Tetrahedron Vol. 45, No. 3, pp. 855 to 862, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00
Pergamon Press plc

NEW SYNTHESIS OF 2′,3′-DIDEOXY-3′-C-CYANO-2′-SUBSTITUTED THYMIDINES BY MICHAEL ADDITION REACTIONS

J.-C. Wu & J. Chattopadhyaya*

Department of Bioorganic Chemistry, University of Uppsala, Biomedical Center, Box 581, S-751 23 Uppsala, Sweden

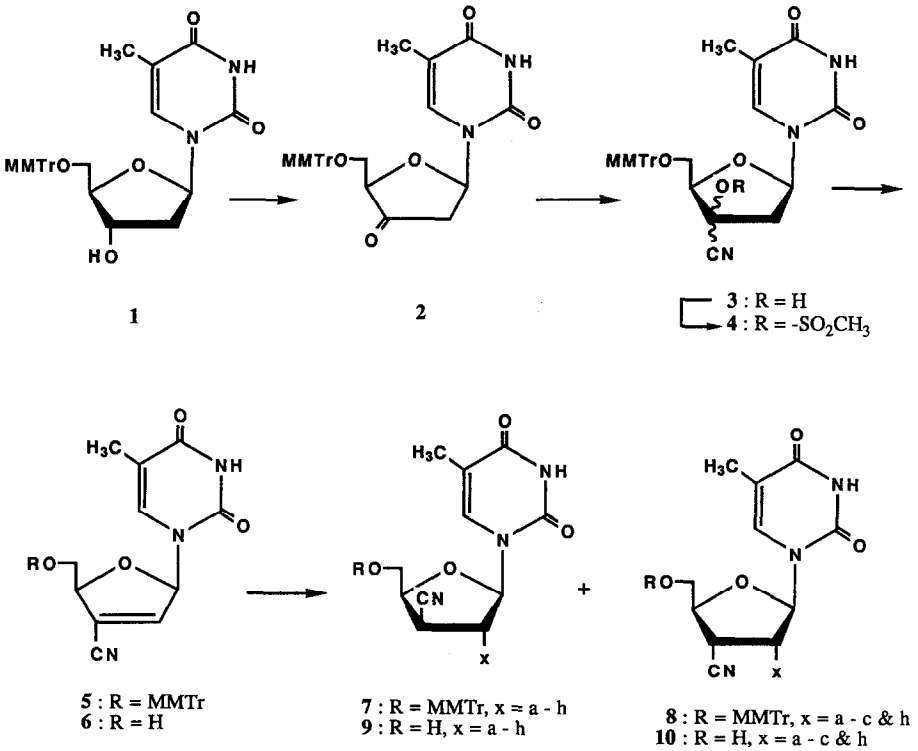
(*Received in UK* 25 *October* 1988)

Abstract : *A new high-yielding preparation of appropriately protected 3′-enenitrile of thymidine* **5** *has been devised directly from the 3′-keto thymidine* **2**. *The 3′-enenitrile* **5** *has been subsequently subjected to various Michael addition reactions with ammonia, primary amines (methylamine and benzylamine), secondary amines (pyrrolidine, piperidine and morpholine) and carbon-nucleophiles (sodium dimethylmalonate and conjugate base of nitromethane) as means to synthesize new 2′,3′-dideoxy-3′-C-cyano-2′-substituted thymidine derivatives which can not be prepared using any known procedure. Most of these nucleophilic addition reactions gave either the trans-isomer as the sole product, such as* **7d - g**, *or as the major product* **7a - c & h** *along with the cis-isomer* **8a - c & h** , *except for the reaction of* **5** *with ammonia where the cis-isomer* **9e** *was the major product formed. The Michael adducts have been finally 5′-deprotected to give nucleosides* **9a - h** , **10a - c & h** *in good yields. Compounds described herein, with free 5′-hydroxyl function, are potential inhibitors of the HIV-reverse transcriptase promoted c-DNA synthesis*

2′,3′-Dideoxynucleosides have shown potent antiretroviral activity against HIV-specific reverse transcriptase[1-3, 27]. In particular, compounds such as 3′-α-azidothymidine, 3′-α-fluorothymidine, 2′,3′-dideoxycytidine, 2′,3′-dideoxy-2′,3′-didehydro-thymidine and cytidine have shown promising potent and selective inhibition of HIV[1-3, 27]. Several other candidates, with general structures such as 2′,3′-dideoxy-2′-substituted or 3′-substituted or 2′,3′-bis-substituted pyrimidine nucleosides, which are capable of forming 5′-triphosphate by cellular kinases and which upon incorporation into DNA by acting as competitive inhibitors or alternate substrates to HIV reverse transcriptase, produce chain termination[1-4, 27]. 3′-deoxy-3′-α-C-cyanothymidine (CNT) was reported in July of 1987 to exhibit anti-HIV activity *in vitro* and was being considered for clinical study[5]. Subsequently, CNT has been prepared by several groups of workers and found to be inactive in standard *in vitro* tests[6-9]. We have been engaged in the mean time in developing synthetic procedures for 2′,3′-dideoxy-3′-C-cyano-2′-substituted thymidine. We herein report that an appropriately 5′-protected 3′-C-cyano-3′-deoxy-2′,3′-didehydrothymidine (3′-enenitrile) acts as a good Michael acceptor and undergoes Michael addition reactions with different nitrogen and carbon nucleophiles to give corresponding 5′-0-(4-monomethoxytrityl) [MMTr]-3′-(α/β)-C-cyano-2′-substituted thymidine derivatives in good yields. Subsequently 5′-0-MMTr group could be selectively removed from pure isomers **7a - h & 8a - c, h** to give corresponding 3′-(α/β)-C-cyano-2′-substituted thymidines **9a - h & 10a - c, h** which are considered as potential substrates for antiretroviral activity.

The ketone **2** was selected to be the starting material for the preparation of the 3′-enenitrile **5** despite the reports[10-11] that a ketone such as **2** is unstable in both acidic and basic conditions to give β-elimination products. Earlier, a 5′-protected-3′-keto thymidine has been used as intermediates only in two cases: the $NaBH_4$ promoted reduction to give the corresponding *threo*-alcohol[10] and the recently reported nucleophilic addition reaction with methylmagnesium chloride-trimethylaluminium at -78 °C[11]. The ketone **2** was prepared in 89% yield by employing a slight modification[12] of the literature procedure[10]. Treatment of the ketone **2** with sodium cyanide (5 equiv.) and sodium bicarbonate (5 equiv.) in ethyl acetate-water mixture (3:1, v/v) ~ 20 °C afforded a mixture of two epimeric 3′-cyanohydrins **3** (ca. 70% estimated

from ^{1}H-NMR) along with by-products formed due to β-elimination of the ketone **2**. The mixture was not separated, it was directly treated with methylsulfonyl chloride in dry pyridine at ~0 °C for 2 h and then left for 2 days at ~20 °C to give the epimeric mixtures of 3′-cyano-mesylates **4** (not isolated, monitored by ^{1}H-NMR). After a standard work-up, the epimeric mixture of 3′-cyano-mesylates **4** was heated under reflux in pyridine and triethylamine till traces of 3′-cyano-mesylates disappeared. The product, 5′-0-(MMTr)-3′-C-cyano-3′-deoxy-2′,3′-didehydrothymidine **5**, was thus obtained in 46% overall yield starting from the labile ketone **2**. The 5′-0-MMTr group from the ene-nitrile **5** was removed to give



[a] : x = $-NH_2$;

[b] : x = $-NHCH_3$;

[c] : x = $-NHCH_2Ph$;

[d] : x = -N

[e] : x = -N

[f] : x = -N O

[g] : x = $-CH(CO_2CH_3)_2$

[h] : x = $-CH_2NO_2$

compound **6** (88%) which was spectroscopically identical to the multistep preparation reported in the literature starting from 1-(β-D-ribofuranosyl)thymine[8].

Nucleophilic addition reactions of α,β-unsaturated nitriles have been well doccumented[13]. To our knowledge, there are no reports of Michael addition reactions of a α,β-enenitrile, such as **5**, as means to functinalize the C-2′ in the nucleoside chemistry. Our experiments showed that the enenitrile **5** reacted smoothly with ammonia, different amines and carbon-nucleophiles to give corresponding Michael addition products in good yields. The reactions of **5** with aqueous ammonia, aqueous methylamine, benzylamine and sodium salt of nitromethane gave two isomeric addition products (trans-isomer was more predominant than the cis-isomer, except for the reaction with ammonia, *vide infra* and experimental section), while the reactions with pyrrolidine, piperidine, morpholine and sodium salt of dimethylmalonate gave only one product (trans-isomer, *vide infra*) in a stereospecific manner. Theoretically four isomeric products can be expected upon addition reactions to the ene-nitrile **5** due to chiralities of C-2′ and C-3′ in the products. The simplicity of the product formation, such as **7** and **8**, however revealed a considerable difference in the assymmetric environment between the diastereotopic α and β olefin-faces of the **5** owing to the defined stereochemical configurations of C-1′ and C-4′[14]. Spectroscopic characterizations have established (*vide infra*) that the stereochemical course of the nucleophilic attack at C-2′ is always from the sterically and electronically less demanding α-face of the pento-enefuranosyl ring. This is consistent with the data available from (1) the nucleophilic addition reactions reported by us on α,β-3′-enesulfones of nucleosides[14], (2) the reduction of 2′-ketonucleosides by $NaBH_4$[15] and $Li(Et)_3BH$[16] and also from (3) the nucleophilic addition reactions of several soft carbon-nucleophiles to the 2′-kenonucleosides[17], except one example[18].

The configuration of C-3′ (cyano "up" [trans] or cyano "down" [cis]) was assesed on the basis of the following observations by ^{1}H- and ^{13}C-NMR spectroscopies: (1) the H-3′ and H-4′ were more deshielded [$\Delta\delta > 0.1$ ppm] in the cis-isomers than the corresponding trans-isomers; (2) the 5′-methylene protons had an almost identical chemical shifts in the trans-isomers in contrast to the cis-isomers in which one of the 5′-methylene protons was shielded by ~0.2 ppm; (3) the ^{13}C chemical shifts of C-2′, C-3′ and -CN of trans-isomers were more upfield than the corresponding resonances in the cis-isomers; and (5) particularly, the chemical shift of C-4′ showed a very specific shift depending upon whether 3′-cyano was "up" or "down": the C-4′ absorbed in the range of 75-77 ppm when the 3′-cyano was "up", while it absorbed in the range of 80-83 ppm when it was in the "down" configuration.

We also envisioned that the conformation around C-4′ and C-5′ bond [γ^+, γ^- and γ^t] would be quite different depending upon the configuration of C-3′[19-26]. Electronegative C-3′ substituents such as -OH, $-N_3$, $-SO_2Ar$, particularly influences the percentage of γ^+ population quite drastically depending upon its configuration "up" or "down"[21, 23, 27, 28,14]. When the electronegative substituent is "down" the γ^+ is still high (>50%) while in the "up" configuration the percentage of γ^+ is found to be lower than 30%. This has been found to be generally true in both purine and pyrimidine nucleosides[19-28,14]. The population of three rotamers [X_{γ^-}, X_{γ^+} and X_{γ^t}, when X denotes mole fraction of each conformer] about the exocyclic C-4′ and C-5′ bond can be estimated from $J_{4',5'}$ and $J_{4',5''}$ coupling constants using the methods of Altona and coworkers[24,29]. When the values for $J_{4',5'}$ and $J_{4',5''}$ are not possbile to extract from the apparent spectrum due to overlaps of absorptions or ambiguous assignnment betweeen H-5′ and H-5″, one may conveniently employ the "sum rule"[29, 13] to obtain the population of γ^+ ($p^{\gamma+}$) in good approximation: $p^{\gamma+} = \frac{13.3 - \Sigma}{9.7}$ [where Σ represents $(J_{4',5'} + J_{4',5''})$]. We have used such a "sum rule" because of overlaps of H-4′ and H-5′/5″ resonance to estimate the γ^+ population of all the isomerically pure products **7a - h** and **8a - c & h** that were obtained in this work. It turned out that in a Michael reaction when both "up" and "down" isomers were obtained, one of them has a high γ^+ population (>50%) and consequently we assigned its 3′-C-cyano configuration as to be "up", while the isomer which showed a low γ^+ population (<40%), we attributed its 3′-C-cyano in the "up" configuration. Those Michael addition reactions which gave only one isomer such as **7d - g** showed a low γ^+ population demonstrating that its 3′-C-cyano configuration is "up". The assignments of the 3′-cyano configuration in compounds **7** and **8** made on the basis of γ^+ rule was consistent with other general spectroscopic trends discussed above.

Subsequently, the 5′-0-MMTr group from compounds **7a - h** and **8a - c & h** were removed using 80% aqueous acetic acid at ~20 °C for around 20 h to give pure **9a - h** and **10a - c & h** in 80-90% yields. Results of their biological studies will be published elsewhere.

Experimental

^{1}H-NMR and ^{13}C-NMR were recorded with Jeol 90 Q at 90 and 23.7 MHz respectively. Tetramethylsilane was used as

the internal standard and the chemical shifts are reported in ppm (δ scale). IR absorption spectra were recorded with Perkin-Elmer 298 spectrometer. Jeol DX 303 instrument was used for recording mass spectra. TLC was carried out by using Merck pre-coated silica gel F_{254} plate and the column chromatographic separation by Merck G60 silica gel.

1-[5′-O-(MMTr)-β-D-glycero-pentofuran-3′-ulosyl]thymine (2) Chromium (VI) oxide (7.44 g, 74.4 mmol) was added to pyridine (12.4 ml, 149 mmol) in dichloromethane (140 ml) and the resulting solution was stirred for 15 min at 20 °C. A solution of compound **1** (9.5 g, 18.5 mmol) in dichloromethane (20 ml) was added, immediately followed by acetic anhydride (7.4 ml, 74.4 mmol). Stirring was continued for 10 min and the mixture was poured onto a short silica gel column which was fulled with ethyl acetate (300 ml) on the top of the gel. The eluate was co-evaporated with toluene and then dichloromethane to give **2** (8.5 g, 89 %). ^{1}H-NMR ($CDCl_3$ + CD_3OD) : 7.65 (d, J = 1.2 Hz , 1H) H-6 ; 7.32-6.83 (m, 14H) arom.; 6.55 (dd, $J_{1',2'}$ = 6.9 Hz , $J_{1',2"}$ = 6.8 Hz ,1H) H-1; 4.18 (t, $J_{4',5'}$ = 2.6 Hz , $J_{4',5"}$ = 2.6 Hz , 1H) H-4′; 3.80 (s, 3H) -OCH_3 ; 3.66 (dd, $J_{5',5"}$ = 10.8 Hz ,1H), H-5′, 3.40 (dd, 1H) H-5", 3.10 (dd, $J_{2',2"}$ = 18.6 Hz ,1H) H-2′; 2.74 (dd, 1H) H-2" ; 1.31 (d, 3H) 5-CH_3 . ^{13}C-NMR ($CDCl_3$+CD_3OD) : 212.3 (s) C-3′; 80.8 (d, J_{CH} = 167.0 Hz) C-1′; 80.0 (d ,J_{CH} = 156.1Hz) C-4′; 62.5 (t, J_{CH} = 164.1 Hz) C-5′ ; 54.5 (q) -OCH_3 ; 41.1 (t, J_{CH} = 134.8 Hz) C-2′; 10.6 (q) 5-CH_3 ; MS (FAB^+) : calc. for $(M-B)^+$ 386.1518, found 386.1490.

1-[5′-O-(MMTr)-2′,3′-dideoxy-3′-C-cyano-β-D-glycero-pento-2′-enofuranosyl]thymine (5) To a suspension of compound **2** (8.5 g, 16.6 mmol) in ethyl acetate (150 ml) and water (50 ml) were added sodium bicarbonate (6.8 g, 83 mmol) and sodium cyanide (4.1 g, 83 mmol). The mixture was stirred at 20 °C for 40 min and then poured into a funnel which contained ethyl acetate (50 ml) . The water phase was separated and the organic phase was washed with water (2 x 50 ml). The organic phase was evaporated and co-evaporated with dry pyridine to dryness. The residue was dissolved into dry pyridine (150 ml) and methylsulfonyl chloride (6.4 ml, 83 mmol) was added at 0 °C. After 2 h the ice bath was removed and the reaction was kept at room temperature for 2 days. The mixture was slowly poured into a cold solution of sodium bicarbonate (500 ml) which was extracted with chloroform (2 x 200 ml). The organic layer was evaporated to give an oil which was dissolved in pyridine (150 ml) and triethylamine (10 ml). The solution was heated under reflux in an oil bath (130-140 °C) for 5 h and the cold solution was evaporated, co-evaporated with toluene to dryness. The residue was dissolved in dichloromethane (200 ml) which was washed with water (80 ml). After evaporation the syrup was separated on a silica gel column eluted with ethyl acetate-hexane (3:7) to give compound **5** (4.02 g, 46 %). ^{1}H-NMR ($CDCl_3$) : 9.80 (br , 1H) -NH ; 7.51 (d, J = 1.1 Hz ,1H) H-6 ; 7.40-6.77 (m, 16H) arom., H-2′, H-1′; 5.01 (m, 1H) H-4′; 3.77 (s, 3H) -OCH_3 ; 3.56 (m, 2H) H-5′, H-5" ; 1.07 (s, 3H) 5-CH_3 . ^{13}C-NMR ($CDCl_3$) : 140.6 (d) C-2′; 118.9 (s) -CN, 88.5 (d, J_{CH} = 171.8 Hz) C-1′; 84.8 (d, J_{CH} = 149.4 Hz) C-4′; 62.3 (t, J_{CH} = 145.5 Hz) C-5′; 10.5 (q) 5-CH_3 . IR ($CHCl_3$) : υ_{max} = 2225 cm^{-1} (-CN) .

1-[5′-O-(MMTr)-2′,3′-dideoxy-3′(S)-3′-C-cyano-2′(R)-2′-amino-β-D-glycero-pentofuranosyl] thymine (7a) and 1-[5′-O-(MMTr)-2′,3′-dideoxy-3′(R)-3′-C-cyano-2′(R)-2′-amino-β-D-glycero-pentofuranosyl]thymine (8a) *Compound* **5** *(468 mg, 0.9 mmol) was treated with aqueous ammonia (10 ml, 32 %)* in tetrahydrofuran (10 ml) at 60 °C overnight. All volatile matters were evaporated and the residue was separated on a silica gel column to give compound **7a** (120 mg, 25 %) and **8a** (203 mg, 42 %). **7a :** ^{1}H-NMR ($CDCl_3$) : 7.36-6.85 (m, 15H) arom.& H-6 ; 5.94 (d, $J_{1',2'}$ = 6.3 Hz, 1H) H-1′; 4.45 (m, $J_{4',5'}$ = 5.7 Hz, $J_{4',5"}$ = 3.5 Hz, 1H) H-4′; 4.01 (t, $J_{2',3'}$ = 6.1 Hz, 1H) H-2′; 3.78 (s, 3H) -OCH_3 ; 3.52 (m, 1H) H-3′; 1.40 (s, 3H) 5-CH_3. ^{13}C-NMR ($CDCl_3$) : 117.3 (s) -CN ; 88.5 (d, J_{CH} = 167.3 Hz) C-1′; 75.9 (d, J_{CH} = 155.0 Hz) C-4′; 63.5 (t, J_{CH} = 144.5 Hz) C-5′; 60.5 (d, J_{CH} = 141.5 Hz) C-2′; 39.3 (d, J_{CH} = 140.4 Hz) C-3′; 11.6 (q) 5-CH_3. IR ($CHCl_3$) : υ_{max} = 2240 cm^{-1} (-CN). **8a :** ^{1}H-NMR ($CDCl_3$) : 7.57 (d, 1H) H-6 ; 7.32-6.86 (m, 14 H) arom.; 5.76 (d, $J_{1',2'}$ = 3.4 Hz, 1H) H-1′; 4.58 (dt, $J_{3',4'}$ = 8.2 Hz, $J_{4',5'}$ = 2.4 Hz, $J_{4',5"}$ = 2.5 Hz, 1H) H-4′; 3.98 (dd, $J_{2',3'}$ = 6.8 Hz, 1H) H-2′; 3.79 (s, 3H) -OCH_3 ; 3.61 (dd, $J_{5',5"}$ = 11.0 Hz, 1H) H-5′ ; 3.35 (dd, 1H) H-5" ; 1.51 (s, 3H) 5-CH_3. ^{13}C-NMR ($CDCl_3$) : 116.0 (s) -CN ; 91.2 (d, J_{CH} = 171.9 Hz) C-1′; 80.3 (d, J_{CH} = 156.1 Hz) C-4′; 61.8 (t, J_{CH} = 147.7 Hz) C-5′; 58.5 (d, J_{CH} = 147.1 Hz) C-2′; 35.8 (d, J_{CH} = 139.3 Hz) C-3′; 11.9 (q) 5-CH_3 . IR ($CHCl_3$) : υ_{max} = 2240 cm^{-1} (-CN) .

1-[5′-O-(MMTr)-2′,3′-dideoxy-3′(S)-3′-C-cyano-2′(R)-2′-methylamino-β-D-glycero-pentofurano syl]thymine (7b) and 1-[5′-O-(MMTr)-2′,3′-dideoxy-3′(R)-3′-C-cyano-2′(R)-2′-methylamino-β-D-glycero-pentofuranosyl]thymine (8b) Compound **5** (250 mg, 0.48 mmol) was treated with aqueous methylamine (5 ml, 40 %) in tetrahydrofuran (5 ml) at room temperature for 1 h. All volatile matters were removed under vacuum and the residue was separated on a silica gel column to give compound **7b** (115 mg, 43 %) and **8b** (50 mg, 19 %). **7b** : ^{1}H-NMR ($CDCl_3$) : 7.40-6.86 (m, 15H) arom.& H-6 ; 5.87 (d, $J_{1',2'}$ = 5.4 Hz, 1H) H-1′; 4.41 (m, $J_{3',4'}$ = 5.2 Hz, $J_{4',5'}$ = 5.2 Hz, 1H) H-4′; 3.80 (s, 3H) -OCH_3 ; 3.65 (t, $J_{2',3'}$ = 4.4 Hz, 1H) H-2′; 3.60 (d, 2H) H-5′, H-5" ; 3.22 (dd,1H) H-3′; 2.54 (s, 3H) NCH_3 ; 1.60 (s, 3H) 5-CH_3. ^{13}C-NMR ($CDCl_3$) : 117.6 (s) -CN ; 87.9 (d, J_{CH} = 166.0 Hz) C-1′; 76.5 (d, J_{CH} = 150.2 Hz) C-4′; 69.1 (d, J_{CH} = 151.4 Hz) C-2′; 63.5 (t, J_{CH} = 142.8 Hz) C-5′; 36.4 (d, J_{CH} = 141.0 Hz) C-3′; 34.2 (q) NCH_3 ; 11.8 (q) 5-CH_3 . IR ($CHCl_3$) : υ_{max} = 2238 cm^{-1} (-CN). **8b** : ^{1}H-NMR ($CDCl_3$) : 9.43 (br, 1H) -NH ; 7.50 (d, J = 1.2 Hz, 1H) H-6 ; 6.34-6.87 (m, 14H) arom.; 5.95 (d, $J_{1',2'}$ = 4.7 Hz, 1H) H-1′; 4.51 (m, $J_{4',5'}$ = 2.5 Hz, $J_{4',5"}$ = 3.0 Hz, 1H) H-4′; 3.81 (s, 3H) -OCH_3 ; 3.78-3.54 (m, 3H) H-5′, H-2′, H-3′; 3.37 (dd, $J_{5',5"}$ = 11.0 Hz, 1H) H-5" ; 2.62 (s, 3H) NCH_3 ; 1.49 (d, 3H) 5-CH_3 . ^{13}C-NMR ($CDCl_3$) : 116.2 (s) -CN ; 88.0 (d, J_{CH} = 167.3 Hz) C-1′; 79.9 (d, J_{CH} = 151.6 Hz) C-4′; 65.4 (d, J_{CH} = 156.2 Hz) C-2′; 62.6 (t, J_{CH} = 143.9 Hz) C-5′; 34.4 (d, J_{CH} = 137.0 Hz) C-3′; 34.4 (q) NCH_3 ; 11.8 (q)5-CH_3 . IR ($CHCl_3$) : υ_{max} = 2240 cm^{-1} (-CN) .

1-[5′-O-(MMTr)-2′,3′-dideoxy-3′(S)-3′-C-cyano-2′(R)-2′-benzylamino-β-D-glycero-pentofurano syl]thymine (7c) and 1-[5′-O-(MMTr)-2′,3′-dideoxy-3′(R)-3′-C-cyano-2′(R)-2′-benzylamino-β-D-glycero-pentofuranosyl]thymine (8c) *Compound* **5** *(260 mg, 0.5 mmol) was treated with benzylamine* (5 ml) at 110 °C for 3 h and the mixture was partitioned between dichloromethane (50 ml) and saturated solution of ammonium chloride (30 ml) . The organic layer was washed with water (30 ml) and evaporated . The residue was separated on a

silica gel column to give **7c** (228 mg, 73 %) and **8c** (25 mg, 8 %). **7c** : ^{1}H-NMR ($CDCl_3$) : 7.45-6.82 (m, 20 H) arom.& H-6 ; 5.89 (d, $J_{1',2'}$ = 5.4 Hz, 1H) H-1' ; 4.41 (m, $J_{3',4'}$ = 7.1 Hz, $J_{4',5'}$ = 4.4 Hz, 1H) H-4' ; 3.93 (s, 2H) NCH_2Ph ; 3.79 (s, 3H) -OCH3 , 3.73 (dd, $J_{2',3'}$ = 7.6 Hz, 1H) H-2' ; 3.53 (d, 2H) H-5', H-5" ; 3.18 (dd, 1H) H-3' ; 1.52 (s, 3H) 5-CH_3. ^{13}C-NMR ($CDCl_3$) : 117.6 (s) -CN ; 88.0 (d, J_{CH} = 168.9 Hz) C-1' ; 76.3 (d, J_{CH} = 153.9 Hz) C-4' ; 66.3 (d, J_{CH} = 145.9 Hz) C-2' ; 63.2 (t, J_{CH} = 144.3 Hz) C-5' ; 51.5 (t, J_{CH} = 136.4 Hz) NCH_2Ph ; 37.1 (d, J_{CH} = 144.9 Hz) C-3' ; 11.7 (q) 5-CH_3 . IR ($CHCl_3$) : υ_{max} = 2300 cm^{-1} (-CN) . **8c** : ^{1}H-NMR ($CDCl_3$) : 9.08 (br, 1H) -NH ; 7.34-6.85 (m, 20H) arom.& H-6 ; 5.96 (d, $J_{1',2'}$ = 5.1 Hz, 1H) H-1' ; 4.53 (m, $J_{4',5'}$ = 2.5 Hz, $J_{4',5"}$ = 3.0 Hz, 1H) H-4' ; 4.01 (s, 2H) NCH_2Ph ; 3.80 (s, 3H) -OCH_3 ; 3.68 (m, 1H) H-2' ; 3.54 (m, 2H) H3', H-5' ; 3.31 (dd, $J_{5',5"}$ = 11.3 Hz, 1H) H-5" ; 1.45 (d, J = 1.2 Hz, 3H) 5-CH_3 . ^{13}C-NMR ($CDCl_3$) : 116.4 (s)-CN ; 88.5 (d, J_{CH} = 171.9 Hz) C-1' ; 80.0 (d, J_{CH} = 156.1 Hz) C-4' ; 62.8 (d, J_{CH} = 150.5 Hz) C-2' ; 62.5 (t, J_{CH} = 142.7 Hz) C-5' ; 51.6 (t, J_{CH} = 136.2 Hz) NCH_2Ph ; 35.0 (d, J_{CH} = 141.5 Hz) C-3' ; 11.8 (q) 5-CH_3 . IR ($CHCl_3$) : υ_{max} = 2240 cm^{-1} (-CN) .

1-[5'-O-(MMTr)-2',3'-dideoxy-3'(S)-3'-cyano-2'(R)-2'-(1-pyrrolidino)-β-D-glycero-pentofurano syl]thymine (7d) Compound **5** (230 mg, 0.44 mmol) was treated with pyrrolidine (0.82 ml, 10 mmol) in tetrahydrofuran (5 ml) . Stirring was continued for 2 h and then all volatile matters were evaporated and co-evaporated with toluene to dryness. The mixture was separated on a silica gel column to give **7d** (203 mg, 78 %). ^{1}H-NMR ($CDCl_3$) : 9.34 (br, 1H) -NH ; 7.50-6.84 (m, 15H) arom.& H-6 ; 6.16 (d, $J_{1',2'}$ = 6.1 Hz, 1H) H-1' ; 4.31 (m, 1H) H-4' ; 3.80 (s, 3H) -OCH3 ; 3.60-3.34 (m, 4H) H-2', H-3', H-5', H-5" ; 2.73 (br, 4H) NCH_2-; 1.82 (br, 4H) $NCH_2\underline{CH_2}$-; 1.57 (d, J = 1.2 Hz, 3H) 5-CH_3 . ^{13}C-NMR ($CDCl_3$) : 118.0 (s) -CN ; 85.6 (d, J_{CH} = 165.1 Hz) C-1' ; 75.5 (d, J_{CH} = 152.7 Hz) C-4' ; 70.7 (d, J_{CH} = 140.2 Hz) C-2' ; 63.2 (t, J_{CH} = 144.3 Hz) C-5' ; 51.2 (t) NCH_2-; 33.9 (d, J_{CH} = 141.5 Hz) C-3' ; 23.2 (t) $NCH_2\underline{CH_2}$-; 11.8 (q) 5-CH_3 . IR ($CHCl_3$) : υ_{max} = 2240 cm-1 (-CN) .

1-[5'-O-(MMTr)-2',3'-dideoxy-3'(S)-3'-C-cyano-2'(R)-2'-(1-piperidino)-β-D-glycero-pentofurano sylthymine (7e) Compound **5** (230 mg, 0.44 mmol) was treated with piperidine (0.98 ml, 10 mmol) in tetrahydrofuran (5 ml) at room temperature for one day. All volatile matters were evaperated and co-evaperated with toluene to dryness. The mixture was separated on a silica gel column to give **7e** (196 mg, 74 %) . ^{1}H-NMR ($CDCl_3$) : 9.76 (br, 1H) -NH ; 7.50-6.86 (m, 15H) arom.& H-6 ; 6.20 (d, $J_{1',2'}$ = 7.6 Hz, 1H) H-1' ; 4.17 (m, $J_{3',4'}$ = 7.8 Hz, $J_{4',5'}$ = 3.0 Hz, 1H) H-4' ; 3.79 (m, $J_{2',3'}$ = 6.5 Hz, 1H) H-2' ; 3.79 (s, 3H) -OCH_3 ; 3.55 (d, 2H) H-5', H-5" ; 3.47 (t, 1H) H-3' ; 2.70 (br, 4H) NCH_2-; 1.57-1.50 (br, 9H) $NCH_2\underline{CH_2CH_2}$- , 5-$CH_3$. ^{13}C-NMR ($CDCl_3$) : 118.1 (s) -CN ; 82.0 (d, J_{CH} = 168.5 Hz) C-1' ; 75.2 (d, J_{CH} = 156.1 Hz) C-4' ; 72.7 (d, J_{CH} = 143.8 Hz) C-2', 63.5 (t, J_{CH} = 144.3 Hz) C-5' ; 50.8 (t) NCH_2 ; 29.4 (d, J_{CH} = 143.6 Hz) C-3' ; 25.4, 23.9 $NCH_2\underline{CH_2}\underline{CH_2}$; 11.6 (q) 5-CH_3 ; IR ($CHCl_3$) : υ_{max} = 2240 cm^{-1} (-CN) .

1-[5'-O-(MMTr)-2',3'-dideoxy-3'(S)-3'-C-cyano-2'(R)-2'-(4-morpholino)-β-D-glycero-pentofurano syl]thymine (7f) Compound **5** (260 mg, 0.5 mmol) was treated with morpholine (5 ml) at 110 °C for tow hr. All volatile matters were evaperated and co-evaperated with toluene to dryness to give **7f** (250 mg, 82 %). ^{1}H-NMR ($CDCl_3$) : 9.83 (br, 1H) -NH ; 7.50-6.85 (m, 15H) arom.& H-6 ; 6.19 (d, $J_{1',2'}$ = 7.3 Hz, 1H) H-1' ; 4.23 (m, 1H) H-4' ; 3.79 (s, 3H) -OCH_3 ; 3.72-3.37 (m, 8H) -OCH_2-, H-2', H-3', H-5', H-5" ; 2.72 (br, 4H) NCH_2- ; 1.50 (s, 3H) 5-CH_3. ^{13}C-NMR ($CDCl_3$) : 117.7 (s) -CN ; 82.5 (d, J_{CH} = 169.8 Hz) C-1' ; 75.4 (d, J_{CH} = 147.1 Hz) C-4' ; 72.4 (d, J_{CH} = 147.1 Hz) C-2' ; 66.4 (t) -OCH_2 ; 63.3 (t, J_{CH} = 144.9 Hz) C-5' ; 50.0 (t) NCH_2-; 30.6 (d, J_{CH} = 142.7 Hz) C-3' ; 11.7 (q) 5-CH_3 . IR ($CHCl_3$) : υ_{max} = 2240 cm^{-1} (-CN) .

1-[5'-O-(MMTr)-2',3'-dideoxy-3'(S)-3'-C-cyano-2'(S)-2'-C-(dimethylmalonate)-β-D-glycero-pento furanosyl]thymine (7g) To a suspension of sodium hydride (75 mg, 2.5 mmol, 80 % in mineral oil) in tetrahydrofuran (8 ml) was added dimethyl malonate (0.28 ml, 2.5 mmol) slowly under argon. After 20 min compound **5** (260 mg, 0.5 mmol) was added and stirring was continued for one day. The mixture was poured into a saturated aqueous solution of ammonium chloride (30 ml) , which was extracted with dichloromethane (3 x 30 ml). The organic phase was evaporated and the residue was separated on a silica gel column to give **7g** (192 mg, 59 %). ^{1}H-NMR ($CDCl_3$) : 9.38 (br, 1H) -NH ; 7.50-6.85 (m, 15H) arom., H-6 ; 6.13 (d, $J_{1',2'}$ = 7.7 Hz, 1H) H-1' ; 4.35 (m, $J_{3',4'}$ = 6.4 Hz, $J_{4',5'}$ = 4.6 Hz, 1H) H-4' ; 3.79 - 3.75 (3 x s, 9H) 3 x -OCH_3 ; 3.94-3.60 (m, 4H) H-3', H-5', H-5", $\underline{CH}(CO_2CH_3)$; 3.23 (dd, 1H) H-2' ; 1.61 (s, 3H) 5-CH_3 . ^{13}C-NMR ($CDCl_3$) : 117.3 (s) -CN ; 85.2 (d, J_{CH} = 169.6 Hz) C-1' ; 76.1 (d, J_{CH} = 156.2 Hz) C-4' ; 63.3 (t, J_{CH} = 143.8 Hz) C-5' ; 53.2 (q) CO_2CH_3 ; 49.6 (d, J_{CH} = 136.0 Hz) $\underline{CH}CO_2CH_3$; 47.9 (d, J_{CH} = 141.5 Hz) C-2' ; 33.7 (d, J_{CH} = 148.3 Hz) C-3' ; 11.8 (q) 5-CH_3. IR ($CHCl_3$) : υ_{max} = 2240 cm^{-1} (-CN) .

1-[5'-O-(MMTr)-2',3'-dideoxy-3'(S)-3'-C-cyano-2'(S)-2'-C-nitromethyl-β-D-glycero-pentofurano syl]thymine (7h) and 1-[5'-O-(MMTr)-2',3'-dideoxy-3'(R)-3'-C-cyano-2'(S)-2'-C-nitromethyl-β-D-glycero-pentofuranosyl]thymine (8h) To a suspension of potassium tert-butoxide (448 mg, 4 mmol) in nitromethane (6 ml) was added compound **5** (418 mg, 0.8mmol) and stirring was continued at room temperature for one day. The mixture was poured into a saturated aqueous solution of ammonium chloride (30 ml), which was extracted with dichloromethane (3 x 30 ml). The organic phase was evaporated and co-evaporated with toluene to dryness . The residue was separated on a silica gel column to give **7h** (180 mg, 39 %) and **8h** (62 mg, 13 %). **7h** : ^{1}H-NMR ($CDCl_3$) : 9.48 (br, 1H) -NH ; 7.40-6.85 (m, 15H) arom.& H-6 ; 6.06 (d, $J_{1',2'}$ = 6.6 Hz, 1H) H-1' ; 4.78 (m, 2H) CH_2NO_2 ; 4.30 (m, 1H) H-4' ; 3.79 (s, 3H) -OCH_3 ; 3.66-3.34 (m, 4H) H-2', H-3', H-5', H-5" ; 1.47 (d, J = 1.2 Hz, 3H) 5-CH_3 . ^{13}C-NMR ($CDCl_3$) : 116.4 (s) -CN ; 84.8 (d, J_{CH} = 170.7 Hz) C-1' ; 76.2 (d, J_{CH} = 151.7 Hz) C-4' ; 72.7 (t, J_{CH} = 150.0 Hz) CH_2NO_2 ; 63.2 (t, J_{CH} = 144.9 Hz) C-5' ; 45.9 (d, J_{CH} = 141.5 Hz) C-2' ; 34.2 (d, J_{CH} = 144.9 Hz) C-3' ; 11.6 (q) 5-CH_3 . IR ($CHCl_3$) : υ_{max} = 2240 cm^{-1} (-CN). **8h** : ^{1}H-NMR ($CDCl_3$) : 9.27 (br, 1H) -NH ; 7.47 (d, J = 1.2 Hz, 1H) H-6 ; 7.35-6.86 (m, 14H) arom. ; 6.09 (d, $J_{1',2'}$ = 8.0 Hz, 1H) H-1' ; 4.89 (2 x d, 2H) CH_2NO_2 ; 4.49 (m, $J_{4',5'}$ =2.5 Hz, 1H) H-4' ; 3.80 (s, 3H) -OCH_3 ; 3.68 (m, 1H) H-3', 3.63 (dd, 1H) H-5' ; 3.43 (m, 1H) H-2' ; 3.36

(dd, $J_{5',5''}$ = 11.1 Hz, 1H) H-5" ; 1.54 (d, 3H) 5-CH_3. ^{13}C-NMR ($CDCl_3$) : 116.1(s) -CN ; 85.6 (d, J_{CH} = 160.7 Hz) C-1'; 80.3(d, J_{CH} = 150.5 Hz) C-4'; 71.8 (t, J_{CH} = 150.1 Hz) CH_2NO_2 ; 63.3 (t, J_{CH} = 143.7 Hz) C-5'; 43.6 (d, J_{CH} = 143.7 Hz) C-2'; 33.9 (d, J_{CH} = 143.8 Hz) C-3', 11.8 (q) 5-CH_3 . IR ($CHCl_3$) : υ_{max} = 2237 cm^{-1} (-CN) .

General procedure for the removal of 5'-O-MMTr group. The protected compounds were treated with 80 % aqueous acetic acid (40 ml /mmol) at room temperature till all starting material disappeared. All volatile matters were evaporated and the residue was co-evaporated with toluene and then ethanol to dryness. The mixture was separated by preparative TLC to give the corresponding deprotected compound.

1-(2',3'-dideoxy-3'-cyano-β-D-glyceropento-2'-enofuranosyl)thymine (6). Yield 88 %. ^{1}H-NMR (DMSO-d_6) : 7.66 (d, J = 1.0 Hz, 1H) H-6 ; 7.14 (t, $J_{1',2'}$ = 1.7 Hz, $J_{1',4'}$ = 2.2 Hz, 1H) H-1'; 7.01 (dd, $J_{2',4'}$ = 3.9 Hz, 1H) H-2'; 5.45 (br, 1H) 5'-OH ; 5.01 (m, 1H) H-4'; 3.74 (br, 2H) H-5', H-5" . ^{13}C-NMR (D_2O+CD_3OD) : 119.8 (s) -CN ; 91.1 (d, J_{CH} = 174.3 Hz) C-1'; 88.0 (d, J_{CH} = 153.9 Hz) C-4'; 61.9 (t, J_{CH} = 144.4 Hz) C-5'; 12.7 (q) 5-CH_3 ; IR (CH_3OH) : υ_{max} = 2225 cm^{-1} (-CN) . MS (FAB^-) : calc. for (M-H)$^-$ 248.0671, found 248.0651.

1-[2',3'-dideoxy-3'(S)-3'-cyano-C-2'(R)-2'-amino-β-D-glycero-pentofuranosyl]thymine (9a) Yield 84 % . ^{1}H-NMR (DMSO-d_6) : 7.74 (d, J = 1.2 Hz, 1H) H-6 ; 5.70 (d, $J_{1',2'}$ = 7.0 Hz, 1H) H-1'; 4.29 (m, 1H) H-4'; 3.70-3.17 (m, 7H) 5'-OH, -NH_2, H-2', H-3; H-5', H-5" ; 1.79 (s, 3H)5-CH_3 . ^{13}C-NMR (DMSO-d_6) : 118.8 (s) -CN ; 88.0 (d, J_{CH} = 167.4 Hz) C-1'; 76.1 (d, J_{CH} = 150.5 Hz) C-4'; 62.0 (t, J_{CH} = 140.0 Hz) C-5'; 59.4 (d, J_{CH} = 141.6 Hz) C-2'; 37.9 (d, J_{CH} = 138.2 Hz) C-3'; 12.4 (q)5-CH_3 . IR (DMSO) : υ_{max} = 2240 cm^{-1} (-CN) .MS (FAB^-) : calc. for (M-H)$^-$ 265.0937, found 265.0941.

1-[2',3'-dideoxy-3'(R)-3'-C-cyano-2'(R)-2'-amino-β-D-glycero-pentofuranosyl]thymine (10a) It was separated as the salt of acetic acid. Yield 70 % . ^{1}H-NMR (D_2O) : 7.62 (s, 1H) H-6; 5.93 (d, $J_{1',2'}$ = 4.4 Hz, 1H) H-1'; 4.59 (dt, $J_{2',3'}$ = 6.7 Hz, $J_{4',5'}$ = 4.1 Hz, $J_{4',5''}$ = 3.9 Hz, 1H) H-4'; 4.13 (dd, $J_{2',3'}$ = 8.1 Hz, 1H) H-2'; 3.92-3.71 (m, 3H) H-3', H-5', H-5" ; 2.02 (s, 3H) acetate ; 1.85 (s, 3H) 5-CH_3 . ^{13}C-NMR (D_2O) : 119.2 (s) -CN ; 92.9 (d, J_{CH} = 169.7 Hz) C-1'; 83.6 (d, J_{CH} = 150.5 Hz) C-4'; 63.1 (t, J_{CH} = 144.9 Hz) C-5'; 58.2 (d, J_{CH} = 153.7 Hz) C-2'; 37.1 (d, J_{CH} = 143.8 Hz) C-3'; 14.2 (q) 5-CH_3 . IR (CH_3OH) : υ_{max} = 2240 cm^{-1} (-CN). MS (FAB^-) : calc. for (M-H)$^-$ 265.0937, found 265.0918.

1-[2',3'-dideoxy-3'(S)-3'-C-cyano-2'(R)-2'-methylamino-β-D-glycero-pentofuranosyl]thymine (9b) Yield 86 %. ^{1}H-NMR (DMSO-d_6) : 7.72 (d, J = 1.2 Hz, 1H) H-6 ; 5.78 (d, $J_{1',2'}$ = 6.6 Hz, 1H) H-1'; 4.29 (m, 1H) H-4'; 3.69-3.53 (m, 6H) 5-OH, NHMe, H-2', H-3, H-5', H-5" ; 2.32 (s, 3H) NCH_3 ; 1.79 (s, 3H) 5-CH_3 . ^{13}C-NMR (DMSO-d_6) : 119.2 (s) -CN ; 86.5 (d, J_{CH} = 167.4 Hz) C-1'; 76.7 (d, J_{CH} = 156.2 Hz) C-4'; 66.7 (d, J_{CH} = 144.9 Hz) C-2'; 61.8 (t, J_{CH} = 141.6 Hz) C-5'; 35.0 (d, J_{CH} = 143.8 Hz) C-3'; 33.4 (q) NCH_3 ; 12.4 (q) 5-CH_3 . IR (DMSO) : υ_{max} = 2240 cm^{-1} (-CN). MS (FAB^-) : calc. for (M-H)$^-$ 279.1093, found 279.1069.

1-[2',3'-dideoxy-3'(R)-3'-C-cyano-2'(R)-2'-methylamino-β-D-glycero-pentofuranosyl]thymine (10b). Yield 86 %. ^{1}H-NMR (CD_3OD) : 7.79 (q, 1H) H-6; 5.90 (d, $J_{1',2'}$ = 4.4 Hz, 1H) H-1'; 4.39 (m, $J_{3',4'}$ = 2.4 Hz, $J_{4',5'}$ = 7.3 Hz, $J_{4',5''}$ = 2.7 Hz, 1H) H-4'; 3.93 (dd, $J_{5',5''}$ = 12.5 Hz, 1H) H-5"; 3.80 (m, 1H) H-3'; 3.64 (m, 1H) H-2'; 3.60 (dd, 1H) H-5'; 2.51 (s, 3H) NCH_3 ; 1.87 (d, J = 1.2 Hz, 3H) 5-CH_3 ; ^{13}C-NMR (CD_3OD) : 118.2 (s) -CN ; 90.4 (d, J_{CH} = 168.5 Hz) C-1'; 83.5 (d, J_{CH} = 157.3 Hz) C-4'; 66.7 (d, J_{CH} = 148.3 Hz) C-2'; 62.3 (t, J_{CH} = 142.7 Hz) C-5'; 35.4 (q) NCH_3 ; 35.1 (d, J_{CH} = 147.2 Hz) C-3'; 12.7 (q) 5-CH_3 ; IR (CH_3OH) : υ_{max} = 2240 cm^{-1} (-CN). MS (FAB^-) : calc. for (M-H)$^-$ 279.1093, found 279.1110.

1-[2',3'-dideoxy-3'(S)-3'-cyano-C-2'(R)-2'-benzylamino-β-D-glycero-pentofuranosyl]thymine (9c) Yield 83 % . ^{1}H-NMR (DMSO-d_6) : 7.69 (s, 1H) H-6 ; 7.35 (s, 5H) arom. ; 5.98 (d, $J_{1',2'}$ = 7.1 Hz, 1H) H-1'; 4.43 (m, 1H) H-4'; 3.92-3.54 (m, 8H) 5-OH, $NHCH_2$Ph, H-2', H-3', H-5', H-5" ; 1.84 (s, 3H) 5-CH_3 . ^{13}C-NMR (DMSO-d_6) : 119.1 (s) -CN ; 86.7 (d, J_{CH} = 169.0 Hz) C-1'; 76.5 (d, J_{CH} = 157.3 Hz) C-4'; 64.1 (d, J_{CH} = 149.0 Hz) C-2'; 61.8 (t, J_{CH} = 141.0 Hz) C-5'; 50.2 (t) NCH_2 ; 35.6 (d, J_{CH} = 143.2 Hz) C-3'; 12.3 (q) 5-CH_3. IR (DMSO) : υ_{max} = 2240 cm^{-1}(-CN). MS (FAB^-) : calc. for (M-H)$^-$ 335.1407, found 335.1435.

1-[2',3'-dideoxy-3'(R)-3'-cyano-2'(R)-2'-benzylamino-β-D-glycero-pentofuranosyl]thymine (10c) Yield 85 %. ^{1}H-NMR ($CDCl_3$) : 7.28 (s, 5H) arom. ; 7.13 (s, 1H) H-6 ; 5.57 (d, $J_{1',2'}$ = 5.3 Hz, 1H) H-1'; 4.50 (dt, $J_{3',4'}$ = 6.1 Hz, $J_{4',5'}$ = 2.0 Hz, $J_{4',5''}$ = 1.8 Hz, 1H) H-4'; 4.01 (dd, 1H) H-5'; 3.94 (s, 2H) NCH_2Ph ; 3.79 (m, 3H) H-2', 5-OH, $NHCH_2$Ph ; 3.76 (m, 1H) H-3'; 3.60 (dd, 1H) H-5" ; 1.85 (d, J =1.2 Hz, 3H) 5-CH_3 . ^{13}C-NMR ($CDCl_3$) : 116.7 (s) -CN ; 92.2 (d, J_{CH} = 166.2 Hz) C-1'; 81.4 (d, J_{CH} = 146.1 Hz) C-4'; 61.8 (d, J_{CH} = 146.0 Hz) C-2'; 61.8 (t, J_{CH} = 143.2 Hz) C-5'; 51.9 (t) NCH_2 ; 34.2 (d, J_{CH} = 142.6 Hz) C-3'; 12.3 (q)5-CH_3 . IR ($CHCl_3$) : υ_{max} = 2240 cm^{-1} (-CN). MS (FAB^-) : calc. for (M-H)$^-$ 335.1407, found 335.1418.

1-[2',3'-dideoxy-3'(S)-3'-C-cyano-2'(R)-2'-(1-pyrrolidino)-β-D-glycero-pentofuranosyl]thymine (9d) Yield 89 %. ^{1}H-NMR ($CDCl_3$+CD_3OD) : 7.68 (d, J = 1.2 Hz, 1H) H-6 ; 6.11 (d, $J_{1',2'}$ = 6.6 Hz, 1H) H-1'; 4.34 (m, $J_{3',4'}$ = 7.7 Hz, $J_{4',5'}$ = 3.7 Hz, 1H) H-4'; 3.93 (d, 2H) H-5', H-5" ; 3.54 (m, 2H) H-2', H-3'; 2.71 (br, 4H) NCH_2 ; 1.95 (d, 3H) 5-CH_3 ; 1.81 (br, 4H) NCH_2CH_2- . ^{13}C-NMR ($CDCl_3$+CD_3OD) : 118.1 (s) -CN ; 86.2 (d, J_{CH} = 168.5 Hz) C-1'; 77.0 (d, J_{CH} = 152.4 Hz) C-4'; 70.4 (d, J_{CH} = 144.2 Hz) C-2'; 61.7 (t, J_{CH} = 143.2 Hz) C-5'; 51.4 (q)NCH2 ; 34.4 (d, J_{CH} = 142.7 Hz) C-3'; 23.0 (t) NCH_2CH_2-; 12.0 (q) 5-CH_3 . IR ($CHCl_3$+CH_3OH): υ_{max} = 2240 cm^{-1} (-CN). MS(FAB^-) : calc. for (M-H)$^-$ 319.1407, found 319.1422.

1-[2',3'-dideoxy-3'(S)-3'-C-cyano-2'(R)-2'-(1-piperidino)-β-D-glycero-pentofuranosyl]thymine (9e) Yield 80 %. ^{1}H-NMR ($CDCl_3$+CD_3OD) : 7.70 (d, J = 1.2 Hz, 1H) H-6; 6.13 (d, $J_{1',2'}$ = 7.6 Hz, 1H) H-1'; 4.26 (m, $J_{3',4'}$ = 6.8 Hz, $J_{4',5'}$ = 3.9 Hz, 1H) H-4'; 3.90 (d, 2H) H-5', H-5" ; 3.70 (m, $J_{2',3'}$ = 5.6 Hz, 1H) H-2';

3.64 (m, 1H) H-3′; 2.65 (br, 4H) NCH_2- ; 1.94 (s, 3H) 5-CH_3 ; 1.54 (br, 6H) $NCH_2\underline{CH_2CH_2}$- ; ^{13}C-NMR ($CDCl_3$+$CD_3OD$) : 118.1 (s) -CN ; 85.8 (d, J_{CH} = 165.1 Hz) C-1′; 76.4 (d, J_{CH} = 154.0 Hz) C-4′; 70.5 (d, J_{CH} = 143.8 Hz) C-2′; 61.6 (t, J_{CH} = 142.1 Hz) C-5′; 50.6 (t) NCH_2 ; 29.6 (d, J_{CH} = 139.3 Hz) C-3′; 25.3, 23.5 (t) $NCH_2\underline{CH_2CH_2}$-; 11.7 (q) 5-$CH_3$; IR ($CHCl_3$+CH_3OH) : υ_{max} = 2240 cm^{-1} (-CN). MS (FAB$^-$) : calc. for (M-H)$^-$ 333.1563, found 333.1600 .

1-[2′,3′-dideoxy-3′(S)-3′-C-cyano-2′(R)-2′-(4-morpholino)-β-D-glycero-pentofuranosyl]thymine (9f) Yield 74 %. ^{1}H-NMR ($CDCl_3$+CD_3OD) : 7.68 (q, J = 1.2 Hz, 1H) H-6 ; 6.04 (d, $J_{1',2'}$ = 7.2 Hz, 1H) H-1′; 4.21 (m, 1H) H-4′; 3.84 (d, 2H) H-5′, H-5" ; 3.62 (m, 6H) OCH_2, H-2′, H-3′; 2.65 (m, 4H) NCH_2-; 1.87 (d, 3H) 5-CH_3 . ^{13}C-NMR ($CDCl_3$+CD_3OD) : 117.9 (s)-CN ; 82.6 (d, J_{CH} = 162.8 Hz) C-1′; 76.5 (d, J_{CH} = 152.3 Hz) C-4′; 71.8 (d, J_{CH} = 148.6 Hz) C-2′; 66.3 (t) OCH_2-; 61.7 (t, J_{CH} = 143.8 Hz) C-5′; 49.7 (t) NCH_2 ; 29.8 (d, J_{CH} = 140.4 Hz) C-3′; 11.8 (q) 5-CH_3 . IR ($CHCl_3$+CH_3OH) : υ_{max} = 2240 cm^{-1} (-CN). MS (FAB$^-$) : calc. for (M-H)$^-$ 335.1356, found 335.1400.

1-[2′,3′-dideoxy-3′(S)-3′-C-cyano-2′(S)-2′-C-(dimethylmalonate)-β-D-glycero-pentofuranosyl] thymine (9g) Yield 81 %. ^{1}H-NMR ($CDCl_3$) : 7.59 (d, J = 1.2 Hz, 1H) H-6 ; 6.10 (d, $J_{1',2'}$ = 8.0 Hz, 1H) H-1′; 4.44 (m, 1H) H-4′; 4.01 (m, 2H) H-5′, H-5" ; 3.95-3.75 (m, 3H) H-3′, $\underline{CH}(CO_2CH_3)$; 5-OH ; 3.80 and 3.75 (2 x s, 6H) 2 x -OCH_3 ; 3.31 (m, 1H) H-2′; 1.95 (d, 3H) 5-CH_3 . ^{13}C-NMR ($CDCl_3$) : 166:9 (s) C=O ; 117.6 (s) -CN ; 86.1 (d, J_{CH} = 167.4 Hz) C-1′; 77.3 (d, J_{CH} = 158.8 Hz) C-4′; 62.5 (t, J_{CH} = 144.4 Hz)C-5′; 53.2 (q) OCH_3 ; 49.9 (d, J_{CH} = 132.5 Hz) $CHCO_2R$; 47.3 (d, J_{CH} = 140.4 Hz) C-2′; 33.4 (d, J_{CH} = 148.3 Hz) C-3′; 12.5 (q) 5-CH_3 . IR ($CHCl_3$) : υ_{max} = 2242 cm^{-1} (-CN). MS (FAB$^-$) : calc. for (M-H)$^-$ 380.1094, found 380.1110.

1-[2′,3′-dideoxy-3′(S)-3′-C-cyano-2′(S)-2′-C-nitromethyl-β-D-glycero-pentofuranosyl]thymine (9h) Yield 88 %. ^{1}H-NMR (DMSO-d_6) : 7.72 (d, 1H) H-6 ; 5.97 (d, $J_{1',2'}$ = 8.0 Hz) H-1′; 5.31 (br, 1H) 5′-OH ; 4.94 (dd, 2H) CH_2NO_2 ; 4.32 (m, 1H) H-4′; 3.83 (m, 1H) H-3′; 3.74 (d, 2H) H-5′, H-5" ; 3.30 (m, 1H) H-2′; 1.80 (d, J = 1.2 Hz, 3H) 5-CH_3 . ^{13}C-NMR (DMSO-d_6) : 118.0 (s) -CN ; 84.7 (d, J_{CH} = 169.7 Hz) C-1′; 77.0 (d, J_{CH} = 152.8 Hz) C-4′; 73.6 (t, J_{CH} = 150.5 Hz) CH_2NO_2 ; 61.6 (t, J_{CH} = 142.7 Hz) C-5′; 44.7 (d, J_{CH} = 144.9 Hz) C-2′; 33.5 (d, J_{CH} = 146.0 Hz) C-3′; 12.4 (q) 5-CH_3. IR (DMSO) : υ_{max} = 2242 cm^{-1} (-CN). MS (FAB$^-$) : calc. for (M-H)$^-$ 309.0835, found 309.0802 .

1-[2′,3′-dideoxy-3′(R)-3′-C-cyano-2′(S)-2′-C-nitromethyl-β-D-glycero-pentofuranosyl]thymine (10h). Yield 76 %. ^{1}H-NMR ($CDCl_3$+CD_3OD) : 7.70 (q, J = 1.2 Hz, 1H) H-6 ; 6.05 (d, $J_{1',2'}$ = 7.5 Hz, 1H) H-1′; 4.91 (2 x d, 2H) CH_2NO_2 ; 4.47 (dt, $J_{3',4'}$ = 5.1 Hz, $J_{4',5'}$ = 2.5 Hz, $J_{4',5"}$ = 2.2 Hz, 1H) H-4′; 3.98 (dd, $J_{5',5"}$ = 12.4 Hz, 1H) H-5′; 3.90 (m, 1H) H-3 ; 3.76 (dd, 1H) H-5"; 3.47 (m, 1H) H-2′; 1.92 (d, 3H) 5-CH_3 . ^{13}C-NMR ($CDCl_3$+CD_3OD) : 116.3 (s) -CN ; 85.9 (d, J_{CH} = 162.9 Hz) C-1′; 81.5 (d, J_{CH} = 152.7 Hz) C-4′; 71.8 (t) CH_2NO_2 ; 61.2 (t, J_{CH} = 143.2) C-5′; 43.0 (d, J_{CH} = 142.7 Hz) C-2′; 32.7 (d, J_{CH} = 147.2 Hz) C-3′; 11.7 (q) 5-CH_3 . IR ($CHCl_3$+CH_3OH) : υ_{max} 2242 cm^{-1} (-CN) . MS (FAB$^-$) : calc. for (M-H)$^-$ 309.0835, found 309.0792 .

Acknowledgement

Authors thank Swedish Board for Technical Development and Swedish Natural Science Research Council for generous financial supports, Anders Sandström for mass spectral data and Ingegärd Schiller for secretarial assistance.

References

1. R. Pauwels, M. Baba, J. Balzarini, P. Herdewign, J. Desmyter, M.J. Robins, R. Zon, D. Madej and E. de Clereq. *Biochem. Pharm.*, **37**, 1317 (1988).
2. R. Dagani. *Chem.& Eng. News*, **20**, 41 (1987).
3. C.-H. Kim, V.E. Marquez, S. Broder, H. Mitsuya and J.S. Driscoll. *J. Med. Chem.*, **30**, 862 (1987).
4. B. Öberg & R. Datema, Astra Läkemedel AB, Sweden, (Personal Comm.)
5. July 10, 1987 Federal Register advertisement (USA).
6. G.W. Fleet, J.C. Son and A.E. Derome. *Tetrahedron*, **44**, 625 (1988).
7. A. Calvo-Mateo, M.-J. Camarasa, A. Diaz-Ortiz and F.G. De Las Heras. *Tetrahedron Lett.*, **29**, 941 (1988).
8. A. Calvo-Mateo, M.-J. Camarasa, A. Diaz-Ortiz and F.G. De Las Heras. *Tetrahedron*, **44**, 4895 (1988).
9. M. Okabe, R.-C. Sun, S. Y.-K. Tam, L.J. Todaro and D.L. Coffen. *J. Org. Chem.*, **53**, 4780 (1988).
10. F. Hansske and M.J. Robins. *Tetrahedron Lett.*, **24**, 1589 (1983).
11. T.R. Webb. *Tetrahedron Lett.*, **29**, 3769 (1988).
12. (a) J.-C. Wu, H. Bazin and J. Chattopadhyaya. *Tetrahedron*, **43**, 2355 (1987).
    (b) O. Dahlman, P.-J. Garegg, H. Mayer and S. Schramek. *Acta Chem. Scand.*, **B40**, 15 (1986).
13. F.Z. Basha, J.F. DeBernardis and S. Spanton. *J. Org. Chem.*, **50**, 4160 (1985); A. Alexakis, J. Berlan and Y. Besace. *Tetrahedron Lett.*, **27**, 1047 (1986); R.A. Holton, A.D. Williams and R.M. Kennedy. *J. Org. Chem.*, 51, 5480 (1986); and references therein.
14. J.-C. Wu, T. Pathak, W. Tong, J.-M. Vial, G. Remaud and J. Chattopadhyaya. *Tetrahedron*, (in press, 1988).
15. F. Hansske, D. Madej and M.J. Robins. *Tetrahedron*, **40**, 125 (1984).
16. F. Hansske and M.J. Robins. *J. Am. Chem. Soc.*, **105**, 6736 (1983).
17. T. Ueda, S. Satoshi and I. Hideo. *Nucleosides and Nucleotides*, **3**, 173 (1984); H. Usui and T. Ueda. *Chem. Pharm. bull.*, **34**, 1518 (1986) and references therein; T. Sano, S. Shuto, H. Inone and T. Ueda. *Chem Pharm. Bull.*, **33**, 3617 (1985) and references therein; T. Ueda, S. Satoshi, M. Satoh and I. Hideo. *Nucleosides and Nucleotides*, **4**, 401 (1985) and references therein.
18. A Matsuda, K. Takenuki, H. Itoh, T. Sasaki and T. Ueda. *Chem. Pharm. Bull.*, **35**, 3967 (1987); A Matsuda, H. Itoh, K. Takenuki, T. Sasaki and T. Ueda. *Chem. Pharm. Bull.*, **36**, 945 (1988).
19. F.A.A.M. de Leeuw and C. Altona. *J. Comp. Chem.*, **4**, 428 (1983); Quantum Chemistry Programme Exchange No 463;

20. C.A.G. Haasnoot, F.A.A.M. de Leeuw and C. Altona. *Org. Magn. Res.*, **15**, 43 (1981);
21. E. Westhof, H. Plach. I Cuno, H.-D. Ludemann. *Nucl. Acids. Res.*, **4**, 939 (1977);
22. L.H. Koole, H.M. Buck, H. Bazin and J. Chattopadhyaya. *Tetrahedron*, **43**, 2989 (1987);
23. L.H. Koole, H.M. Buck, A. Nyilas and J. Chattopadhyaya. *Can. J. Chem.*, **65**, 2089 (1987);
24. C.A.G. Hassnoot, F.A.A.M. de Leeuw, H.P.M. de Leeuw and C. Altona. *Recl. Trav. Chim. Pays-Bas.*, **98**, 576 (1979);
25. L.H. Koole, H.-M. Moody, H.M. Buck, A. Grouiller, H. Essadiq, J.-M. Vial and J. Chattopadhyaya. *Recueil des trav. Chim. pays-bas.*, **107**, 343 (1988);
26. J.-M. Vial, L.H. Koole and J. Chattopadhyaya. *Acta Chem. Scand., Ser. B*, (in press, 1988).
27. L. Vrang, H. Bazin, G. Remaud, J. Chattopadhyaya and B. Öberg. *Antiviral Res.*, **7**, 139 (1987);
28. H. Bazin, J. Chattopadhyaya, R. Datema, A.-C. Ericson, G. Gilljam, N.G. Johansson, J. Hansen, R. Koshida, K. Moelling, B. Öberg, G. Remaud, G. Stening, L. Vrang, B. Wahren and J.-C. Wu. *Pharm. Biochem.*, (in press, 1988);
29. C.S.M. Olsthhoorn, L.J. Bostelaar, J.H. van Boom and C. Altona. *Eur. J. Chem.*, **112**, 95 (1980).