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New Synthesis of 2', 3'-Dideoxy-2', 3'-Didehydro-3'-C-Substituted Thymidines

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Abstract: The Michael addition reaction of phenylthiolate anion with 2',3'-dideoxy-2',3'-didehydro-3'-nitro-thymidine 1 and subsequent Henry reaction at C-3' with various electron deficient reagents as formaldehyde, methylvinyl ketone and acrylonitrile has produced various diastereomeric mixtures of 1-(2,3-dideoxy-3-C-substituted-2-thiophenyl-3-nitro-β-D-pentofuranosyl)thymines 4 - 12 [α-substitution (major), β-substitution (minor)] in 29-82% yield. The stereochemistry of products formed in this reaction clearly indicates that the carbanion generated at C3' of diastereomeric 2/3 (1.3 · 1 ratio, ^{1}H-NMR) preferentially attacks the electron-deficient reagent from the α-face of the pentofuranose ring. Subsequently, the 3'-nitro and 2'-phenylthio groups from 4, 5, 8 and 11 were eliminated upon treatment with Bu_3SnH and AIBN to afford 2',3'-dideoxy-2',3'-didehydro-3'-C-substituted thymidines 13 - 18 in 79-85% yield The results detailed in this paper represent the first examples of a facile synthesis of 2',3'-dideoxy-2',3'-didehydro-3'-C-branched thymidines using a three-step procedure. (1) Michael addition of the phenylthiolate to nitro-olefin, (2) Henry reaction with electron-deficient reagents, and (3) subsequently, free-radical induced elimination of phenylthio and nitro groups

Several 2',3'-dideoxy-3'-substituted nucleosides have been found to date which are effective inhibitors of HIV-reverse transcriptase. Amongst these nucleoside derivatives, 3'-azidothymidine (AZT), 2',3'-dideoxyinosine (ddI) and 2',3'-dideoxycytidine (ddC) are available today for the treatment of AIDS as FDA approved drug. Several examples of unsaturated nucleosides, such as 2',3'-didehydro-2',3'-dideoxycytidine (d_4C) and its thymidine analogue (d_4T), have also been shown to exhibit promising in-vitro activity against HIV-reverse transcriptase.[1-3] A number of different methods have been developed for the synthesis of d_4C, d_4T, d_4U, d_4A and d_4G, and they can be classified under the following categories basing on the types of reactions used for their synthesis: (a) radical treatment of 2',3'-bis-xanthates[4] or 2',3'-bis-sulphone[6] or reductive elimination of 2',3'-halo acetates[5,9], (b) ring-opening of the 2,3'-O-anhydro-nucleosides by NaH[7], (c) ring-opening of the 3',5'-O-anhydro-nucleosides by NaH[7] or KOtBu[8], (d) treatment of 2',3'-cyclic thiocarbonates with triethyl phosphite[4,9] at elevated temperature, and (e) oxidation of 3'-phenylselenyl thymidine with m-choloroperbenzoic acid[10]. It should therefore be apparent that the design of efficient route for the synthesis of 2',3'-substituted-2',3'-dideoxy-2',3'-didehydro-nucleosides is important for the structure-activity studies against HIV-reverse transcriptase In this connection, we have developed several new methods for the synthesis of various 2',3'-substituted-2',3'-dideoxy-2',3'-didehydro-nucleosides based on both Michael type addition reactions[11-17] on 2',3'-double bond of nucleosides and also by the use of free-radical chemistry[18-20]. Other workers have also designed new synthesis of 2'- or 3'-substituted-2',3'-dideoxy-2',3'-didehydro-nucleosides

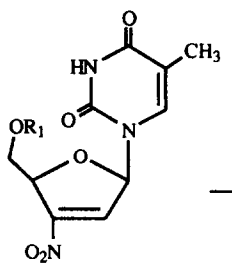
including 2'-C-substitution[21-28], 3'-C-substitution[23-31], 2'-halo-substitution[27,28,32], 3'-halo-substitution[27,28,33], 2'-thio-substitution[6], 2'-O-alkyl substitution[32,34,35] and 3'-O-alkyl substitution [35].

The results described herein constitute the first report of the synthesis of 2',3'-dideoxy-2',3'-didehydro-3'-C-substituted-thymidines **13** - **18** from 2',3'-dideoxy-2',3'-didehydro-3'-nitro-thymidine **1**. This has been demonstrated from the Michael addition reaction[11-17,41,42] of the phenylthiolate anion with **1** to give diastereomeric mixture of 2',3'-dideoxy-2'-thiophenyl-3'-nitro-thymidines **2** and **3** in 78 % yield, Subsequently, Henry reaction[36-42] with various electron deficient reagents as formaldehyde, methyl vinyl ketone or acrylonitrile gave various diastereomeric mixtures of 1-(2,3-dideoxy-3-C-substituted-2-thiophenyl-3-nitro-β-D-pentofuranosyl)thymines **4** - **12** [α-substitution (major); β-substitution (minor)] in 29-82 % yield. The radical treatment of these 3-C-substituted-2-phenylthio nucleosides with tributyltin hydride[41,42] subsequently gave the corresponding 2',3'-dideoxy-2',3'-didehydro-3'-C-substituted thymidine **13** - **18** in 79-85 % yield.

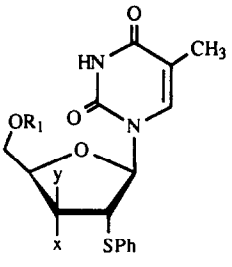
Preparation of 1-(2,3-dideoxy-2-thiophenyl-3-nitro-β–D-ribofuranosyl)thymine (2) and 1-(2,3-dideoxy-2-thiophenyl-3-nitro-β–D-xylofuranosyl)thymine (3): 2',3'-Dideoxy-2',3'-didehydro-3'-nitro-thymidine **1** was synthesised by our literature procedure[15]. Treatment of **1** with thiophenol (4 equiv) in the presence of 1,1,3,3-tetramethylguanidine (2 equiv) in acetonitrile at room temperature for 30 min gave an inseparable diastereomeric mixture of **2** *(ribo)* and **3** *(xylo)* in a 1.3 : 1 ratio (^{1}H-NMR) in a total yield of 78 %. Clearly, compounds **2** and **3** were formed due to the attack of the phenylthiolate ion at the C2' center of the 3'-nitro-olefin **1** exclusively from the α-face, which is consistent with the other examples of Michael addition reactions in which the nucleophile preferentially attacks from the less hindered α-face of the 2',3'-double bond in a sugar moiety[11-17]. The following trends of chemical shifts and coupling constants were observed in the ^{1}H-NMR spectra of **2** and **3**. (1) The H-1' was more deshielded (0.16 ppm) in **2** than in the isomer **3**. (2) The $J_{1',2'}$ of **3** was smaller (3.8 Hz) than that of its epimer **2**. (3) The two 5'-methylene protons of **2** were more separated (0.31 ppm), compared to those of **3** (0.10 ppm) These trends are in accordance with our previous work describing the Michael addition reaction of nitrogen, carbon and oxygen nucleophiles with 2',3'-dideoxy-2',3'-didehydro-3'-nitro thymidine[15] which unambiguously suggest the *ribo* configuration in the case of **2**, and the *xylo* configuration for **3**.

Reaction of 1 or 2 + 3 with formaldehyde, acrylonitrile, and methyl vinyl ketone : Treatment of a mixture of the diastereomeric 5'-O-(4-monomethoxytrityl)-2',3'-dideoxy-2'-thiophenyl-3'-nitro-thymidine **2** and **3** with 35 % aqueous formaldehyde in acetonitrile and in the presence of 1,1,3,3-tetramethylguanidine (2 equiv) for 30 min at room temperature gave a mixture of diastereomers which were separated by silica gel column chromatography to afford pure 3'-(R)-hydroxymethyl-3'-nitro-2'-(R)-thiophenyl-thymidine **4** (18 %) and 3'-(S)-hydroxymethyl-3'-nitro-2'-(R)-thiophenyl-thymidine **5** (64 %). Compounds **4** & **5** were also prepared in a one-pot-two-step reaction from **1** [**1** → (**2** + **3**) → (**4** + **5**)]. Accordingly, treatment of **1** with thiophenol (4 equiv) and 35 % aqueous formaldehyde in the presence of 1,1,3,3-tetramethylguanidine (2 equiv) in acetonitrile gave a mixture of two compounds which were separated on silica gel column chromatography to give pure **4** (12 %) and **5** (66 %). The completion of this one-pot-two-step reaction took ~2 h at room temperature. The proton NMR chemical shifts of H-2', H-4', H5'/5" and *3'-CH_2*-OH were remarkably different in both **4** and **5** [for **4**: δ4.04 (H-2'), δ4.77 (H-4'), δ3.78 and δ3.58 (H5'/5"), δ4.38 and δ4.12 (*3'-CH_2*-OH), and for **5**: δ4.71 (H-2'), δ4.49 (H-4'), δ3.54 and δ3.40 (H5'/5"), δ4.29 (*3'-CH_2*-OH)] (see the experimental part for the detailed ^{1}H- and ^{13}C-NMR). Treatment of the diastereomeric mixture of **2** and **3** with acrylonitrile in THF in the presence of tetrabutylammonium fluoride (0.2 equiv) for 10 min gave 2'-(R)-thiophenyl-3'-(S)-(β-cyanoethyl)-3'-nitro-

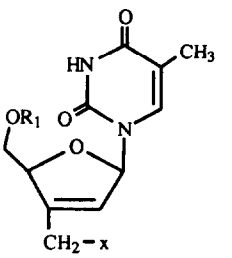
thymidine **8** (66 %) as the major product (minor product was not isolable). Similarly, the reaction of the diastereomeric mixture of **2** and **3** with methyl vinyl ketone for 20 min gave the diastereomeric mixture of 2'-(R)-thiophenyl-3'-(R)-(3-oxobutyl)-3'-nitro-thymidine **10** [δ4.02 (H-2')] and 2'-(R)-thiophenyl-3'-(S)-(3-oxobutyl)-3'-nitro-thymidine **11** [δ4.73 (H-2')] and 3'-nitro-olefin **1**[15] in a 1 : 17: 5 ratio (^{1}H-NMR). From this mixture, pure **11** was isolated in 29 % yield. The formation of 3'-nitro-olefin **1** in the latter reaction clearly originated from the competing base catalyzed elimination of 2'-phenylthio group in the starting **2** and **3**. It is also clear from the results of the above reactions that the incipient carbanion preferentially attacks the electron-



1: R_1 = MMTr



2. R_1 = MMTr, x = NO_2, y = H
3. R_1 = MMTr, x = H, y = NO_2
4. R_1 = MMTr, x = NO_2, y = CH_2OH
5 R_1 = MMTr, x = CH_2OH, y = NO_2
6. R_1 = H, x = NO_2, y = CH_2OH
7. R_1 = H, x = CH_2OH, y = NO_2
8 R_1 = MMTr, x = CH_2CH_2CN, y = NO_2
9 R_1 = H, x = CH_2CH_2CN, y = NO_2
10. R_1 = MMTr, x = NO_2, y = $CH_2CH_2COCH_3$
11 R_1 = MMTr, x = $CH_2CH_2COCH_3$, y =NO_2
12 R_1 = H, x = $CH_2CH_2COCH_3$, y = NO_2



13: R_1 = MMTr, x = OH
14. R_1 = H, x = OH
15: R_1 = MMTr, x = CH_2CN
16 R_1 = H, x = CH_2CN
17: R_1 = MMTr, x = CH_2COCH_3
18 R_1 = H, x = CH_2COCH_3

deficient reagents from the α-face of the pentofuranose ring [**4** / **5** = 1 · 4; **10** / **11** = 1 : 17; *vide infra* for NMR arguments for the unequivocal assignment of the configuration at C3']. These results are consistent with our earlier results of Michael addition reactions of the 2',3'-enenitrile[11], 2',3'-enesulfone[12] and 2',3'-eneselenone[13-14] and derivatives of nucleosides with various carbon or nitrogen nucleophiles in which it has been shown that 2',3'-trans-substituted nucleosides are by far the major products formed. Subsequently, the 5'-O-MMTr group from **4**, **5**, **8** and **11** was removed by a brief treatment of 80% aqueous acetic acid at RT to give **6** (88 %), **7** (83 %), **9** (86 %) and **12** (83 %), respectively

Assignment of configurations in compounds 4 - 12 . The following trends of chemical shifts were observed in the ^{1}H-NMR spectra of **4** - **12**: (1) The H-2' was more shielded (0.39 - 0.71 ppm) in the case of **4**, **6** and **10** in comparison with their respective epimers **5**, **7** and **11**. (2) The H-4' in epimers **4** and **6** was more deshielded (0.28 - 0.31 ppm) than in their corresponding epimers **5** and **7**. (3) The difference in chemical shift of H-5' and H-5" in the case of **4**, **6** and **10** was larger (0.20 - 0 42 ppm) in comparison with those in their counterparts **5**, **7** and **11** (0.00 - 0.14 ppm). Above spectroscopic characteristics clearly suggested two distinctly different trends of chemical shifts for the pair of 3'-epimers with C-substituent at the β-face (*i.e.* **4**, **6** and **10**) or at the α-face (*i e.* **5**, **7**, **8**, **9**, **11** and **12**). These spectroscopic results are also consistent with our previous work on 2',3'-dideoxy-3'-nitro-thymidine that the electron-deficient reagent preferentially react from the α-face of the

pentofuranose ring[40].

Radical promoted elimination of 2'-phenylthio and 3'-nitro groups in 2',3'-disubstituted nucleosides. The free-radical promoted elimination[41,42] of the tertiary 3'-nitro and 2'-phenylthio groups from **4**, **5**, **8** and **11** were performed in the following manner. Treatment of **4** with tributyltin hydride (3 equiv) and α, α'-azobisisobutyronitrile (AIBN) (1 equiv) in dry toluene at 100 °C for 30 min gave 2',3'-dideoxy-2',3'-didehydro-3'-C-hydroxymethyl-thymidine **13** which was isolated in 83 % yield upon purification by column chromatography. Similarly, the 2'-phenylthio and 3'-nitro groups from pure diastereomeric **5** was eliminated to give pure **13** (85 %). We have also performed the radical-promoted elimination reaction on the mixture of diastereomeric **4** + **5** to give exclusively **13** in 78% yield. The reaction of **8** under the above radical reaction condition gave 2',3'-dideoxy-2',3'-didehydro-3'-C-(β-cyanoethyl)-thymidine **15** (82 %). In the similar manner, **11** was converted to 2',3'-dideoxy-2',3'-didehydro-3'-C-(3-oxobutyl)-thymidine **17** (79 %). Subsequently, the 5'-O-MMTr group from **13**, **15** and **17** was removed by a brief treatment of 80% aqueous acetic acid at RT to give **14** (86 %), **16** (87 %) and **18** (83 %), respectively. The present method thus provides a facile synthetic route for the preparation of 2',3'-dideoxy-2',3'-didehydro-3'-C-branched thymidines using a simple three-step procedure: (1) Michael addition of the phenylthiolate to nitro-olefin, (2) Henry reaction with electron-deficient reagents, and (3) subsequently, free-radical induced elimination of phenylthio and nitro groups. We believe that the straightforward synthetic route described above should be useful for the preparation of various other analogous 2',3'-vinyl- C-substituted nucleosides.

EXPERIMENTALS

^{1}H-NMR spectra were recorded (in δ scale) with Jeol GX-270 at 270 MHz using TMS as internal reference (0.00 ppm). ^{13}C-NMR were recorded at 67.8 MHz using both ^{1}H-coupled and ^{1}H-decoupled or INEPT modes. UV absorption spectra were recorded with Varian-Cary 2200 instrument. Jeol DX 303 instrument was used for recording mass spectra. TLC was carried out using Merck pre-coated silica gel F_{254} plates. Column chromatography was carried out using Merck G60 silica gel using mixtures dichloromethane and methanol for gradient elution.

1-[5-O-(MMTr)-2,3-dideoxy-2-thiophenyl-3-nitro-β-D-ribofuranosyl]thymine (2) & 1-[5-O-(MMTr)-2,3-dideoxy-2-thiophenyl-3-nitro-β-D-xylofuranosyl]thymine (3). To a solution of **1** (1.08 g, 2.0 mmol) and thiophenol (800 µl, 8 mmol) in acetonitrile (20 ml) was added 1,1,3,3-tetramethylguanidine (460 mg, 4 mmol), and kept it standing at RT for 30 min. The reaction mixture was poured in saturated aqueous solution of NH_4Cl (150 ml) and was extracted with CH_2Cl_2 (3 x 75 ml). The organic phase was washed with water (2 x 50 ml) and dried over $MgSO_4$. All volatiles were removed and the residue was purified by a silica gel column to give isomeric mixture **2** and **3** (1.02 g, 78 %) in 1.3 : 1 ratio (^{1}H-NMR). Compound **2**: ^{1}H-NMR ($CDCl_3$): 8.00 (br, 1H) NH; 7.47-7.13 (m, 18H) arom, H-6; 6.88-6.79 (m, 2H) arom; 6.55 (d, $J_{1'2'}$ = 9.7 Hz, 1H) H-1'; 5.24 (dd, 1H) H-3'; 4.64 (ddd, $J_{3'4'}$ = 4.8 Hz, 1H) H-4'; 4.14 (dd, $J_{2'3'}$ = 7.1 Hz, 1H) H-2'; 3.80 (s, 3H) OMe; 3.69 (dd, $J_{4'5'}$ = 2.7 Hz, $J_{5'5''}$ = 11.0 Hz, 1H) H-5'; 3.38 (dd, $J_{4'5''}$ = 2.2 Hz, 1H) H-5''; 1.29 (d, $J_{6,CH3}$ = 1.1 Hz, 3H) 5-CH_3. Compound **3**: ^{1}H-NMR ($CDCl_3$): 7.82 (br, 1H) NH; 7.47-7.13 (m, 18H) arom, H-6; 6.88-6.79 (m, 2H) arom; 6.39 (d, $J_{1'2'}$ = 5.9 Hz, 1H) H-1'; 5.27 (dd, 1H) H-3'; 4.82 (dd, $J_{2'3'}$ = 6.3 Hz, 1H) H-2'; 4.37 (ddd, $J_{3'4'}$ = 7.5 Hz, 1H) H-4'; 3.80 (s, 3H) OMe; 3.62 (dd, $J_{4'5'}$ = 4.0 Hz, $J_{5'5''}$ = 10.9 Hz, 1H) H-5'; 3.52 (dd, $J_{4'5''}$ = 3.9 Hz, 1H) H-5''; 1.76 (d, $J_{6,CH3}$ = 1.2 Hz, 3H) 5-CH_3.

1-[5-O-(MMTr)-2,3-dideoxy-2-(R)-thiophenyl-3-(R)-hydroxymethyl-3-nitro-β-D-pentofuranosyl]thymine (4) & 1-[5-O-(MMTr)-2,3-dideoxy-2-(R)-thiophenyl-3-(S)-hydroxymethyl-3-nitro-β-D-pentofuranosyl] thymine (5). *Method A:* To a solution of **1** (540 mg, 1 mmol), thiophenol (400 µl, 4 mmol) and 35 % aqueous formaldehyde (1 ml) in acetonitrile (10 ml) was added 1,1,3,3-tetramethylguanidine (230 mg, 4 mmol), and kept it standing at RT for 2 h. The reaction mixture was poured in saturated aqueous solution of NH_4Cl (100

ml) and was extracted with CH_2Cl_2 (3 x 50 ml). The organic phase was washed with water (2 x 40 ml), dried over $MgSO_4$. All volatiles were removed and the residue was purified by a silica gel column to give **4** (81 mg, 12 %) & **5** (448 mg, 66 %).

Method B: To a solution of mixture of **2** and **3** (325 mg, 0.5 mmol) and 35 % aqueous formaldehyde (0.5 ml) in acetonitrile (5 ml) was added 1,1,3,3-tetramethylguanidine (115 mg, 1 mmol), and kept it standing at RT for 30 min. The reaction mixture was poured in saturated aqueous solution of NH_4Cl (75 ml) and was extracted with CH_2Cl_2 (3 x 40 ml). The organic phase was washed with water (2 x 30 ml), dried over $MgSO_4$. All volatiles were removed and the residue was purified by a silica gel column to give **4** (62 mg, 18 %) & **5** (216 mg, 64 %).

Compound **4**: ^{1}H-NMR ($CDCl_3$): 8.04 (br, 1H) NH; 7.48-7.19 (m, 18H) arom, H-6; 6.86-6.83 (m, 2H) arom; 6.41 (d, $J_{1'2'}$ = 9.5 Hz, 1H) H-1'; 4.77 (dd, 1H) H-4'; 4.38 (dd, $J_{Ha,OH}$ = 5.7 Hz, $J_{Ha,Hb}$ = 12.8 Hz, 1H) 3'-CH_a; 4.12 (dd, $J_{Hb,OH}$ = 7.8 Hz, 1H) 3'-CH_b; 4.04 (d, 1H) H-2'; 3.81 (s, 3H) OMe; 3.78 (dd, $J_{4'5'}$ = 4.2 Hz, $J_{5'5''}$ = 11.3 Hz, 1H) H-5'; 3.58 (dd, $J_{4'5''}$ = 1.9 Hz, 1H) H-5''; 2.47 (dd, 1H) OH; 1.15 (d, $J_{6,CH3}$ = 1.1 Hz, 3H) 5-CH_3; ^{13}C-NMR ($CDCl_3$): 111.9 (s) C-5; 99.2 (s) C-3'; 88.4 (d, J_{CH} = 173.1 Hz) C-1'; 87.7 (s) MMTr; 81.8 (d, J_{CH} = 152.6 Hz) C-4'; 62.3 (t, J_{CH} = 145.8 Hz) 3'-CH_2OH; 61.4 (t, J_{CH} = 148.2 Hz) C-5'; 55.3 (d, J_{CH} = 142.8 Hz) C-2'; 55.2 (q, J_{CH} = 144.1 Hz) OMe; 11.1 (q, J_{CH} = 127.2 Hz) 5-CH_3. Compound **5**: ^{1}H-NMR ($CDCl_3$): 8.69 (br, 1H) NH; 7.53-7.16 (m, 18 H) arom, H-6; 6.83-6.80 (m, 2H) arom; 6.41 (d, $J_{1'2'}$ = 9.5 Hz, 1H) H-1'; 4.71 (d, 1H) H-2'; 4.49 (dd, 1H) H-4'; 4.29 (m, 2H) 3'-CH_2; 3.79 (s, 3H) OMe; 3.54 (dd, $J_{4'5'}$ = 3.6 Hz, $J_{5'5''}$ = 11.0 Hz, 1H) H-5'; 3.40 (dd, $J_{4'5''}$ = 2.7 Hz, 1H) H-5''; 1.22 (d, $J_{6,CH3}$ = 1.1 Hz, 3H) 5-CH_3; ^{13}C-NMR ($CDCl_3$): 112.2 (s) C-5; 94.2 (s) C-3'; 87.9 (s) MMTr; 86.1 (d, J_{CH} = 176 0 Hz) C-1'; 79.4 (d, J_{CH} = 154 9 Hz) C-4'; 64.8 (t, J_{CH} = 148.0 Hz) 3'-CH_2OH; 62.3 (t, J_{CH} = 145.7 Hz) C-5'; 58.2 (d, J_{CH} = 143.0 Hz) C-2'; 55.1 (q, J_{CH} = 143.9 Hz) OMe; 11.2 (q, J_{CH} = 128.9 Hz) 5-CH_3.

1-[2,3-Dideoxy-2-(R)-thiophenyl-3-(R)-hydroxymethyl-3-nitro-β-D-pentofuranosyl]thymine (6). *General procedure for the removal of 5'-O-(4-monomethoxytrityl) group.* **4** (68 mg, 0.1 mmol) was treated with 80 % aqueous acetic acid (2.5 ml) overnight at RT. The solvent was removed in vacuo and coevaporated with toluene and ethanol. The residue was purified by a silica gel column to give **6** (36 mg, 88 %). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.39-7.25 (m, 6 H) arom, H-6; 6.01 (d, $J_{1'2'}$ = 9.4 Hz, 1H) H-1'; 4.75 (dd, 1H) H-4'; 4.51 (d, $J_{Ha,Hb}$ = 12.7 Hz, 1H) 3'-CH_a; 4.34 (d, 1H) H-2'; 4.26 (d, 1H) 3'-CH_b; 4.06 (dd, $J_{4'5'}$ = 1.7 Hz, $J_{5'5''}$ = 12.7 Hz, 1H) H-5'; 3.96 (dd, $J_{4'5''}$ = 3.2 Hz, 1H) H-5''; 1.78 (d, $J_{6,CH3}$ = 1.2 Hz, 3H) 5-CH_3; ^{13}C-NMR ($CDCl_3$): 137.3 (d) C-6; 111.4 (s) C-5; 99.7 (s) C-3'; 91.4 (d, J_{CH} = 171.2 Hz) C-1'; 83.5 (d, J_{CH} = 154.5 Hz) C-4'; 61.1 (t, J_{CH} = 144.8 Hz) C-5'; 60.3 (t, J_{CH} = 148.2 Hz) 3'-CH_2OH; 52 6 (d, J_{CH} = 144.8 Hz) C-2'; 11.9 (q, J_{CH} = 134.0 Hz) 5-CH_3. UV (EtOH): λ_{max} 264 nm (ε = 8910) (pH 7); 260 nm (ε = 9060) (pH 2); 267 nm (ε = 25810) (pH 12). MS (FAB^-): cal. for $(M-H)^-$ 408.0865 found 408.0865.

1-[2,3-Dideoxy-2-(R)-thiophenyl-3-(S)-hydroxymethyl-3-nitro-β-D-pentofuranosyl]thymine (7). 5 (136 mg, 0.2 mmol) gave **7** (68 mg, 83 %) using a condition described for **6**. ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.47-7.22 (m, 6H) arom, H-6; 6.23 (d, $J_{1'2'}$ = 9.4 Hz, 1H) H-1'; 4.73 (d, 1H) H-2'; 4.44 (t, $J_{4'5'}$ = 3.3 Hz, 1H) H-4'; 4.27 (m, 2H) 3'-CH_a, 3'-CH_b; 3.83 (d, 2H) H-5', H-5''; 1.72 (d, $J_{6,CH3}$ = 1.1 Hz, 3H) 5-CH_3; ^{13}C-NMR ($CDCl_3$ + CD_3OD): 135.2 (d, J_{CH} = 181.9 Hz) C-6; 111.5 (s) C-5; 94.3 (s) C-3'; 88.0 (d, J_{CH} = 171.2 Hz) C-1'; 80.9 (d, J_{CH} = 155.5 Hz) C-4'; 64.0 (t, J_{CH} = 147.7 Hz) 3'-CH_2OH; 61.0 (t, J_{CH} = 144.3 Hz) C-5'; 57.4 (d, J_{CH} = 144.8 Hz) C-2'; 11.7 (q, J_{CH} = 130.7 Hz) 5-CH_3. UV (EtOH): λ_{max} 264 nm (ε = 7530) (pH 7); 260 nm (ε = 7860) (pH 2); 264 nm (ε = 19640) (pH 12). MS (FAB^-): cal. for $(M-SPh)^-$ 300.0832, found 300.0853.

1-[5-O-(MMTr)-2,3-dideoxy-2-(R)-thiophenyl-3-(S)-(β-cyanoethyl)-3-nitro-β-D-pentofuranosyl]thymine (8). *Method C:* To a cooled solution (0 °C) of mixture of **2** and **3** (326 mg, 0.5 mmol) and acrylonitrile (65 µl, 1 mmol) in THF (5 ml) was added tetrabutyl ammonium fluoride (26 mg, 0.1 mmol), and kept it standing at RT for 10 min. The reaction mixture was poured in saturated aqueous solution of NH_4Cl (25 ml) and was extracted with CH_2Cl_2 (3 x 50 ml). The organic phase was washed with water (2 x 40 ml), dried over $MgSO_4$. All volatiles were removed and the residue was purified by a silica gel column to give **8** (232 mg, 66 %). ^{1}H-NMR ($CDCl_3$): 8.10 (br, 1H) NH; 7.49-7 12 (m, 18H) arom, H-6; 6.85-6.82 (m, 2H) arom; 6.23 (d, $J_{1'2'}$ = 9.2 Hz, 1H) H-1'; 4.66 (d, 1H) H-2'; 4.08 (t, $J_{4'5'}$ = 3.8 Hz, 1H) H-4'; 3.81 (s, 3H) OMe; 3.47 (d, 2H) H-5', H-5''; 2.85-2.40 (m, 4H) 3'-$\underline{CH_2}$, $\underline{CH_2}$CN; 1.37 (d, $J_{6,CH3}$ = 1.2 Hz, 3H) 5-CH_3; ^{13}C-NMR ($CDCl_3$): 112.3 (s) C-5; 94.0 (s) C-3'; 88.2 (d, J_{CH} = 174.1 Hz) C-1'; 86.4 (s) MMTr; 81.9 (d, J_{CH} = 152 1 Hz) C-4'; 62.1 (t, J_{CH} = 145.3 Hz) C5'; 58.7 (d, J_{CH} = 145.7 Hz) C-2', 55 2 (q, J_{CH} = 143.9 Hz) OMe; 31.1 (t, J_{CH} = 135.2 Hz) 3'-CH_2; 13 1 (t, J_{CH} = 138.8 Hz) $\underline{C}H_2$CN; 11.6 (q, J_{CH} = 129.2 Hz) 5-CH_3

1-[2,3-Dideoxy-2-(R)-thiophenyl-3-(S)-(β-cyanoethyl)-3-nitro-β-D-pentofuranosyl]thymine (9). 8 (141 mg, 0.2 mmol) gave **9** (74 mg, 86 %) using a condition described for **6** ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.72-7,27 (m,

5H) arom; 7.18 (d, $J_{6,CH3}$ = 1.2 Hz, 1H) H-6; 6.17 (d, $J_{1'2'}$ = 9.0 Hz, 1H) H-1'; 4.71 (d, 1H) H-2'; 4.22 (dd, 1H) H-4'; 3.87 (dd, $J_{4'5'}$ = 4.2 Hz, $J_{5'5''}$ = 11.9 Hz, 1H) H-5', 3.80 (dd, $J_{4'5''}$ = 4.2 Hz, 1H) H-5"; 2.95-2.60 (m, 4H) 3'-$\underline{CH_2}$, $\underline{CH_2}$CN; 1.77 (d, 3H) 5-CH_3; ^{13}C-NMR ($CDCl_3$ + CD_3OD): 134.1 (d, J_{CH} = 179.6 Hz) C-6; 112.2 (s) C-5; 94.3 (s) C-3'; 87.3 (d, J_{CH} = 164.1 Hz) C-1'; 82.4 (d, J_{CH} = 151.2 Hz) C-4'; 60.9 (t, J_{CH} = 144.3 Hz) C5'; 58.5 (d, J_{CH} = 145.7 Hz) C-2'; 30.8 (t, J_{CH} = 133.8 Hz) 3'-CH_2; 13.0 (t, J_{CH} = 135.7 Hz) $\underline{C}H_2$CN; 12.2 (q, J_{CH} = 129.5 Hz) 5-CH_3. UV (EtOH): λ_{max} 265 nm (ε = 9140) (pH 7); 259 nm (ε = 10600) (pH 2); 243 nm (ε = 13200) (pH 12). MS (FAB$^-$): cal. for (M-SPh)$^-$ 323.0992, found 323.0988.

1-[5-O-(MMTr)-2,3-dideoxy-2-(R)-thiophenyl-3-(R)-(3-oxobutyl)-3-nitro-β-D-pentofuranosyl]thymine (10) & 1-[5-O-(MMTr)-2,3-dideoxy-2-(R)-thiophenyl-3-(S)-(3-oxobutyl)-3-nitro-β-D-pentofuranosyl] thymine (11). Mixture of the **2** and **3** (326 mg, 0.5 mmol) gave a mixture of **10, 11** and **1** in 1 : 17 : 5 ratio (^{1}H-NMR) using a condition described for **8** [methylvinyl ketone (80 µl, 1.0 mmol)] (*Method C*). Diasteremerically pure **11** was isolated (106 mg, 29 %) by preparative TLC [40% EtOAc-hexane (bp 40-60°)]. Compound **10**: ^{1}H-NMR ($CDCl_3$): 8.13 (br, 1H) NH; 7.67-7.14 (m, 18H) arom, H-6; 6.84-6.81 (m, 2H) arom; 6.54 (d, $J_{1'2'}$ = 8.1 Hz, 1H) H-1'; 4.02 (d, 1H) H-2'; 3.80 (s, 3H) OMe; 3.71 (dd, $J_{4'5'}$ = 2.6 Hz, $J_{5'5''}$ = 10.9 Hz, 1H) H-5'; 3.29 (dd, $J_{4'5''}$ = 4.0 Hz, 1H) H-5"; 2.86- 2.42 (m, 4H) 3'-$\underline{CH_2}$, $\underline{CH_2}COCH_3$; 2.13 (s, 3H) $COCH_3$; 1.05 (d, $J_{6,CH3}$ = 1.2 Hz, 3H) 5-CH_3. Compound **11**: ^{1}H-NMR ($CDCl_3$): 8.13 (br, 1H) NH; 7.67-7.14 (m, 18H) arom, H-6; 6.84-6.81 (m, 2H) arom; 6.29 (d, $J_{1'2'}$ = 9.0 Hz, 1H) H-1'; 4.73 (d, 1H) H-2'; 4.11 (dd, 1H) H-4'; 3.80 (s, 3H) OMe; 3.51 (dd, $J_{4'5'}$ = 3.2 Hz, $J_{5'5''}$ = 11.1 Hz, 1H) H-5'; 3.40 (dd, $J_{4'5''}$ = 3.1 Hz, 1H) H-5"; 2.86- 2.42 (m, 4H) 3'-$\underline{CH_2}$, $\underline{CH_2}COCH_3$; 2.13 (s, 3H) $COCH_3$; 1.21 (d, $J_{6,CH3}$ = 1.0 Hz, 3H) 5-CH_3; ^{13}C-NMR ($CDCl_3$): 111.8 (s) C-5; 94.5 (s) C-3'; 88.0 (d, J_{CH} = 173.2 Hz) C-1'; 86.9 (s) MMTr; 82.7 (d, J_{CH} = 151.2 Hz) C-4'; 62.4 (t, J_{CH} = 145.3 Hz) C5'; 58.4 (d, J_{CH} = 142.1 Hz) C-2'; 55.1 (q, J_{CH} = 143.9 Hz) OMe; 38 1 (t, J_{CH} = 126.0 Hz) $\underline{C}H_2CO$; 29.8 (q) $COCH_3$; 29.6 (t) 3'-CH_2; 11.4 (q, J_{CH} = 129.8 Hz) 5-CH_3.

1-[2,3-Dideoxy-2-(R)-thiophenyl-3-(S)-(3-oxobutyl)-3-nitro-β-D-pentofuranosyl]thymine (12). **11** (144 mg, 0.2 mmol) gave **12** (68 mg, 82 %) using a condition described for **6**. ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.45-7.22 (m, 6 H) arom, H-6; 6.13 (d, $J_{1'2'}$ = 8.9 Hz, 1H) H-1'; 4.82 (d, 1H) H-2'; 4.13 (t, $J_{4'5'}$ = 3.3 Hz, 1H) H-4'; 3.83 (d, 2H) H-5', H-5"; 2.99- 2.49 (m, 4H) 3'-$\underline{CH_2}$, $\underline{CH_2}COCH_3$; 2.19 (s, 3H) $COCH_3$; 1.75 (d, $J_{6,CH3}$ = 1.0 Hz, 3H) 5-CH_3; ^{13}C-NMR ($CDCl_3$ + CD_3OD) : 134.9 (d, J_{CH} = 181.4 Hz) C-6; 111.1 (s) C-5; 94.7 (s) C-3'; 88.8 (d, J_{CH} = 177.8 Hz) C-1'; 83.6 (d, J_{CH} = 156.7 Hz) C-4'; 61.5 (t) C5'; 57.4 (d, J_{CH} = 148.5 Hz) C-2'; 38.0 (t, J_{CH} = 126.5 Hz) $\underline{C}H_2CO$; 29.8 (q) $COCH_3$; 29.0 (t, J_{CH} = 133.3 Hz) 3'-CH_2; 12.2 (q, J_{CH} = 129.4 Hz) 5-CH_3. UV (EtOH): λ_{max} 266 nm (ε = 9890) (pH 7); 258 nm (ε = 11010) (pH 2); 245 nm (ε = 13490) (pH 12). MS (FAB$^-$): cal. for (M-SPh)$^-$ 340.1145, found 340.1159.

1-[5-O-(MMTr)-2,3-dideoxy-2,3-dehydro-3-C-hydroxymethyl-β-D-pentofuranosyl]thymine (13). *General procedure for free-radical elimination of 2'-phenylthio and 3'-nitro group*: A mixture of **5** (170 mg, 0.25 mmol), Bu_3SnH (200 µl, 0.75 mmol) and AIBN (40 mg, 0.25 mmol) in toluene (10 ml) was heated at 100 °C for 30 min. The solvent was removed in vacuo and the residue was purified by a silica gel column to give **13** (112 mg, 85 %). ^{1}H-NMR ($CDCl_3$): 8.23 (br, 1H) NH; 7.57 (q, $J_{6,CH3}$ = 1.1 Hz, 1H) H-6; 7.38-7.23 (m, 12H) arom; 7.04 (m, $J_{1'4'}$ = 3.7 Hz, $J_{1'2'}$ = 1 4 Hz, 1H) H-1'; 6 85-6 82 (m, 2H) arom; 5.82 (m, $J_{2'4'}$ = 1.7 Hz, 1H) H-2'; 4.88 (m, 1H) H-4'; 4.26 (m, 2H) 3'-$\underline{CH_2}$OH; 3.79 (s, 3H) OMe; 3.59 (dd, $J_{4'5'}$ = 2.9 Hz, $J_{5'5''}$ = 10.9 Hz, 1H) H-5'; 3.28 (dd, $J_{4'5''}$ = 3.1 Hz, 1H) H-5"; 2.03 dd, 1H) OH; 1.18 (d, 3H) 5-CH_3; ^{13}C-NMR ($CDCl_3$): 148.5 (s) C-3'; 120.5 (d, J_{CH} = 175 1 Hz) C-2'; 111.2 (s) C-5, 88.5 (d, J_{CH} = 170.5 Hz) C-1'; 86.8 (s) MMTr; 84.7 (d, J_{CH} = 148.5 Hz) C-4'; 63.6 (t, J_{CH} = 143.4 Hz) C-5'; 58.3 (t, J $_{CH}$ = 141.2 Hz) 3'-CH_2OH; 55.1 (q, J_{CH} = 143.9 Hz) OMe; 10.9 (q, J_{CH} = 129.5 Hz) 5-CH_3.

1-[2,3-Dideoxy-2,3-didehydro-3-C-hydroxymethyl-β-D-pentofuranosyl]thymine (14). **13** (105 mg, 0.2 mmol) gave **14** (44 mg, 86 %) using a condition described for **6**. ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.73 (q, $J_{6,CH3}$ = 1.2 Hz, 1H) H-6; 6.92 (m, $J_{1'4'}$ = 3.3 Hz, $J_{1'2'}$ = 2.2 Hz, 1H) H-1'; 5.73 (m, $J_{2'4'}$ = 2.1 Hz, 1H) H-2'; 4.81 (m, 1H) H-4'; 4.32 (m, 2H) 3'-$\underline{CH_2}$OH, 3.83 (d, $J_{4'5'}$ = 2.6 Hz, 2H) H-5', H-5"; 1.86 (d, 3H) 5-CH_3; ^{13}C-NMR ($CDCl_3$ + CD_3OD): 147.8 (s) C-3'; 137.1 (d, J_{CH} = 181.5 Hz) C-6; 120.9 (d, J_{CH} = 175.0 Hz) C-2', 110.2 (s) C-5; 88.5 (d, J_{CH} = 171.4 Hz) C-1'; 86.6 (d, J_{CH} = 155 8 Hz) C-4'; 61.8 (t, J_{CH} = 142 5 Hz) C-5'; 57.2 (t, J $_{CH}$ = 142.5 Hz) 3'-CH_2OH; 11.6 (q, J_{CH} = 128.9 Hz) 5-CH_3. UV (EtOH): λ_{max} 267 nm (ε = 10130) (pH 7); 265 nm (ε = 10020) (pH 2), 264 nm (ε = 8600) (pH 12). MS (FAB$^-$): cal for (M-H)$^-$ 253.0825, found 253.0827.

1-[5-O-(MMTr)-2,3-dideoxy-2,3-didehydro-3-C-(β-cyanoethyl)-β-D-pentofuranosyl]thymine (15). **8** (177

mg, 0.25 mmol) gave **15** (113 mg, 82 %) using a condition described for **13**. ^{1}H-NMR ($CDCl_3$): 8.20 (br, 1H) NH; 7.68 (q, $J_{6,CH3}$ = 1.2 Hz, 1H) H-6; 7.38-7.22 (m, 12H) arom; 7.05 (m, $J_{1'4'}$ = 3.8 Hz, $J_{1'2'}$ = 1.4 Hz, 1H) H-1'; 6.86-6.83 (m, 2H) arom; 5.76 (m, $J_{2'4'}$ = 1.8 Hz, 1H) H-2'; 4.79 (m, 1H) H-4'; 3.80 (s, 3H) OMe; 3.69 (dd, $J_{4'5'}$ = 2.2 Hz, $J_{5'5''}$ = 11.0 Hz, 1H) H-5'; 3.20 (dd, $J_{4'5''}$ = 2.7 Hz, 1H) H-5", 2 63-2 57 (m, 2H) $\underline{CH_2}$CN; 2.49-2.25 (m, 2H) 3'-$\underline{CH_2}$; 1.14 (d, 3H) 5-CH_3; ^{13}C-NMR ($CDCl_3$): 143.2 (s) C-3'; 121.6 (d, J_{CH} = 172.3 Hz) C-2'; 111.4 (s) C-5; 88.6 (d, J_{CH} = 170.5 Hz) C-1'; 86 8 (s) MMTr; 86.0 (d, J_{CH} = 148.5 Hz) C-4'; 62.9 (t, J_{CH} = 143.4 Hz) C-5'; 55.1 (q, J_{CH} = 143 9 Hz) OMe; 22.8 (t, J_{CH} = 131.5 Hz) 3'-CH_2, 15.5 (t, J_{CH} = 134.3 Hz) $\underline{C}H_2$CN; 10.9 (q, J_{CH} = 129.5 Hz) 5-CH_3

1-[2,3-Dideoxy-2,3-didehydro-3-$\underline{C}$-(β-cyanoethyl)-β-D-pentofuranosyl]thymine (16). 15 (110 mg, 0.2 mmol) gave **16** (48 mg, 87 %) using a condition described for **6**. ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.61 (q, $J_{6,CH3}$ = 1.2 Hz, 1H) H-6; 6.95 (m, $J_{1'4'}$ = 3.8 Hz, $J_{1'2'}$ = 1.4 Hz, 1H) H-1'; 5.67 (m, $J_{2'4'}$ = 1.8 Hz, 1H) H-2'; 4.76 (m, 1H) H-4'; 3.93 (dd, $J_{4'5'}$ = 2.9 Hz, $J_{5'5''}$ = 12.5 Hz, 1H) H-5'; 3.79 (dd, $J_{4'5''}$ = 2.4 Hz, 1H) H-5"; 2.74-2.69 (m, 2H) $\underline{CH_2}$CN; 2.65-2.40 (m, 2H) 3'-$\underline{CH_2}$; 1.87 (d, 3H) 5-CH_3; ^{13}C-NMR ($CDCl_3$ + CD_3OD): 144.7 (s) C-3'; 136.8 (d, J_{CH} = 175.0 Hz) C-6; 121 6 (d, J_{CH} = 171.4 Hz) C-2'; 110.7 (s) C-5; 88.9 (d, J_{CH} = 170.4 Hz) C-1'; 87.5 (d, J_{CH} = 154.9 Hz) C-4', 61.5 (t, J_{CH} = 142.5 Hz) C-5'; 22.9 (t, J_{CH} = 129.6 Hz) 3'-CH_2; 15.7 (t, J_{CH} = 137.4 Hz) $\underline{C}H_2$CN; 12.1 (q, J_{CH} = 129.2 Hz) 5-CH_3. UV (EtOH): λ_{max} 267 nm (ε = 8940) (pH 7), 266 nm (ε = 8840) (pH 2); 262 nm (ε = 6450) (pH 12). MS (FAB$^-$): cal. for (M-H)$^-$ 276.0984, found 276 1000.

1-[5-O-(MMTr)-2,3-dideoxy-2,3-didehydro-3-$\underline{C}$-(3-oxobutyl)-β-D-pentofuranosyl]thymine (17). 11 (180 mg, 0.25 mmol) gave **17** (112 mg, 79 %) using a condition described for **13**. ^{1}H-NMR ($CDCl_3$): 8.27 (br, 1H) NH; 7.67 (q, $J_{6,CH3}$ = 1.2 Hz, 1H) H-6; 7.40-7.22 (m, 12H) arom; 6 97 (m, $J_{1'4'}$ = 3.8 Hz, $J_{1'2'}$ = 1.4 Hz, 1H) H-1'; 6.84-6.81 (m, 2H) arom; 5.48 (m, $J_{2'4'}$ = 1.8 Hz, 1H) H-2'; 4.76 (m, 1H) H-4'; 3.79 (s, 3H) OMe; 3.65 (dd, $J_{4'5'}$ = 2.0 Hz, $J_{5'5''}$ = 10.9 Hz, 1H) H-5', 3.22 (dd, $J_{4'5''}$ = 2.9 Hz, 1H) H-5"; 2.68 (m, 2H) $\underline{CH_2}COCH_3$; 2.44-2.22 (m, 2H) 3'-$\underline{CH_2}$; 2.14 (s, 3H) $COCH_3$; 1.09 (d, 3H) 5-CH_3; ^{13}C-NMR ($CDCl_3$): 147.6 (s) C-3'; 119.7 (d, J_{CH} = 172.3 Hz) C-2'; 111 1 (s) C-5; 88 6 (d, J_{CH} = 179 7 Hz) C-1', 86.6 (s) MMTr; 86.6 (d, J_{CH} = 158.5 Hz) C-4'; 63.1 (t, J_{CH} = 143.5 Hz) C5', 55.1 (q, J_{CH} = 143.9 Hz) OMe; 41.0 (t, J_{CH} = 125.7 Hz) CH_2CO, 29.7 (q, J_{CH} = 127.4 Hz) $CO\underline{C}H_3$; 20.6 (t, J_{CH} = 127 9 Hz) 3'-CH_2; 10.9 (q, J_{CH} = 129.8 Hz) 5-CH_3.

1-[2,3-Dideoxy-2,3-didehydro-3-$\underline{C}$-(3-oxobutyl)-β-D-pentofuranosyl]thymine (18). 17 (113 mg, 0.2 mmol) gave **18** (49 mg, 83 %) using a condition described for **6**. ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.68 (q, $J_{6,CH3}$ = 1.2 Hz, 1H) H-6, 6.88 (m, $J_{1'4'}$ = 3.8 Hz, $J_{1'2'}$ = 1 4 Hz, 1H) H-1'; 5 40 (m, $J_{2'4'}$ = 1.8 Hz, 1H) H-2'; 4.70 (m, 1H) H-4'; 3.87 (d, $J_{4'5'}$ = 2.2 Hz, 2H) H-5', H-5"; 2.80 (m, 2H) $\underline{CH_2}COCH_3$; 2.55-2.33 (m, 2H) 3'-$\underline{CH_2}$; 2.22 (s, 3H) $COCH_3$; 1.87 (d, 3H) 5-CH_3; ^{13}C-NMR ($CDCl_3$ + CD_3OD)· 147.0 (s) C-3'; 137.1 (d, J_{CH} = 180.5 Hz) C-6; 119.4 (d, J_{CH} = 173 2 Hz) C-2'; 110.3 (s) C-5; 88.8 (d, J_{CH} = 171 4 Hz) C-1'; 86.6 (d, J_{CH} = 146.6 Hz) C-4'; 61.4 (t, J_{CH} = 142.5 Hz) C5', 40.7 (t, J_{CH} = 125.6 Hz) $\underline{C}H_2CO$; 29 7 (q, J_{CH} = 127.7 Hz) $CO\underline{C}H_3$; 20.3 (t, J_{CH} = 127.8 Hz) 3'-CH_2, 11.9 (q, J_{CH} = 128.9 Hz) 5-CH_3 UV (EtOH). λ_{max} 267 nm (ε = 9710) (pH 7); 266 nm (ε = 9710) (pH 2); 264 nm (ε = 8830) (pH 12) MS (FAB$^-$): cal for (M-H)$^-$ 293.1137, found 293.1154.

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REFERENCES

1. Lin, T. S.; Prusoff, W. H., Schinazi, R. F. *Biochem Pharm.* **1987**, *36*, 2713-2718.
2. De Clercq, E. *Adv Drug Res.* **1988**, *17*, 1.
3. De Clercq, E.; Aerschot, A. V., Herdewijn, P.; Baba, M.; Pauwels, R.; Balzarini, J. *Nucleosides & Nucleotides* **1989**, *8*, 659-671.
4. Chu, C. K.; Bhadti, V. S.; Doboszewski, B.; Gu, Z. P.; Kosugi, Y.; Pullaiah, K. C.; Roey, P. V. *J. Org. Chem.* **1989**, *54*, 2217-2225.
5. Dorland, E.; Serafinowski, P *Synthesis* **1992**, 477-481
6. Johnson, R., Joshi, B V ; Neidle, S , Reese, C. B.; Snook, C. F. *Tetrahedron Lett.* **1992**, *33*, 8151-8154.

7. Joshi, B. V.; Rao, T. S.; Reese, C. B. *J. Chem. Soc. Perkin Trans 1* **1992**, 2537-2544.
8. Mansuri, M. M.; Starrett, J. E. Jr.; Ghazzouli, I.; Hitchcock, M. J. M.; Sterzycki, R. Z.; Brankovan, V.; Lin, T-S.; August. E. M.; Prusoff, W. H.; Sommadossi. J-P.; Martin, J. C. *J. Med. Chem.* **1989**, *32*, 461-466.
9. Mansuri, M. M.; Starrett, J. E. Jr.; Wos, J. A.; Tortolani, D. R.; Brodfuehrer, P. R.; Howell, H. G.; Martin, J. C. *J. Org. Chem.* **1989**, *54*, 4780-4785.
10. Vial, J.-M.; Agback, P.; Chattopadhyaya, J. *Nucleosides & Nucleotides* **1990**, *9*, 245-258.
11. Wu, J. C.; Chattopadhyaya, J. *Tetrahedron* **1989**, *45*, 855-862.
12. Wu, J. C.; Pathak, T.; Tong, W.; Vial, J-M.; Remaud, G.; Chattopadhyaya, J. *Tetrahedron* **1988**, *44*, 6705-6722.
13. Wu, J. C.; Chattopadhyaya, J. *Tetrahedron* **1989**, *45*, 4507-4522.
14. Tong, W.; Xi, Z.; Gioeli, C.; Chattopadhyaya, J.*Tetrahedron* **1991**, *47*, 3431-3450.
15. Hossain, N.; Papchikhin, A.; Garg, N.; Fedrov, I.; Chattopadhyaya, J. *Nucleosides & Nucleotides* (in press).
16. Tong, W.; Wu, J. C.; Sandström, A.; Chattopadhyaya, J. *Tetrahedron* **1990**, *46*, 3037-3060.
17. Wu, J. C.; Chattopadhyaya, J. *Tetrahedron* **1990**, *46*, 2587-2592.
18. Wu, J. C.; Xi, Z.; Gioeli, C.; Chattopadhyaya, J. *Tetrahedron* **1991**, *47*, 2237-2254.
19. Xi, Z.; Agback, P.; Sandström, A.; Chattopadhyaya, J. *Tetrahedron* **1991**, *47*, 9675-9690.
20. Xi, Z.; Agback, P.; Palvec, J.; Sandström, A.; Chattopadhyaya, J. *Tetrahedron* **1992**, *48*, 349-370.
21. Samano, V.; Robins, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 4007-4008.
22. Hassan, A. A. A.; Matsuda, A. *Hetrocycles* **1992**, *34*, 657-661.
23. Samano, V.; Robins, M. J. *Can. J. Chem* . **1993**, *71*, 186-191.
24. Ioannidis, P.; Söderman, P.; Samuelsson, B.; Classon, B. *Tetrahedron Lett.* **1993**, *34*, 2993-2994.
25. Czernecki, S.; Ezzitouni, A. *Tetrahedron Lett.* **1993**, *34*, 315-318.
26. Matsuda, A.; Okajima, H.; Masuda, A.; Kakefuda, A.; Yoshimura, Y.; Ueda, T. *Nucleosides and Nucleotides* **1992**, *11*, 197-226.
27. Haraguchi, K.; Itoh, Y.; Tanaka, H.; Akita, M.; Miyasaka, T. *Tetrahedron* **1993**, *49*, 1371-1390.
28. Haraguchi, K.; Itoh, Y.; Tanaka, H.; Miyasaka, T. *Tetrahedron Lett.* **1991**, *32*, 3391-3394.
29. Czernecki, S.; Ezzitouni, A.; Krausz, P. *Synthesis* **1990**, 651-653.
30. Matsuda, A.; Okajima, H.; Ueda, T. *Hetrocycles* **1989**, *29*, 25-29.
31. Ashwell, M.; Jones, A. S.; Walker, R.T. *Nucleic Acid* Research **1987**, *15*, 2157-2166.
32. Calvo-Mateo, A.; Camarasa, M.-J.; Dfaz-Ortfz, A.; Heras, F. G. De las. *Tetrahedron* **1988**,*44*, 4895-4903.
33. Aerschot, A. V.; Herdewijn, P.; Balzarini, J.; Pauwels, R.; De Clercq, E. *J Med. Chem.* **1989**, *32*, 1743-1749.
34. Haraguchi, K.; Tanaka, H.; Itoh, Y.; Miyasaka, T. *Tetrahedron Lett* **1991**, *32*, 777-780.
35. Haraguchi, K.; Tanaka, H.; Maeda, H.; Itoh, Y.; Saito, S.; Miyasaka, T. *J. Org. Chem.* **1991**, *56*, 5401-5408.
36. Henry, L. *C. R. Hebd. Seance Acad. Sci.* **1895**, *120*, 1265.
37. Seebach, D.; Beck, A. K.; Mukhopadhyay, T.; Thomas, E. *Helv. Chim. Acta.* **1982**, *65*, 1101- 1133.
38. Aebischer, B.; Bieri, J. H.; Prewo, R.; Vasella, A. *Helv. Chim Acta.* **1982**, *65*, 2251- 2272.
39. Baumberger, F.; Vasella, A. *Helv Chim. Acta.* **1983**, *66*, 2210- 2222.
40. Garg, N.; Palvec, J.; Chattopadhyaya, J. *Tetrahedron* **1993**,*49*, 5189-5202.
41. Motherwell, W. B.; Crich, D. Free Radical Chain Reaction in Organic Synthesis; Academic Press: London. **1992**; pp.144.
42. Ono, N.; Kamimura, A.; Kaji, A. *Tetrahedron Lett.* **1984**, *25*, 5319-5322.