e,l,m,q], (6) ring contraction of 3-amino-glucopyanosyl nucleoside,[5] (7) Aldol condensation at the C3' of the enolate generated from the 2',3'-enol-ester of uridine,[6] (8) Pd catalyzed cross coupling or base catalyzed reactions of 2',3'-bromovinylnucleosides[7], and (9) base catalyzed addition reaction at C3' of 2',3'-dideoxy-3'-nitro thymidine with electron-deficient reagents.[1(o)]

We have earlier shown that the nitro group conjugated to a double bond acts as a strong electron withdrawing group[8-14] which can be used as a powerful handle for the functionalization of 2'- and 3'-carbons by nitrogen and carbon substituents in nucleosides.[1e,1n-q] We herein report the use of the 3'-*exo*-nitromethylene function in a nucleoside, as in **3**, for the first time, as a general intermediate in the nucleophilic addition reaction to give varieties of 3'-substituted nucleosides. The addition of the conjugate base of the nitromethyl group to a 2'-keto-adenosine was first demonstrated by Baker *et al.*[2k] On the other hand, Moffatt *et al* have first successfully shown the initial conjugate addition of an amine to a 5'-nitro-olefin derivative of uridine followed by the addition of the resultant anion to the uracil ring to give carbon-bridged cyclonucleoside.[15] Similarly, the 2'-*exo*-nitromethylene derivatives of uridine were first prepared by Ueda *et al*[2j] who converted it to a carbon-bridged cyclonucleoside by the treatment of $NaBH_4$.

Results and discussions

(A) Preparation of 3'-C-exo-nitromethylene derivative (3). 1[5-O-(4-monomethoxytrityl)-2-O-*t*-butyldimethyl silyl-β-D-*xylo*furanosyl]thymine was used for the preparation of 3'-ketonucleoside **1**[16] (90% yield) which served as the precursor for the preparation of protected 3'-C-*exo*-nitromethylene nucleoside (**3**) (Scheme 1). The compound **1** was treated with nitromethane[2k,j] and 1 N NaOMe in methanol at room temperature for 30 min to give **2** (81%). Compound **2** was then treated with acetic anhydride and DMSO[2j] at room temperature for 48 h to give **3** (88%) as an isomeric mixture of Z and E (5 : 1 ratio from ^{1}H-NMR spectrum at 270 MHz) which could not be separated by silica gel column chromatography. Acidic treatment of **3** yielded only pure 5' deprotected Z isomer **5** (63%). The minor E isomer of **3** was isolated by a different procedure (*vide infra*). The configuration of E isomer of **3** was determined through one-dimensional ^{1}H NOE difference spectroscopy: saturation of 3'-*exo*-methylenic proton at δ7.04 shows an enhancement at H2' at δ5.27 (0.8%), proving the E configuration along the *exo*-methylenic double bond.

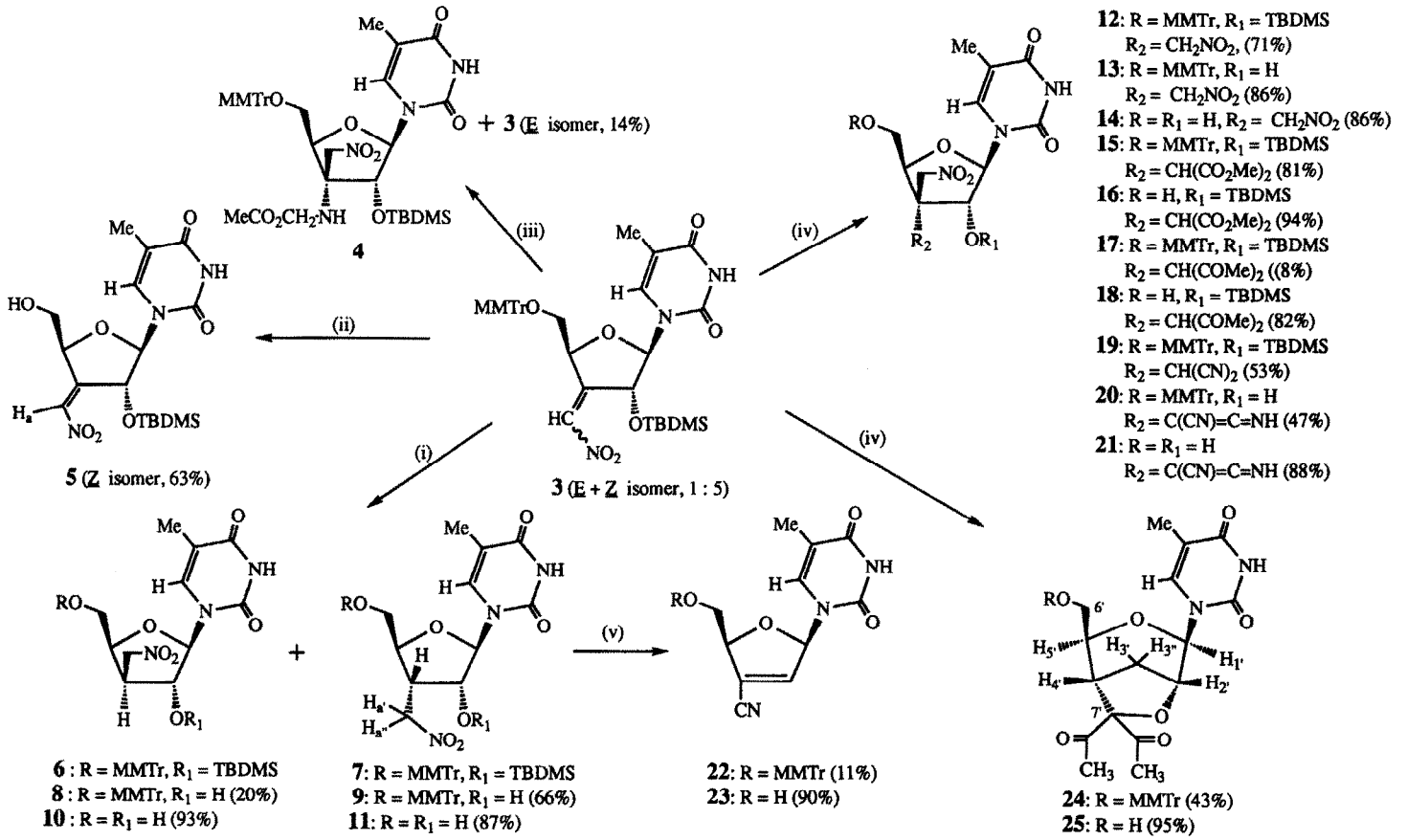


1 **2** (81%) **3** (E + Z isomer, 1 : 5) (88%)

Reagents: (i) $MeNO_2$ / NaOMe, (ii) Ac_2O / DMSO

Scheme 1

(B) Synthetic utility of 3'-C-exo-nitromethylene nucleoside (3). The *exo*-carbon-carbon double bond in **3** (Z / E = 5 / 1) was reduced with sodium borohydride in ethanol to give an inseparable mixture of **6** [2'-(R), 3'-(S)] and **7** [2'-(R), 3'-(R)] (90%) in 1 : 2.5 ratio (^{1}H-NMR at 270 MHz). During the reduction the hydride attack took place preferentially from the β-face of the sugar moiety yielding *ribo* derivative **7** [2'-(R), 3'-(R)] as the major product along with the minor *xylo* derivative **6** [2'-(R), 3'-(S)] (Scheme 2). Several attempts to separate **6** and **7** by column chromatography were unsuccesful. However, both of the stereoisomers were separated when the *t*-butyldimethylsilyl (TBDMS) group was removed from 2' position in **6** and **7** by treatment with tetrabutylammonium fluoride in tetrahydrofuran to yield **8** [2'-(R),3'-(S)] (20%) and **9** [2'-(R), 3'-(R)] (66%), respectively. The configurations of **8** and **9** were determined through one-dimensional ^{1}H NOE difference spectroscopy at 500 MHz. The key NOE contacts in **8** between H1' and H3' (2.6%) and between H5" and $H_{a"}$ of 3'-C-nitromethyl group (1.2%) unequivocally show that nitromethyl group is at the β-face of pentofuranose ring (*i.e.* 3'-(S) configuration). In addition, the trans orientation of H3' relative to H2' is clearly evident from large $J_{2',3'}$ of 10.3 Hz (the sugar moiety in **8** is predominantly in the South conformation as



Reagents: (i) $NaBH_4$ / EtOH, (ii) 80% aq. AcOH, (iii) $MeCO_2CH_2NH_2.HCl$ / Et_3N/ THF, (iv) Michael addition of the conjugate bases of $MeNO_2$, $CH_2(CO_2Me)_2$, $CH_2(COMe)_2$ and $CH_2(CN)_2$, (v) PhOC(S)Cl / DMAP / MeCN.

Scheme 2

evident from $J_{1',2'}$ = 7.0 Hz). The absence of $J_{1',2'}$ (0 Hz) and large $J_{3',4'}$ (10.7 Hz) in **9** are consistent with a high preference for the North sugar conformation of *ribo*-furanosyl moiety in **9** and also confirm its 3'-(R) configuration.

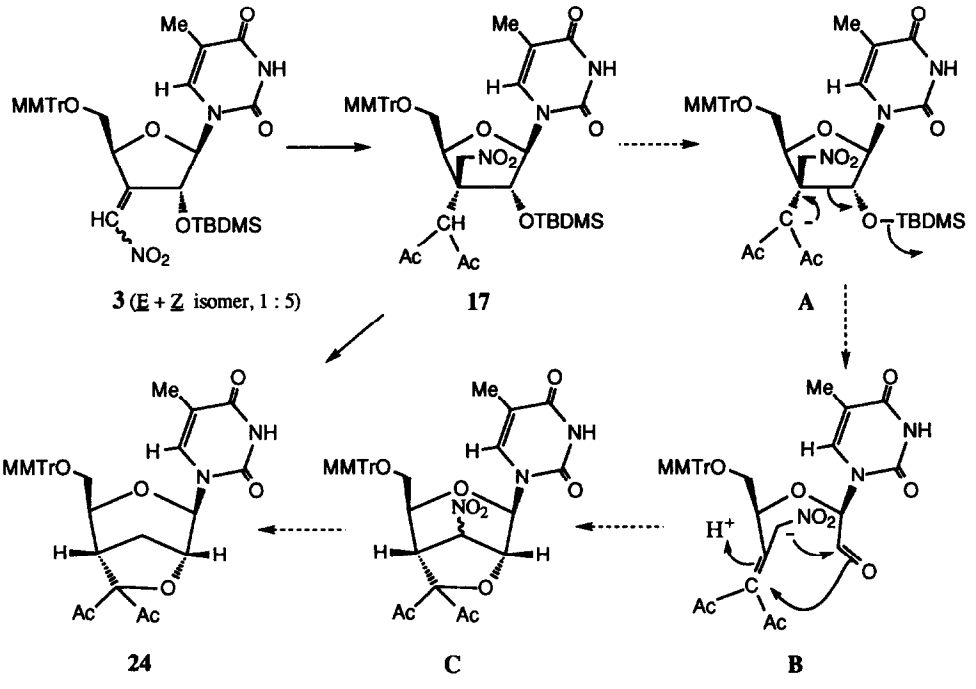
The 3'-C-*exo*-nitromethylene **3** was also subjected to several Michael additon reactions with N- and C-nucleophiles (Scheme 2). A mixture of Z / E isomers of **3** was treated with glycine methyl ester hydrochloride which yielded **4** [2'-(R),3'-(R)] along with the unreacted E isomer of **3**. The reaction of **3** with the conjugate base of nitromethane afforded **12** as a major product (71%). Similarly, the conjugate bases of dimethyl malonate and malononitrile yielded **15** [2'-(R),3'-(R)] (81%) and **19** [2'-(R),3'-(R)] (53%), respectively. In contrast, the reaction of **3** with conjugate base of acetylacetone yielded the expected addition product **17** [2'-(R),3'-(R)] in a poor yield (8%) along with an unexpectedly rearranged major product **24** [2'-(R),4'-(S)] (43%) which was contaminated with an inseparable minor component (*vide infra* for detailed spectroscopic characterization). It may be noted that *all Michael addition reactions reported here reacted exclusively from the α-face of the sugar moiety*. The TBDMS group from **12** [2'-(R)] or **19** [2'-(R), 3'-(R)] was removed by treatment with NH_4F[17] or n-tetrabutylammonium fluoride to afford **13** [2'-(R)] (86%) or **20** [2'-(R), 3'-(R)] (47%). However, the attempts to remove 2'-O-TBDMS group from **15** and **17** were unsuccessful and resulted in the formation of a complex mixture of products, which were not identified. The 5'-O-(4-monomethoxy trityl) group from **8, 9, 13, 15, 17, 20, 22,** and **24** was removed by the treatment of 80% aqueous acetic acid at room temperature to afford **10** (93%), **11** (87%), **14** (86%), **16** (94%) **18** (82%) and **21** (88%), **23** (90%) and **25** [95%, contaminated with an inseparable and unidentifiable byproduct (<15%)].

Our attempt to prepare 2'-O-phenoxythiocarbonyl derivative of **9** was unsuccessful (Scheme 2). The treatment of **9** with phenoxythiocarbonyl chloride and N^4,N^4, dimethylaminopyridine in acetonitrile yielded **22** (11%) along with several byproducts.

Characterization of Michael addition adducts. The one-dimensional ^1H NOE difference spectroscopy at 500 MHz has been used to establish the configurations of the chiral centers in **15** [2'-(R), 3'-(R)], **17** [2'-(R), 3'-(R)] and **19** [2'-(R), 3'-(R)]. The saturation of $H_{a'}$ of CH_2NO_2 group in **15** gives the key NOE enhancements at H6 (1.2%), H5' (0.4%) and H5" (1.5%), whereas saturation of H1' gives the key enhancement at H_b of dimethyl malonate group (0.4%), which confirm that CH_2NO_2 group is on the β-face and malonate is on the α-face [3'-(R)]. The saturation of H5" in **17** shows the key NOE enhancements at $H_{a'}$ (1.7%) and $H_{a''}$ (2.4%) of CH_2NO_2 group, which prove that 3'-CH_2NO_2 is on the β-face [*i.e.* 3'-(R) configuration]. Similarly, NOE contacts of H1' with H_b of 3'-malononitrile (0.1%) and Ha' of CH_2NO_2 group with H6 (0.4%) prove 3'-(R) configuration in **19**. The structure of **20** [2'-(R), 3'-(R)] was proved by the absence of H_b of malononitrile and the presence of two exchangeable protons at δ5.29 in ^1H-NMR spectrum. Furthermore, one of the nitrile carbon resonances in 110-125 ppm[18] region was absent in the ^{13}C-NMR spectra of **20** and **21** [2'-(R),3'-(R)] in comparison with **19**. The sp hybridized ketenimine-carbon in **20** and **21** appeared at δ166.3 and δ166.9[18a,19], respectively in ^{13}C-NMR spectrum, whereas the sp^2 hybridized ketenimine-carbon appeared upfield either at δ56.5 or δ57.5 in the former, and at δ54.1 or δ57.3[18a,19] in the later. The exact assignment of ^{13}C resonances in these regions turned out to be quite difficult because one of them is from the quartarnary C3' and the other is from sp^2 hybridized carbon. These chemical shifts are consistent with what are expected from the keteneimine fragments[18a,19]. Finally, the high resolution mass spectra of **3** - **25** are consistent with their structures shown in Scheme 2 (see experimental section).

The structural identity of **25** was confirmed by detailed one- and two-dimensional ^1H and ^{13}C-NMR

spectroscopy at 500 MHz and high resolution mass spectrum. An inverse ^{13}C-^{1}H correlation spectrum clearly showed in both F_1 and F_2 dimensions a set of sugar resonances from the rearranged **25** (see formula **25** in Scheme 2 for the numbering system). Analysis of the resonances in both ^{13}C (F_1 dimension) and ^{1}H (F_2 dimension) domain show *six sugar carbons* [δ86.7 (C1'), δ81.7 (C5'), δ64.7 (C2'), δ62.3 (C6'), δ42.5 (C4'), δ25.5 (C3')] which give cross-peaks with the corresponding carbon-linked sugar protons (see the experimental section for detailed assignments). The six sets of sugar protons which showed cross-peaks to their corresponding α-carbons in ^{13}C-^{1}H correlation spectrum (except for H1', $J_{1',2'} = 0$ Hz) also show clear J-coupling network in the DQF-COSY spectrum. This observed J-coupling network clearly establish that these six set of sugar protons are located vicinal to each other and form the one J-relay system which was also evident from the HOHAHA spectrum. Both H2' and H4' are coupled to H3' and H3" ($J_{2',3'} = 6.2$ Hz, $J_{2',3''} = 7.4$ Hz, $J_{3',4'} = 6.0$ Hz, $J_{3'',4'} = 8.4$ Hz) of methylene group, H4' is in addition coupled to H5' ($J_{4',5'} = 9.0$ Hz) which, in turn is coupled to H6' and H6" ($J_{5',6'} = 2.4$ Hz and $J_{5',6''} = 4.1$ Hz). The ^{13}C-NMR INEPT experiment and 2D ^{13}C-^{1}H corelation spectra clearly confirmed that the 3'-CH_2 resonates resonably upfield at δ25.5. The presence of two acetyl groups at C7' in **25**, beside thymine C5-methyl resonance (δ12.1), is clear from two methyl resonances at δ29.6 and δ29.8 and two carbonyl resonances at δ203.7 and δ203.9. The unusual downfield chemical shift of C7' at δ209.1 and the absence of any proton associated with this carbon in two-dimensional ^{13}C-^{1}H corelation spectra suggests its quarternary nature and is consistent with the fact that it is covalently linked with three electron-withdrawing substituents. The final structural evidence of the fused



Scheme 3

pentofuranose[3.2.1]hexopyranose ring system came from the high resolution mass spectra which is consistent with the formula shown for **25**. The proposed fused furanose[3.2.1]hexopyranose structure is also clear from the chemical shifts of protons and carbons at the ringjunction in **25** [H2' (δ4.25) and C2' (δ64.7); H4' (δ2.92) and C4' (δ42.5)]. The configurations at C2' and C4' of **25** were determined by one-dimensional ^{1}H NOE difference spectroscopy at 500 MHz. The saturation of H6" in **25** results in the key NOE enhancements at near isochronous H3' and H3" (0.4%), whereas saturation of H3' and H3" gave enhancement at H6 (0.1%), weak enhancements at H5' and H5" (≈0.1%), H2' (1.3%) and H4' (0.9%) which clearly show that the methylene protons at C3' of hexopyranosyl moiety is up [*i.e.* 2'-(R), 4'-(S) configurations] and on the same side (β-face) as H2' and H4'. This shows that the furanose ring is *cis*-fused and is on the α-face of the hexopyranose ring.

(C) Discussion on the tentative mechanism of formation of 24. Treatment of **3** with the conjugate base of acetylacetone at room temperature afforded **24** [2'-(R), 4'-(S)] (43%) along with the expected Michael adduct **17** [2'-(R), 3'-(R)] (8%). The driving force to break the C2'-C3' bond in **17** is initiated both by the generation of an incipient carbanion (intermediate **A** in Scheme 3) and the ability of 2'-O-TBDMS group to act as a good leaving group, which leads to the formation of the intermediate **B**. Intermediate **B** then undergoes intramolecular aldol condensation giving the intermediate **C** with *cis* fused pentofuranosyl and hexopyranosyl rings (Scheme 3). In the later stage the intermediate **C** is transformed to **24** by the replacement of the nitro group by hydrogen presumably by the electron transfer reaction[20] promoted by the potassium salt of acetyl acetone.

EXPERIMENTALS

^{1}H-NMR spectra were recorded (in δ scale) with Jeol GX-270 at 270 MHz and Bruker AMX-500 spectrometer at 500 MHz using TMS as internal reference (0.0 ppm). ^{13}C-NMR were recorded at 67.8 MHz using both ^{1}H-coupled and ^{1}H-decoupled or INEPT modes. Joel DX 303 instrument was used for recording high resolution mass spectra (HRMS). TLC was carried out using Merck pre-coated silica gel F_{254} plates. The column chromatography were carried out using Merck G60 silica gel. The protons of CH_2NO_2 in **4, 6-21** are labelled as $H_{a'}$ and $H_{a''}$ and the proton on 3'-C<u>H</u>(R_1R_2) in **12 - 21** is labelled as H_b in Michael addition products.

1-[5-O-(MMTr)-2-(R)-O-TBDMS-3-(S)-3-hydroxy-3-C-nitromethyl-β-D-pentofuranosyl]thymine (2). Compound **1** (2.9 g, 4.5 mmol) was treated with sodium methoxide (360 mg, 6.8 mmol) in nitromethane (20 mL) and anhydrous methanol (10 mL). After stirring for 2 h at RT the reaction mixture was neutralized with Dowex 50 (H^+) resin. The resin was filtered and the volatile materials from the filtrate was removed in vacuo. The residue was then purified by silica gel column chromatography to give **2** (2.56 g, 81%). ^{1}H-NMR ($CDCl_3$): 8.98 (br. s, 1H) NH; 7.64 (q, 1H) H6; 7.43-6.82 (m, 14 H) arom; 5.76 (s, 1H) H1'; 4.72-4.36 (m, 3H) H2' and C<u>H</u>$_2$NO$_2$; 3.93 (dd, 1H) H4'; 3.81 (s, 4H) MMTr and H5'; 3.53 (dd, $J_{4',5''}$ = 3.7 Hz, $J_{5',5''}$ = 11.0 Hz, 1H) H5"; 1.79 (d, 3H) 5C<u>H</u>$_3$; 0.86 (m, 9H), 0.22 (s, 3H), 0.11 (s, 3H) TBDMS; ^{13}C-NMR ($CDCl_3$): 163.9 (s) C4; 150.2 (s) C2; 136.5 (d, J_{CH} = 185.1 Hz) C6; 109.6 (s) C5; 91.6 (d, J_{CH} = 172.3 Hz) C1'; 88.1 (s) MMTr; 81.6 (d, J_{CH} = 157.6 Hz), 80.8 (d, J_{CH} = 149.4 Hz) C4' and C2'; 79.7 (s) C3'; 75.3 (t, J_{CH} = 146.6 Hz) <u>C</u>H$_2$NO$_2$; 61.1 (t, J_{CH} = 144.8 Hz) C5'; 55.1 (q, J_{CH} = 143.9 Hz) MMTr; 25.7 (q, J_{CH} = 125.2 Hz), 17.7 (s) TBDMS; 12.4 (q, J_{CH} = 130.1 Hz) 5C<u>H</u>$_3$; -4.8 (q), -5.5 (q) TBDMS.

1-[5-O-(MMTr-2-(R)-2-O-TBDMS-3-C-*exo*-(Z/E)-nitromethylene-β-D-pentofuranosyl]thymine (3). Compound **2** (3.5 g, 5.0 mmol) was treated with acetic anhydride (35 mL) and DMSO (10 mL) at RT for 2 days. The mixture was poured into ice water (500 mL), stirred and the precipitate was filtered through celite and washed thouroughly with water to remove traces of DMSO. The precipitate was dissolved in dichloromethane, evaporated in vacuo and the residue was purified by silica gel column chromatography to give an inseparable Z / E mixture of **3** (3.0 g, 88%) in the ratio of 5 : 1 (^{1}H-NMR spectrum at 270 MHz). Z-Isomer: ^{1}H-NMR ($CDCl_3$): 8.29 (br. s, 1H) NH; 7.49-7.30 (m, 13 H) arom and H6; 6.82 (d, 2H) arom; 6.76 (m, 1H) C<u>H</u>NO$_2$; 5.87 (d, $J_{1',2'}$ = 1.6 Hz, 1H) H1'; 5.58 (m, 1 H) H2', 5.02 (m, 1H) H4'; 3.80 (s, 3H) MMTr;

3.68 (dd, $J_{4',5'}$ = 4.0 Hz, $J_{5',5''}$ = 10.8 Hz, 1H) H5'; 3.46 (dd, $J_{4',5''}$ = 3.7 Hz, 1H) H5''; 1.51 (d, $J_{6,CH3}$ = 1.0 Hz, 3H) $5CH_3$; 0.94 (s, 9H), 0.19 (s, 3H), 0.12 (s, 3H) TBDMS. ^{13}C-NMR ($CDCl_3$, Z-isomer): 163.8 (s) C4; 150.2 (s) C2; 135.3 (d, J_{CH} = 187.9 Hz) C6; 111.3 (s) C5; 92.6 (d, J_{CH} = 171.3 Hz) C1'; 87.2 (s) MMTr; 79.0 (d, J_{CH} = 150.6 Hz), 74.5 (d, J_{CH} = 159.6 Hz) C4' and C2'; 62.4 (t, J_{CH} = 144.2 Hz) C5'; 55.0 (q, J_{CH} = 143.9 Hz) MMTr; 25.4 (q, J_{CH} = 123.9 Hz), 17.8 (s) TBDMS; 11.8 (q, J_{CH} = 129.1 Hz) $5CH_3$; -4.9 (q), -5.4 (q) TBDMS. HRMS (FAB^-): calcd. for $(M-H)^-$ 684.2741, found 684.2759. E-isomer: ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.07 (br. s, 1H) NH; 7.67 (d, $J_{6,CH3}$ = 1.1 Hz, 1H) H6; 7.37-7.20 (m, 12 H) arom; 7.04 (dd, $J_{Ha,2'}$ = 2.5 Hz, $J_{Ha,4'}$ = 2.0 Hz, 1H) $CHNO_2$; 6.82 (d, 2H) arom; 6.07 (d, $J_{1',2'}$ = 8.0 Hz, 1H) H1'; 5.48 (m, 1H) H4'; 5.27 (ddd, $J_{2',4'}$ = 1.3 Hz, 1H) H2', 3.85 (dd, $_{4',5'}$ = 1.7 Hz, 1H) H5'; 3.80 (s, 3H) MMTr; 3.49 (dd, $J_{4',5''}$ = 2.3 Hz, $J_{5',5''}$ = 12.8 Hz, 1H) H5''; 1.46 (d, 3H) $5CH_3$; 0.94 (s, 9H) TBDMS; 0.15 (s, 3H) TBDMS; 0.02 (s, 3H) TBDMS; ^{13}C-NMR ($CDCl_3$, E-isomer): 162.8 (C4), 150.0 (C2), 134.6 (C6); 112.3 (C5); 87.7 (C1'); 87.7 (MMTr); 84.8, 75.4 (C4' and C2'); 63.9 (C5'); 55.2 (MMTr); 25.3, 17.7 TBDMS; 11.5 C5-CH_3; -5.8, -5.0 TBDMS. HRMS (FAB^-): calcd. for $(M-H)^-$ 684.2741, found 684.2759.

1-[5-O-(MMTr-2-(R)-O-TBDMS-3-C-nitromethyl-3-(R)-(N-glycine methyl ester)-β-D-pentofuranosyl] thymine (4). To a solution of glycine methyl ester hydrochloride (660 mg) in THF (10 mL) triethylamine (140 μL) was added. After stirring for 5 min, **3** (343 mg, 0.5 mmol) was added, and the stirring continued overnight at RT. The reaction mixture was partitioned between saturated aqueous solution of ammonium chloride (10 mL) and dichloromethane (50 mL). The organic layer was washed with water (2 x 5 mL) and evaporated to dryness. The residue was purified by silica gel column chromatography to give **4** (273 mg, 70%) and unreacted minor E-isomer **3** (54 mg, 14%). ^{1}H-NMR ($CDCl_3$): 8.23 (br. s, 1H) NH; 7.84 (d, $J_{6,CH3}$ = 1.0 Hz, 1H) H6; 7.46-6.82 (m, 14 H) arom; 6.33 (d, $J_{1',2'}$ = 7.6 Hz, 1H) H1'; 4.70 (d, 1H) H2'; 4.62 (d, $J_{Ha',Ha''}$ = 13.2 Hz, 1H) $H_{a'}$; 4.52 (d, 1H) $H_{a''}$; 4.21 (dd, 1H) H4'; 3.84 (dd, $J_{4',5'}$ = 3.4 Hz; 1H) H5'; 3.80 (s, 3H) MMTr; 3.71 (s, 3H) COOMe; 3.64 (2H) NCH_2; 3.22 (dd, $J_{4',5''}$ = 1.4 Hz, $J_{5',5''}$ = 11.9 Hz; 1H) H5''; 1.18 (d, 3H) $5CH_3$; 0.91 (s, 9H), 0.21 (s, 3H), 0.17 (s, 3H) TBDMS. ^{13}C-NMR ($CDCl_3$): 171.5 (s) COOMe; 162.7 (s) C4; 150.2 (s) C2; 135.6 (d, J_{CH} = 179.6 Hz) C6, 111.6 (s) C5, 88.0 (d, J_{CH} = 172.3 Hz) C1'; 87.0 (s) MMTr; 85.9 (d, J_{CH} = 149.4 Hz), 81.5 (d) C2' and C4'; 74.8 (t, J_{CH} = 148.5 Hz) CH_2NO_2; 62.3 (t, J_{CH} = 143.8 Hz) C5'; 54.9 (q, J_{CH} = 143.9 Hz) MMTr, 51.7 (q, J_{CH} = 147.4 Hz) COOMe; 44.0 (s) C3'; 25.2 (q, J_{CH} = 125.2 Hz), 17.4 (s) TBDMS; 10.6 (q, J_{CH} = 129.4 Hz) $5CH_3$; -4.7 (q), -5.3 (q) TBDMS.

1-[2-(R)-O-TBDMS-3-C-*exo*-(Z)-nitromethylene-β-D-pentofuranosyl]thymine (5). A mixture of (E / Z) **3** (200 mg, 0.29 mmol) was treated with 80% aqueous acetic acid (3 mL) at room temperature for 5 h. After usual work up the residue was purified by analytical t.l.c plate to give pure **5** (75 mg, 63%). ^{1}H-NMR ($CDCl_3$ + CD_3OD, 500 MHz): 7.42 (d, $J_{6,CH3}$ = 1.1 Hz, 1H) H6; 6.98 (dd, $J_{Ha,1'}$ = 2.2 Hz, $J_{Ha,4'}$ = 2.2 H, 1H) $CHNO_2$; 5.58 (d, $J_{1',2'}$ = 7.8 Hz, 1H) H1'; 5.49 (m, 1H) H4'; 5.33 (d, 1H) H2'; 4.10 (dd, $J_{4',5'}$ = 1.5 Hz, $J_{5',5''}$ = 11.9 Hz, 1H) H5'; 3.95 (dd, $J_{4',5''}$ = 1.9 Hz, 1H) H5''; 1.96 (d, 3H) $5CH_3$; 0.90 (s, 9H), 0.10 (s, 3H), -0.05 (s, 3H) TBDMS. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 163.4 (s) C4; 154.6 (s) C3'; 150.6 (s) C2; 137.2 (d, J_{CH} = 185.1 Hz) C6; 133.7 (d, J_{CH} = 196.1 Hz) $CHNO_2$; 112.0 (s) C5; 89.7 (d, J_{CH} = 166.8 Hz) C1'; 79.6 (d, J_{CH} = 157.6 Hz), 73.5 (d, J_{CH} = 148.5 Hz) C4' and C2'; 62.5 (t, J_{CH} = 145.7 Hz) C5'; 25.3 (q, J_{CH} = 124.3 Hz), 17.4 (s) TBDMS; 12.0 (q, J_{CH} = 129.2 Hz) $5CH_3$; -4.7 (q), -5.3 (q) TBDMS. HRMS (FAB^-): calcd. for $(M-H)^-$ 412.1540, found 412.1543.

1-[5-O-(MMTr)-2-O-TBDMS-3-deoxy-3-C-nitromethyl-β-D-*xylo*-pentofuranosyl]thymine (6) & 1-[5-O-(MMTr)-2-O-TBDMS-3-deoxy-3-C-nitromethyl-β-D-*ribo*-pentofuranosyl]thymine (7). The isomeric (E / Z) mixture of **3** (800 mg, 1.2 mmol) was treated with $NaBH_4$ (177 mg, 4.7 mmol) in dry ethanol (12 mL) in ice water bath for 2 h. The reaction mixture was neutralised with acetic acid, extracted with dichloromethane (2 x 60 mL). The organic layer was washed with water (2 x 10 mL) and evaporated to dryness. The residue was purified by silica gel column chromatography to give inseparable mixture of **6** and **7** (720 mg, 90%), (1 : 2.5, from ^{1}H-NMR, 270 MHz). ^{1}H-NMR ($CDCl_3$): 8.72 (br. s) NH (major); 8.64 (br. s) NH (minor); 7.77 (d) H6 (minor); 7.69 (q, $J_{6,CH3}$ = 1.2 Hz) H6 (major); 7.44-7.26 (m) arom; 6.84 (d) arom; 6.06 (d, $J_{1',2'}$ = 7.1 Hz) H1' (minor); 5.76 (d, $J_{1',2'}$ = 1.3 Hz) H1' (major); 4.64-4.55 (m) Ha' and H2'; 4.16-4.00 (m) H4' and Ha''; 3.80 (s) MMTr; 3.72 (dd, $J_{4',5'}$ = 2.5 Hz, $J_{5',5''}$ = 11.3 Hz) H5'; 3.25 (dd, $J_{4',5''}$ = 3.0 Hz) H5''; 3.09 (m) H3'; 1.48 (d) $5CH_3$; 0.87 (s), 0.22 (s), 0.09 (s) TBDMS. ^{13}C-NMR ($CDCl_3$): 164.2 (s) C4; 150.4 (s) C2; 134.9 (d, J_{CH} = 185.8 Hz) C6; 110.6 (s) C5; 91.3 (d, J_{CH} = 174.4 Hz) C1'; 87.2 (s) MMTr; 80.4 (d, J_{CH} = 148.4 Hz), 76.4 (d, J_{CH} = 154.7 Hz) C4' and C2'; 70.2 (t, J_{CH} = 146.4 Hz) CH_2NO_2; 61.8 (t, J_{CH} = 142.3 Hz) C5'; 55.1 (q, J_{CH} = 143.9 Hz) MMTr; 40.7 (d, J_{CH} = 136.0 Hz) C3'; 25.6 (q, J_{CH} = 124.9 Hz), 17.8 (s) TBDMS; 11.9 (q, J_{CH} =

129.4 Hz) $5CH_3$; -4.5 (q), -6.0 (q) TBDMS.

1-[5-O-(MMTr)-3-deoxy-3-C-nitromethyl-β-D-*xylo*-pentofuranosyl]thymine (8) & 1-[5-O-(MMTr)-3-deoxy-3-C-nitromethyl-β-D-*ribo*-pentofuranosyl]thymine (9). A mixture of **6** and **7** (600 mg, 0.87 mmol) was treated with 0.5 M tetrabutylammonium fluoride (1.5 mL) in tetrahydrofuran (9 mL) at RT for 30 min. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give **8** (20%) and **9** (100 mg, 330 mg, 66%). Compound **8** : ^{1}H-NMR ($CDCl_3$ + CD_3COCD_3, 500 MHz) 10.27 (br. s, 1H) NH; 7.74 (d, $J_{6,CH3}$ = 1.0 Hz, 1H) H6; 7.47-6.82 (m, 14 H) arom; 6.01 (d, $J_{1',2'}$ = 7.0 Hz, 1H) H1'; 4.67 (dd, $J_{3',Ha'}$ = 4.5 Hz, $J_{Ha',Ha''}$ = 14.9 Hz, 1H) $H_{a'}$; 4.61 (ddd, $J_{3',4'}$ = 8.8 Hz, 1H) H4'; 4.55 (dd, $J_{3',Ha''}$ = 10.1 Hz, 1H) $H_{a''}$; 4.44 (dd, $J_{2',3'}$ = 10.3 Hz, 1H) H2'; 3.79 (s, 3H) MMTr; 3.74 (dd, $J_{4',5'}$ = 3.3 Hz, $J_{5',5''}$ = 11.5 Hz, 1H) H5'; 3.32 (m, 1H) H3'; 3.08 (dd, $J_{4',5''}$ = 2.0 Hz, 1H) H5''; 1.38 (d, 3H) $5CH_3$. ^{13}C-NMR ($CDCl_3$): 164.3 (s) C4; 151.9 (s) C2; 136.0 (d, J_{CH} = 182.4 Hz) C6; 111.3 (s) C5; 88.0 (d, J_{CH} = 172.3 Hz) C1'; 87.9 (s) MMTr; 77.2 (d, J_{CH} = 151.2 Hz), 74.4 (d, J_{CH} = 147.5 Hz) C4' and C2'; 72.7 (t, J_{CH} = 146.2 Hz) $\underline{C}H_2NO_2$; 62.6 (t, J_{CH} = 142.0 Hz) C5'; 55.0 (q, J_{CH} = 143.9 Hz) MMTr; 43.4 (d, J_{CH} = 139.7 Hz) C3'; 11.5 (q, J_{CH} = 129.5 Hz) $5CH_3$. Compound **9**:^{1}H-NMR (500 MHz, $CDCl_3$) 10.30 (br. s, 1H) NH; 7.89 (d, $J_{6,CH3}$ = 1.2 Hz, 1H) H6; 7.48-6.85 (m, 14 H) arom; 5.80 (s, 1H) H1'; 5.40 (br. s, 1H) 2'-OH; 4.78 (dd, $J_{3',Ha'}$ = 9.1 Hz, $J_{Ha',Ha''}$ = 14.3 Hz, 1H) $H_{a'}$; 4.59 (d, $J_{2',3'}$ = 5.0 Hz, 1H) H2'; 4.24 (ddd, $J_{3',4'}$ = 10.7 Hz, 1H) H4'; 4.01 (dd, $J_{3',Ha''}$ = 4.6 Hz, 1H) $H_{a''}$; 3.79 (s, 3H) MMTr; 3.77 (dd, $J_{4',5'}$ = 2.3 Hz, $J_{5',5''}$ = 11.6 Hz, 1H) H5'; 3.22 (dd, $J_{4',5''}$ = 2.7 Hz, 1H) H5''; 3.17 (m, 1H) H3'; 1.46 (d, 3H) $5CH_3$. ^{13}C-NMR ($CDCl_3$): 164.5 (s) C4, 150.6 (s) C2, 135.2 (d, J_{CH} = 181.5 Hz) C6; 110.7 (s) C5; 92.8 (d, J_{CH} = 175.9 Hz) C1'; 87.2 (s) MMTr; 81.3 (d, J_{CH} = 152.1Hz), 75.9 (d, J_{CH} = 156.7 Hz) C4' and C2'; 69.9 (t, J_{CH} = 147.1 Hz) $\underline{C}H_2NO_2$; 61.4 (t, J_{CH} = 142.5 Hz) C5'; 55.1 (q, J_{CH} = 144.2 Hz) MMTr; 39.5 (d, J_{CH} = 138.4 Hz) C3'; 12.0 (q, J_{CH} = 128.9 Hz) $5CH_3$.

1-[3-Deoxy-3-C-nitromethyl-β-D-*xylo*-pentofuranosyl]thymine (10). Compound **8** (70 mg, 0.12 mmol) was treated with 80% aqueous acetic acid (3 mL) at RT overnight. The solvent was removed in vacuo and co-evaporated with toluene and methanol. The residue was purified by silica gel column chromatography to give **10** (34 mg, 93%). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.91 (d, $J_{6,CH3}$ = 1.2 Hz, 1H) H6; 5.88 (d, $J_{1',2'}$ = 7.0 Hz, 1H) H1'; 4.77 (m, 2H) $H_{a'}$, $H_{a''}$; 4.45 (br. d, 1H) H4'; 4.28 (dd, $J_{2',3'}$ = 10.3 Hz, 1H) H2'; 3.87 (dd, $J_{4',5'}$ = 2.5 Hz, $J_{5',5''}$ = 12.4 Hz, 1H) H5'; 3.67 (dd, $J_{4',5''}$ = 1.5 Hz, 1H) H5''; 3.24 (m, 1H) H3'; 1.90 (d, 3H) $5CH_3$. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 136.7 (d, J_{CH} = 142.4 Hz) C6; 110.2 (s) C5; 88.2 (d, J_{CH} = 166.8 Hz) C1'; 77.4 (d, J_{CH} = 151.2 Hz) C4'; 73.0 (d, J_{CH} = 141.1 Hz) C2'; 60.6 (t, J_{CH} = 141.6 Hz) C5'; 43.8 (d, J_{CH} = 131.0 Hz) C3'; 11.0 (q, J_{CH} = 128.9 Hz) $5CH_3$, after few hours in ^{1}H-NMR spectrum $\underline{C}H_2NO_2$ has been exchanged with ^{2}H atoms and in the INEPT experiment $\underline{C}H_2NO_2$ disappeared. HRMS (FAB^-): calcd. for $(M-H)^-$ 300.0832, found 300.0831.

1-[3-Deoxy-3-C-nitromethyl-β-D-*ribo*-pentofuranosyl]thymine (11). Compound **9** (114 mg, 0.2 mmol) was treated with 80% aqueous acetic acid (2 mL) overnight at RT. The solvent was removed in vacuo and co-evaporated with toluene and methanol. The residue was purified by silica gel column chromatography to give **11** (52 mg, 87%). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.97 (d, $J_{6,CH3}$ = 1.0 Hz, 1H) H6; 5.72 (s, 1H) H1'; 4.85 (dd, $J_{3',Ha'}$ = 8.5 Hz, $J_{Ha',Ha''}$ = 14.1 Hz, 1H) $H_{a'}$; 4.45 (dd, $J_{3',Ha''}$ = 5.4 Hz, 1H) $H_{a''}$; 4.43 (d, 1H) H2'; 4.17 (m, $J_{3',4'}$ = 10.0 Hz, 1H) H4'; 3.75 (dd, $J_{4',5'}$ = 2.1 Hz, $J_{5',5''}$ = 12.6 Hz, 1H) H5'; 3.23 (dd, $J_{4',5''}$ = 1.6 Hz, 1H) H5''; 3.10 (m, 1H) H3'; 1.90 (d, 3H) $5CH_3$. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 164.3 (s) C4; 150.9 (s) C2, 136.0 (d, J_{CH} = 183.7 Hz) C6; 110.3 (s) C5; 92.3 (d, J_{CH} = 173.4 Hz) C1'; 82.4 (d, J_{CH} = 149.5 Hz), 75.9 (d, J_{CH} = 154.6 Hz) C4' and C2'; 70.6 (t, J_{CH} = 150.5 Hz) CH_2NO_2; 60.1 (t, J_{CH} = 142.2 Hz) C5'; 38.6 (d, J_{CH} = 136.0 Hz) C3'; 12.1 (q, J_{CH} = 130.3 Hz) $5CH_3$. HRMS (FAB^-): calcd. for $(M-H)^-$ 300.0832, found 300.0821.

1-[5-O-(MMTr)-2-(R)-O-TBDMS-3-deoxy-3-C-bis(nitromethyl)-β-D-pentofuranosyl]thymine (12). Potassium *tert*-butoxide (61 mg, 0.5 mmol) was added to nitromethane (3 mL) and kept at room temperature for 30 min. The reaction mixture was cooled in an ice-water bath for 15 min and a mixture of (E / Z) **3** (170 mg, 0.25 mmol) was added and kept stirring for 2 h in ice water bath. The reaction mixture was poured into aqueous solution of ammonium chloride (10 mL) which was extracted with dichloromethane (3 x 15 mL). The organic layer was washed with water (2 x 5 mL). The organic phase was evaporated and the residue was purified by silica gel column chromatography to give **12** (131 mg, 71%). ^{1}H-NMR ($CDCl_3$): 8.20 (br. s, 1H) NH; 7.78 (d, $J_{6,CH3}$ = 1.2 Hz, 1H) H6; 7.34-6.82 (m, 14 H); 6.13 (d, $J_{1',2'}$ = 7.1 Hz, 1H) H1'; 5.07-4.76 (m, 5H) 2 x CH_2NO_2 and H2'; 4.22 (m, 1H) H4'; 3.81 (s, 3H) MMTr; 3.78 (dd, $J_{4',5'}$ = 3.5 Hz, 1H) H5'; 3.20 (dd, $J_{4',5''}$ = 1.6 Hz, $J_{5',5''}$ = 11.7 Hz, 1H) H5''; 1.57 (d, 3H) $5CH_3$; 0.84 (s, 9H), 0.13 (s, 3H), 0.03 (s, 3H) TBDMS. ^{13}C-

NMR ($CDCl_3$): 163.1 (s) C4; 150.7 (s) C2; 135.5 (d, J_{CH} = 181.6 Hz) C6; 112.5 (s) C5; 88.6 (d, J_{CH} = 167.1 Hz) C1'; 87.2 (s) MMTr; 80.9 (d, J_{CH} = 151.6 Hz), 76.9 (J_{CH} = 147.4 Hz) C4' and C2'; 73.7 (t, J_{CH} = 148.5 Hz) $\underline{C}H_2NO_2$; 73.4 (t, J_{CH} = 149.5 Hz) $\underline{C}H_2NO_2$; 62.1 (t, J_{CH} = 143.8 Hz) C5'; 55.2 (q, J_{CH} = 144.3 Hz) MMTr; 49.2 (s) C-3'; 25.3 (q, J_{CH} = 123.9 Hz), 17.7 (s) TBDMS; 11.0 (q, J_{CH} = 129.8 Hz) $5CH_3$; -4.7 (q), -5.1 (q) TBDMS.

1-[5-O-(MMTr)-2-(R)-hydroxy-3-deoxy-3-C-bis(nitromethyl)-β-D-pentofuranosyl]thymine (13). Compound **12** (112 mg, 0.15 mmol) was gently refluxed with NH_4F (22 mg, 0.6 mmol) in methanol (2 mL) for 6 h. The reaction mixture was concentrated in vacuo and the residue was purified by silica gel column chromatography to give pure **13** (82 mg, 86%). ^{1}H-NMR ($CDCl_3$): 7.65 (d, $J_{6,CH3}$ = 1.2 Hz, 1H) H6; 7.39-6.82 (m, 14 H) arom; 5.94 (d, $J_{1',2'}$ = 6.1 Hz, 1H) H1'; 5.06-4.66 (m, 5 H) 2 x CH_2NO_2 and H2'; 4.38 (dd, 1H) H4'; 3.78 (s, 3H) MMTr; 3.74 (dd, $J_{4',5'}$ = 2.8 Hz, 1H) H5'; 3.19 (dd, $J_{4',5''}$ = 2.5 Hz, $J_{5',5''}$ = 11.6 Hz, 1H) H5"; 1.34 (d, 3H) $5CH_3$. ^{13}C-NMR ($CDCl_3$): 163.8 (s) C4; 151.7 (s) C2, 135.3 (d, J_{CH} = 185.2 Hz) C6; 111.6 (s) C5; 88.2 (d, J_{CH} = 169.5 Hz) C1'; 88.0 (s) MMTr; 81.7 (d, J_{CH} = 150.6 Hz), 78.0 (d, J_{CH} = 154.0 Hz) C4' and C2'; 75.2 (t, J_{CH} = 149.8 Hz) $\underline{C}H_2NO_2$; 73.4 (t, J_{CH} = 148.5 Hz) $\underline{C}H_2NO_2$; 61.9 (t, J_{CH} = 143.9 Hz) C5'; 55.1 (q, J_{CH} = 144.2 Hz) MMTr; 47.7 (s) C3'; 11.5 (q, J_{CH} = 129.2 Hz) $5CH_3$.

1-[2-(R)-Hydroxy-3-deoxy-3-C-bis(nitromethyl)-β-D-pentofuranosyl]thymine (14). Compound **13** (63 mg, 0.1 mmol) was treated with 80% aqueous acetic acid (2 mL) overnight at RT. The solvent was removed in vacuo, co-evaporated with toluene and methanol. The residue was purified by silica gel column chromatography to give **14** (31 mg, 86%). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.71 (d, $J_{6,CH3}$ = 1.1 Hz, 1H) H6; 5.76 (d, $J_{1',2'}$ = 6.7 Hz, 1H) H1'; 5.32-4.83 (m, 4H) 2 x CH_2NO_2; 4.69 (d, 1H) H2'; 4.34 (dd, 1H) H4'; 3.94 (dd, $J_{4',5'}$ = 3.1 Hz, $J_{5',5''}$ = 12.8 Hz, 1H) H5'; 3.67 (dd, $J_{4',5''}$ = 2.5 Hz, 1H) H5";1.92 (d, 3H) $5CH_3$. HRMS (FAB^-): calcd. for $(M-H)^-$ 359.0839, found 359.0869.

1-[5-O-(MMTr)-2-(R)-O-TBDMS-3-deoxy-3-C-nitromethyl-3-(R)-C-(α-dimethylmalonate)-β-D-pentofuranosyl]thymine (15). Potassium *tert*-butoxide (289 mg, 2.4 mmol) was added to dimethyl malonate (5 mL) and kept at room temperature for 30 min. The reaction mixture was cooled in an ice water bath for 20 min, the mixture of (E / Z) **3** (500 mg, 0.73 mmol) was added and kept stirring for 4 h at room temperature. The reaction mixture was poured into aqueous solution of ammonium chloride (20 mL) which was extracted with dichloromethane (2 x 50 mL). The organic layer was washed with water (2 x 20 mL) and evaporated to dryness. The residue was purified by a silica gel column chromatography to give **15** (480 mg, 81%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.39 (br. s, 1H) NH; 7.52 (d, $J_{6,CH3}$ = 1.1 Hz, 1H) H6; 7.48-6.82 (m, 14 H) arom; 5.82 (d, $J_{1',2'}$ = 7.1 Hz, 1H) H1'; 5.20 (dd, 1H) H4'; 5.10 (d, $J_{Ha',Ha''}$ = 12.4 Hz, 1H) $H_{a'}$; 5.01 (d, 1H) H2'; 4.63 (d, 1H) $H_{a''}$; 4.13 (s, 1H) $C\underline{H}(CO_2Me)_2$; 3.79 (s, 6H) $CO_2C\underline{H}_3$ and MMTr; 3.66 (dd, $J_{4',5'}$ = 3.2 Hz, $J_{5',5''}$ = 11.3 Hz, 1H) H5'; 3.59 (s, 3H) $CO_2C\underline{H}_3$; 3.03 (dd, $J_{4',5''}$ = 2.3 Hz, 1H) H5";1.31 (d, 3H) $5CH_3$; 0.83 (s, 9H), 0.10 (s, 3H), -0.07 (s, 3H) TBDMS. ^{13}C-NMR ($CDCl_3$): 135.9 (d, J_{CH} = 178.5 Hz) C6; 111.4 (s) C5; 88.0 (d, J_{CH} = 166.0 Hz) C1'; 87.1 (s) MMTr; 78.3 (d), 76.9 (d) C4' and C2'; 75.9 (t) $\underline{C}H_2NO_2$; 61.5 (t, J_{CH} = 143.8 Hz) C5'; 54.6 (q, J_{CH} = 143.9 Hz) MMTr; 52.5 (q, J_{CH} = 152.3 Hz) $CO_2\underline{C}H_3$; 52.2 (q, J_{CH} = 152.3 Hz) $CO_2\underline{C}H_3$; 50.0 (d, J_{CH} = 133.9 Hz) $\underline{C}H(CO_2Me)_2$; 49.3 (s) C3'; 25.0 (q, J_{CH} = 125.6 Hz), 17.4 (s) TBDMS; 10.6 (q, J_{CH} = 129.4 Hz) $5CH_3$; -5.1 (q), -6.1 (q) TBDMS.

1-[2-(R)-O-TBDMS-3-deoxy-3-C-nitromethyl-3-(R)-C-(α-dimethylmalonate)-β-D-pentofuranosyl] thymine (16). Compound **15** (50 mg, (0.06 mmol) was treated with 80% aqueous acetic acid (3 mL) at RT for overnight. After a usual work up the residue was purified by silica gel column chromatography to give **16** (31 mg, 94%). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.18 (q, $J_{6,CH3}$ = 1.1 Hz, 1H) H6; 5.45 (d, $J_{1',2'}$ = 6.6 Hz, 1H) H1'; 5.38 (d, $J_{Ha',Ha''}$ = 12.7 Hz, 1H) $H_{a'}$; 5.24 (d, 1H) H2'; 5.16 (br. s, 1H) H4'; 4.97 (d, 1H) $H_{a''}$; 4.02 (s, 1H) $C\underline{H}(CO_2Me)_2$; 3.90 (d, $J_{5',5''}$ = 13.7 Hz, 1H) H5'; 3.79, 3.77 (2 x s, 6H) 2 x CO_2Me; 3.69 (d, 1H) H5"; 1.93 (d, 3H) $5CH_3$; 0.81 (s, 9H), 0.05 (s, 3H), -0.08 (s, 3H) TBDMS. ^{13}C-NMR ($CDCl_3$): 168.4 (s) $\underline{C}OOMe$; 168.1 (s) $\underline{C}OOMe$; 163.5 (s) C4; 150.6 (s) C2; 140.0 (d, J_{CH} = 185.8 Hz) C6; 111.2 (s) C5; 96.2 (d, J_{CH} = 168.2 Hz) C1'; 80.9 (d, J_{CH} = 153.6 Hz), 77.4 (d, J_{CH} = 158.8 Hz) C4' and C2'; 78.1 (t, J_{CH} = 150.0 Hz) $\underline{C}H_2NO_2$; 61.4 (t, J_{CH} = 144.3 Hz) C5'; 53.0 (q, J_{CH} = 148.0 Hz) $CO_2\underline{Me}$; 52.7 (q, J_{CH} = 147.7 Hz) $CO_2\underline{Me}$; 50.5 (d, J_{CH} = 134.9 Hz) $\underline{C}H(CO_2Me)_2$; 50.2 (s) C3'; 25.5 (q, J_{CH} = 125.2 Hz), 17.9 (s) TBDMS; 12.0 (q, J_{CH} = 130.0 Hz) $5CH_3$; -5.3, -5.2 (2 x q, J_{CH} = 119.0 Hz) TBDMS. HRMS (FAB^-): calcd. for $(M-H)^-$ 544.1963, found 544.1949.

1-[5-O-(MMTr)-2-(R)-O-TBDMS-3-deoxy-3-C-nitromethyl-3-(R)-C-(α-acetylacetone)-β-D-pentofura-

nosyl]thymine (17). The reaction condition used was as described for **15** using potassium *tert*-butoxide (289 mg, 2.4 mmol), acetylacetone (5 mL) and **3** (500 mg, 0.73 mmol) to give **17** (50 mg, 8%) and **24** (200 mg, 43%). Compound **17**: ^{1}H-NMR ($CDCl_3$, 500 MHz) 8.77 (br. s, 1H) NH; 7.70 (q, $J_{6,CH3}$ = 1.2 Hz) H6; 7.45-6.80 (m, 14 H) arom; 5.79 (d, $J_{1',2'}$ = 8.0 Hz, 1H) H1'; 5.29 (dd, 1H) H4'; 5.14 (d, $J_{Ha',Ha''}$ = 11.4 Hz, 1H) $H_{a'}$; 4.93 (d, 1H) H2'; 4.78 (s, 1H) C$\underline{H}$(COCH$_3$)$_2$; 4.37 (d, 1H) $H_{a''}$; 3.86 (dd, $J_{4',5'}$ = 3.3 Hz, $J_{5',5''}$ = 11.6 Hz, 1H) H5'; 3.79 (s, 3H) MMTr; 3.03 (dd, $J_{4',5''}$ = 1.0 Hz, 1H) H5''; 2.66 (s, 3H) C$\underline{H_3}$CO; 2.24 (s, 3H) C$\underline{H_3}$CO; 0.97 (d, 3H) 5CH$_3$; 0.90 (s, 9H), 0.21 (s, 3H), -0.02 (s, 3H) TBDMS. ^{13}C-NMR ($CDCl_3$): 202.8 (s) $\underline{C}$OCH$_3$; 200.9 (s) $\underline{C}$OCH$_3$; 163.2 (s) C4; 150.9 (s) C2; 135.6 (d, J_{CH} = 178.5 Hz) C6; 112.1 (s) C5; 88.0 (d, J_{CH} = 166.0 Hz) C1'; 86.0 (s) MMTr; 78.6 (d, J_{CH} = 151.5 Hz), 78.2 (d, J_{CH} = 158.8 Hz) C4' and C2'; 77.6 (t, J_{CH} = 143.2 Hz) CH_2NO_2; 62.5 (d, J_{CH} = 139.1 Hz) $\underline{C}$H(COCH$_3$)$_2$; 62.1 (t, J_{CH} = 145.8 Hz) C5'; 55.1 (q, J_{CH} = 143.9 Hz) MMTr; 51.6 (s) C3'; 34.2 (q, J_{CH} = 129.0 Hz) C$\underline{H_3}$CO; 31.2 (q, J_{CH} = 128.0 Hz) $\underline{C}$H$_3$CO; 26.0 (q, J_{CH} = 125.6 Hz), 19.0 (s) TBDMS; 10.5 (q, J_{CH} = 130.0 Hz) 5CH$_3$; -5.5 (q), -4.0 (q) TBDMS. Compound **24**: (for numbering see Scheme 2): ^{1}H-NMR ($CDCl_3$) 8.51 (br. s, 1H) NH; 7.47-7.16 (m, 12 H) arom; 6.97 (d, $J_{6,CH3}$ = 1.1 Hz, 1H) H6; 6.82 (m, 2H) arom; 5.21 (s, 1H) H1'; 4.10 (dd, 1H) H2'; 4.01 (m, 1H) H5'; 3.78 (s, 3H) MMTr; 3.50 (dd, $J_{5',6'}$ = 4.0 Hz, $J_{6',6''}$ = 10.7 Hz, 1H) H6'; 3.43 (dd, $J_{5',6''}$ = 5.1 Hz, 1H) H6''; 2.81 (m, 1H) H4'; 2.16 (s, 3H) C$\underline{H_3}$CO; 2.13 (s, 3H) C$\underline{H_3}$CO; 1.95 (m, 2H) H3',H3''; 1.82 (d, 3H) 5CH$_3$. ^{13}C-NMR ($CDCl_3$): 209.1 (s) C7'; 203.0 (s) $\underline{C}$OCH$_3$; 202.7 (s) $\underline{C}$OCH$_3$; 163.4 (s) C4; 149.7 (s) C2; 138.4 (d, J_{CH} = 181.6 Hz) C6; 111.7 (s) C5; 86.9 (s) MMTr; 85.6 (d, J_{CH} = 161.9 Hz) C1'; 80.6 (d, J_{CH} = 152.6 Hz) C5'; 64.5 (d, J_{CH} = 129.7 Hz) C2'; 64.2 (t, J_{CH} = 145.3 Hz) C6'; 55.0 (q, J_{CH} = 143.9 Hz) MMTr; 43.6 (d, J_{CH} = 133.9 Hz) C4'; 29.3 (q, J_{CH} = 128.4 Hz) CO$\underline{C}$H$_3$; 29.2 (q, J_{CH} = 128.4 Hz) CO$\underline{C}$H$_3$; 25.6 (t, J_{CH} = 130.8 Hz) C3'; 12.0 (q, J_{CH} = 129.7 Hz) 5CH$_3$.

1-[2-(R)-O-TBDMS-3-deoxy-3-C-nitromethyl-3-(R)-C-(α-acetylacetone)-β-D-pentofuranosyl]thymine (18). Compound **17** (30 mg, 0.04 mmol) was treated with 80% aqueous acetic acid (3 mL) at RT for overnight. After a usual work up the residue was purified by silica gel column chromatography to give **18** (16 mg, 82%). ^{1}H-NMR ($CDCl_3$): 7.13 (d, $J_{6,CH3}$ = 1.1 Hz, 1H) H6; 5.45 (d, $J_{Ha',Ha''}$ = 11.7 Hz, 1H) $H_{a'}$; 5.33 (br. s, 1H) H4'; 5.31 (d, $J_{1',2'}$ = 6.0 Hz, 1H) H1'; 5.15 (d, 1H) H2', 4.65 (d, 1H) $H_{a''}$; 4.48 (s, 1H) C$\underline{H}$(COCH$_3$)$_2$; 3.99 (dd, $J_{4',5'}$ = 3.7 Hz, $J_{5',5''}$ = 12.9 Hz, 1H) H5'; 3.70 (d, 1H) H5''; 2.50 (s, 3H) C$\underline{H_3}$CO; 2.48 (s, 3H) C$\underline{H_3}$CO; 1.92 (d, 3H) 5CH$_3$; 0.82 (s, 9H), 0.08 (s, 3H), -0.02 (s, 3H) TBDMS. ^{13}C-NMR ($CDCl_3$): 201.7 (s) $\underline{C}$OCH$_3$; 201.0 (s) $\underline{C}$OCH$_3$; 163.3 (s) C4; 150.6 (s) C2; 140.0 (d, J_{CH} = 181.6 Hz) C6; 111.3 (s) C5; 95.8 (d, J_{CH} = 167.1 Hz) C1'; 80.8 (d, J_{CH} = 160.9 Hz), 77.5 (d, J_{CH} = 156.7 Hz) C4' and C2'; 79.1 (t, J_{CH} = 151.0 Hz) $\underline{C}$H$_2$NO$_2$; 64.7 (d, J_{CH} = 133.9 Hz) C$\underline{H}$(COCH$_3$)$_2$; 61.7 (t, J_{CH} = 144.3 Hz) C5'; 52.0 (s) C3'; 33.0 (q, J_{CH} = 128.0 Hz) $\underline{C}$H$_3$CO; 32.5 (q, J_{CH} = 128.4 Hz) $\underline{C}$H$_3$CO; 25.9 (q, J_{CH} = 124.9 Hz), 18.1 (s) TBDMS; 12.0 (q, J_{CH} = 130.0 Hz) 5CH$_3$; -5.3 (q, J_{CH} = 118.7 Hz), -4.8 (q, J_{CH} = 119.4 Hz) TBDMS. HRMS (FAB$^-$): calcd. for (M-H)$^-$ 512.2065, found 512.2068.

1-[5-O-(MMTr)-2-(R)-O-TBDMS-3-deoxy-3-C-nitromethyl-3-(R)-C-(α-malononitrile)-β-D-pentofuranosyl]thymine (19). The reaction condition used was as described for **15** using potassium *tert*-butoxide (289 mg, 2.4 mmol), malononitrile (600 mg, 9 mmol) and **3** (500 mg, 0.73 mmol) to give **19** (290 mg, 53%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.49-6.82 (m, 15 H) arom and H6; 5.41 (d, $J_{1',2'}$ = 5.3 Hz, 1H) H1'; 5.09 (d, 1H) H2', 4.96 (d, $J_{Ha',Ha''}$ = 14.8 Hz, 1H) $H_{a'}$; 4.67 (s, 1H) C$\underline{H}$(CN)$_2$; 4.63 (d, 1H) $H_{a''}$; 4.61 (dd, 1H) H4'; 3.80 (s, 3H) MMTr; 3.48 (dd, $J_{4',5'}$ = 5.7 Hz, 1H) H5'; 3.38 (dd, $J_{4',5''}$ = 4.2 Hz, $J_{5',5''}$ = 11.2 Hz, 1H) H5''; 1.76 (d, 3H) 5CH$_3$; 0.92 (s, 9H), 0.11 (s, 3H), -0.05 (s, 3H) TBDMS. ^{13}C-NMR ($CDCl_3$): 163.6 (s) C4; 149.9 (s) C2; 138.5 (d, J_{CH} = 178.5 Hz) C6; 112.2, 111.2, 110.7 (3 x s) C5 and 2 x CN; 95.4 (d, J_{CH} = 164.0 Hz) C1'; 88.1 (s) MMTr; 80.4 (d, J_{CH} = 150.5 Hz) C4'; 75.2 (d, J_{CH} = 152.6 Hz) C2'; 75.1 (t, J_{CH} = 150.5 Hz) CH_2NO_2; 60.9 (t, J_{CH} = 144.3 Hz) C5'; 55.1 (q, J_{CH} = 144.3 Hz) MMTr; 51.0 (s) C3', 26.5 (d, J_{CH} = 145.3 Hz) $\underline{C}$H(CN)$_2$; 25.4 (q, J_{CH} = 126.3 Hz), 17.7 (s) TBDMS; 11.8 (q, J_{CH} = 130.0 Hz) 5CH$_3$; -5.2, -4.9 (2 x q) TBDMS. HRMS (FAB$^+$): calcd. for $C_{40}H_{46}N_5O_8Si$ 752.3116, found 752.3110.

1-[5-O-(MMTr)-2-(R)-2-hydroxy-3-deoxy-3-C-nitromethyl-3-(R)-C-(α-ketenimine-α-cyano)-β-D-pentofuranosyl]thymine (20) Compound **19** (200 mg, 0.27 mmol) was treated with tetrabutylammonium fluoride (0.5 M in THF, 0.56 mL) in tetrahydrofuran (3 mL) at room temperature for 2 h. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give **20** (80 mg, 47%). ^{1}H-NMR ($CDCl_3$): 8.86 (br. s, 1H) NH; 7.46-6.82 (m, 15 H) arom and H6; 5.91 (d, $J_{1',2'}$ = 4.8 Hz, 1H) H1'; 5.47 (d, 1H) H2'; 5.29 (br. s, 2H) 2'OH and C=N$\underline{H}$; 4.78 (d, $J_{Ha',Ha''}$ = 12.6 Hz, 1H) $H_{a'}$; 4.54 (d, 1H) $H_{a''}$; 4.47 (dd, 1H) H4'; 3.80 (s, 3H) MMTr; 3.47 (dd, $J_{4',5'}$ = 5.5 Hz, $J_{5',5''}$ = 10.9 Hz, 1H) H5'; 3.27 (dd, $J_{4',5''}$ = 3.3 Hz, 1H) H5''; 1.65 (d, $J_{6,CH3}$ = 1.1 Hz, 3H) 5CH$_3$. ^{13}C-NMR ($CDCl_3$): 166.3 (s) C(CN)=$\underline{C}$=NH; 163.6 (s) C4; 150.5 (s) C2; 135.9 (d, J_{CH} = 184.8 Hz) C6; 115.9 (s) CN; 112.3 (s) C5; 90.7 (d, J_{CH} = 165.0 Hz) C1'; 89.3 (d, J_{CH} = 163.0 Hz), 85.9 (d, J_{CH} = 151.5 Hz) C4' and C2'; 87.7 (s) MMTr; 75.8 (t, J_{CH} = 150.0 Hz) CH_2NO_2; 61.4 (t, J_{CH} =

143.8 Hz) C5'; 57.5, 56.5 (2 x s) C3' and C(CN)=C=NH; 55.1 (q, J_{CH} = 143.6 Hz) MMTr; 11.8 (q, J_{CH} = 130.0 Hz) $5CH_3$. HRMS (FAB^-): calcd. for $(M-H)^-$ 636.2095, found 636.2070.

1-[2-(R)-2-Hydroxy-3-deoxy-3-C-nitromethyl-3-(R)-C-(α-ketenimine-α-cyano)-β-D-pentofuranosyl]-thymine (21). Compound **20** (40 mg, 0.06 mmol) was treated with 80% aqueous acetic acid (3 mL) at RT for 4 h. After usual work up the residue was purified by silica gel column chromatography to give **21** (20 mg, 88%). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.59 (d, $J_{6,CH3}$ = 1.1 Hz, 1H) H6; 5.82 (d, $J_{1',2'}$ = 4.5 Hz, 1H) H1'; 5.41 (d, 1H) H2'; 5.08 (d, $J_{Ha',Ha''}$ = 12.8 Hz, 1H) $H_{a'}$; 4.97 (d, 1H) $H_{a''}$; 4.40 (t, 1H) H4'; 3.88 (dd, $J_{4',5'}$ = 3.9 Hz, $J_{5',5''}$ = 12.6 Hz, 1H) H5'; 3.72 (dd, $J_{4',5''}$ = 3.0 Hz, 1H) H5''; 1.93 (d, 3H) $5CH_3$. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 166.9 (s) C(CN)=C=NH; 164.2 (s) C4; 150.6 (s) C2; 136.9 (d, J_{CH} = 179.6 Hz) C6; 116.7 (s) CN; 110.0 (s) C5; 91.8 (d, J_{CH} = 168.2 Hz) C1'; 89.2 (d, J_{CH} = 165.0 Hz), 87.0 (d, J_{CH} = 152.6 Hz) C4' and C2'; 76.2 (t, J_{CH} = 148.4 Hz) CH_2NO_2; 59.9 (t, J_{CH} = 142.7 Hz) C5'; 57.3 (s), 54.1 (s) C3' and C(CN)=C=NH; 11.8 (q, J_{CH} = 129.4 Hz) $5CH_3$. Overnight the two CH_2NO_2 protons were exchanged with ^{2}H atoms. HRMS (FAB^-): calcd. for $(M-H)^-$ 364.0894, found 364.0898.

1-[5-O-(MMTr)-2,3-dideoxy-2,3-didehydro-3-cyano-pentofuranosyl]thymine (22). Compound **8** (400 mg, 0.7 mmol) was treated with phenoxythiocarbonyl chloride (388 μL) and 4,4-N-dimethylaminopyridine (420 mg, 1.75 mmol) in acetonitrile (6 mL) at room temperature for 6 h. The reaction mixture was poured into aqueous NH_4Cl solution which was extracted with dichloromethane (2 x 50 mL). The organic phase was washed with aqueous $NaHCO_3$ solution (3 x 20 mL). The organic phase was concentrated in vacuo to give a foam. The residue was purified by silica gel column chromatography to give **22** (40 mg, 11%). ^{1}H-NMR ($CDCl_3$): 8.38 (br. s, 1H) NH; 7.51-7.45 (m, 13 H) arom and H6; 7.19 (dd, $J_{1',2'}$ = 1.3 Hz, $J_{1',4'}$ = 4.4 Hz, 1H) H1'; 6.84 (m, 2H) arom; 6.75 (m, 1H) H2'; 5.02 (m, 1H) H4'; 3.79 (s, 3H) MMTr; 3.62 ($J_{4',5'}$ = 1.8 Hz, $J_{5',5''}$ = 11.4 Hz, 1H) H5'; 3.52 (dd, $J_{4',5''}$ = 2.6 Hz, 1H) H5''; 1.07 (d, $J_{CH3,H6}$ = 1.1 Hz, 3H) $5CH_3$. ^{13}C-NMR ($CDCl_3$): 163.2 (s) C4; 150.2 (s) C2; 140.3 (d, J_{CH} = 182.4 Hz) C2'; 135.1 (d, J_{CH} = 179.6 Hz) C6; 119.6, 112.3, 111.6 (3 x s) C5, C3' and CN; 88.7 (d, J_{CH} = 171.4 Hz) C1'; 87.3 (s) MMTr; 85.2 (d, J_{CH} = 153.0 Hz) C4'; 62.5 (t, J_{CH} = 143.9 Hz) C5'; 55.1 (q, J_{CH} = 143.9 Hz) MMTr; 10.7 (q, J_{CH} = 129.5 Hz) $5CH_3$. HRMS (FAB^-): calcd. for $(M-H)^-$ 520.1873, found 520.1894.

1-[2,3-dideoxy-2,3-didehydro-3-cyano-pentofuranosyl]thymine (23). Compound **22** (20 mg, 0.04 mmol) was treated with 80% aqueous acetic acid (3 mL) at room temperature for 5 h. After usual workup the residue was purified by silica gel column chromatography to give **23** (8.5 mg, 90%). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.71 (q, $J_{CH3,H6}$ = 1.2 Hz, 1H) H6; 7.12 (dd, $J_{1',2'}$ = 1.5 Hz, $J_{1',4'}$ = 3.9 Hz, 1H) H1'; 6.67 (br, s, 1H) H2'; 4.99 (m, 1H) H4'; 3.96 (br, s, 2H) H5', 5''; 1.88 (d, 3H) $5CH_3$. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 164.3 (s) C4; 150.6 (s) C2; 140.4 (d, J_{CH} = 179.6 Hz) C2'; 136.3 (d, J_{CH} = 181.4 Hz) C6; 119.1, 111.6, 111.2 (3 x s) C5, C3' and CN; 89.0 (d, J_{CH} = 173.2 Hz) C1'; 86.7 (d, J_{CH} = 161.3 Hz) C4'; 60.8 (t, J_{CH} = 143.0 Hz) C5'; 11.9 (q, J_{CH} = 129.2 Hz) $5CH_3$. HRMS (FAB^-): calcd. for $(M-H)^-$ 248.0671, found 248.0672.

Compound 25. Compound **24** (160 mg, 0.26 mmol) was treated with 80% aqueous acetic acid (5 mL) at RT for 5 h. After usual work up the residue was purified by silica gel column chromatography to give **25** (86 mg, 95%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 6.99 (q, $J_{6,CH3}$ = 1.1 Hz, 1H) H6; 5.07 (s, 1H) H1'; 4.25 (dd, $J_{2',3'}$ = 6.2 Hz, $J_{2',3''}$ = 7.4 Hz, 1H) H2'; 4.05 (m, $J_{4',5'}$ = 9.0 Hz, 1H) H5'; 3.97 (dd, $J_{5',6'}$ = 2.4 Hz, $J_{6',6''}$ = 12.5 Hz, 1H) H6'; 3.81 (dd, $J_{5',6''}$ = 4.1 Hz) H6''; 2.92 (ddd, $J_{3',4'}$ = 6.0 Hz, $J_{3'',4'}$ = 8.4 Hz, 1H) H4'; 2.27 (s, 3H) CH_3CO; 2.25 (s, 3H) CH_3CO; 2.06 (m, 2H) H3', H3''; 1.90 (d, 3H) $5CH_3$. ^{13}C-NMR ($CDCl_3$): 209.1 (s) C7'; 203.9 (s) $COCH_3$; 203.7 (s) $COCH_3$; 164.1 (s) C4; 150.2 (s) C2; 139.5 (d, J_{CH} = 180.6 Hz) C6; 111.5 (s) C5; 86.7 (d, J_{CH} = 160.9 Hz) C1'; 81.7 (d, J_{CH} = 145.3 Hz) C5'; 64.7 (d, J_{CH} = 135.0 Hz) C2'; 62.3 (t, J_{CH} = 144.3 Hz) C6'; 42.5 (d, J_{CH} = 130.9 Hz) C4'; 29.8 (q, J_{CH} = 128.4 Hz) CH_3CO; 29.6 (q, J_{CH} = 128.0 Hz) CH_3CO; 25.5 (t, J_{CH} = 130.8 Hz) C3'; 12.1 (q, J_{CH} = 129.0 Hz) $5CH_3$. HRMS (FAB^-): calcd. for $(M-H)^-$ 351.1192, found 351.1185 (100%), m/z 251 [67%, $(M-H)^-$ - ($C_5H_8O_2$)], m/z 239 [19%, $(M-H)^-$ - ($C_5H_4O_3$)], m/z 235 [19%, $(M-H)^-$ - ($C_5H_8O_3$)]. The observed fragments in MS are equivalents of the loss of bis-acetylfuranose moiety from the molecular ion of **25**.

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