Pergamon

Tetrahedron Vol. 50, No. 46, pp. 13251-13260, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00840-X

Reactions of 2',3'-Di-O-mesyl-*lyxo*-uridine with Secondary Amines: First Report on the One-Pot Conversion of Mesylated Nucleosides to Enaminonucleosides and the Crystal Structure of α-Enamine#.

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Abstract: 2',3'-Di-O-mesyl-5'-O-trityl-*lyxo*-uridine **1** reacted with secondary amines to produce enaminonucleosides **2a-d** and **3a-d**. Intermediacy of 2'-ketouridine was essential for the anomerisation and enamine formation to take place. The structure of the β-enamine was established unambiguously by analysing the hydrolysed product and that of α-enamine was proved with the help of crystal structure analysis.

INTRODUCTION

Since the discovery of the anti-HIV activities of AZT[1], various attempts have been made to devise newer methods to functionalise the 2'- and 3'-sites of the nucleosides[2]. Among them, the functionalisation of the double bond of the 2'-enenucleosides was found to be the most difficult and least useful method because of the unusual inert nature of these double bonds; at least six different reagents which are supposed to react with double bonds failed to react with 2'-enenucleosides[3]. Phenyl sulphenyl chloride, the only reagent which reacted with the 2'-ene-adenosine[4], also reacted with 2'-ene-uridine but led to the formation of 2,2'-O-anhydro-3'-deoxy-3'-alkylthiol uridine through the formation of the episulphonium intermediates[3]. The problem, however, was circumvented by making use of the electron deficient double bonds which were used as Michael acceptors[5]. The synthesis and use of electron-rich double bond such as enamines in nuccleoside chemistry, on the other hand, is an area which is studied least-the only reported enamine nucleoside so far, was synthesised from 5'-aldehydo derivative[6].

We have reported[7] recently that 2',3'-di-O-mesyl-5'-O-trityluridine on reaction with secondary amines produced *iso*cytidine derivatives, 1-(2,3-O-anhydro-5-O-trityl-β-D-*lyxo*furanosyl)-2-dialkylamino-4- pyrimidones, *via* the formation of 2,2'-O-anhydro-3'-O-mesyl-5'-O-trityluridine. Although the procedure gave access to hitherto unknown *iso*cytidine derivatives, the starting material was not particularly useful for the functionalisation of the sugar moiety as the first step, especially in the presence of basic reagents like amines, was always the 2,2'-O-anhydro ring formation. We, therefore, reasoned that a study on the reactions between amines and 1-(2, 3-di-O-mesyl-5-O-trityl- β-D-*lyxo*furanosyl)uracil **1** (ref. 8) would give new insight into the area of the functionalisation of the nucleosides, as unlike in the case of the *ribo*- derivative, compound **1** would

not undergo any intramolecular cyclisation. As a result of that study, we report herein, that compound **1** on reaction with secondary amines undergoes a hitherto unknown "one-pot-multistep" conversion to generate a new class of 1-(2,3-dideoxy-2-N-dialkylamino-5-O-trityl-**D**-glycero-pent-2-enofuranosyl)uracil **2a-d** and **3a-d**.

RESULTS AND DISCUSSION

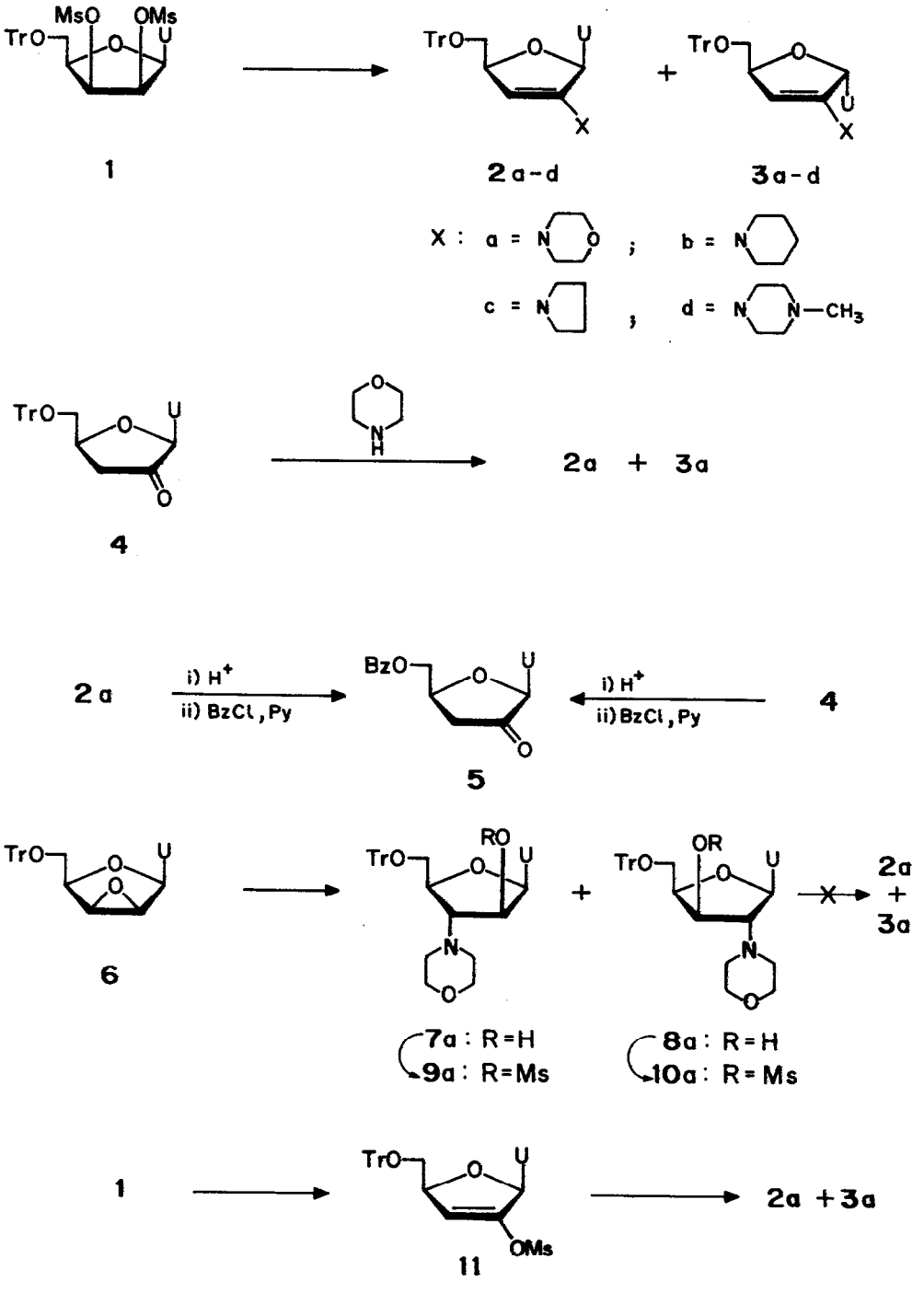
In a typical procedure, compound **1** was treated with neat morpholine at reflux temperature for 12h. The amine was removed under reduced pressure and the oily residue was purified by column chromatography to produce an anomeric mixture of isomers **2a** and **3a** in 75% yield. The pure α-isomer **3a** was crystallised out from methanol (or isopropanol) in 26% yield. Piperidine, pyrrolidine and N-methylpiperazine reacted in similar fashion to produce compounds **2b-d** and **3b-d** in 71%, 65% and 70% yields respectively; the α-isomers, namely, compounds **3b**, **3c** and **3d** were separated from the mixture through crystallisation in 20-25% yields. The β-isomers were always contaminated with varying amounts of α-isomers depending on the amine. In case of pyrrolidine enamines α-anomer was predominant in the mixture; even after crystallisation the mother liquer contained a mixture of both the isomers in a ratio β:α 3:2. Separation of the anomers of pyrrolidine enamine was most difficult to achieve: after repeated crystallisation, the α-anomer **3c** was contaminated with 5-10% of the β anomer. Attempts to react compound **1** with primary amines failed as the reaction produced an inseparable mixture of compounds indicating the degradation of the starting material.

In order to prove the structures of compounds formed in these reactions, the known[9] 2'-β-ketouridine **4** was reacted with neat morpholine as was done in case of the dimesyl derivative. The mixture of products obtained from the reaction was identical and similar to the products **2a** and **3a** obtained from the reactions of compound **1** and morpholine; treatment of compound **4** with 10 equivalents pyrrolidine in a mixture of toluene and acetonitrile (1:1)[6] produced compounds **2c** and **3c**.

The identity of the β-isomers present in the mother liquor were established through the hydrolysed product of the representative example **2a**. As, the attempted hydrolysis of the pure crystallined isomer **3a** under neutral conditions (THF-water, 1:1; reflux; 12h) produced an anomeric mixture of the 2'-ketonucleosides[10] and a single 2'-ketonucleoside under acidic conditions, the enamine **2a** was hydrolysed using acid (THF-water 5:1; conc. HCl, 3eqv.; reflux; 12h). The detritylated 2'-ketonucleoside was converted to 5'-O-benzoyl-3'-deoxy-2'-ketouridine **5** (Benzoyl chloride; pyridine; 0°C to room temp.; 2h). The known[9] 5'-O-trityl-3'-deoxy-2'-keto-β-uridine **4** was detritylated and benzoylated under similar conditions to produce the authentic 5'-O-benzoyl-3'-deoxy-2'-keto-β-uridine **5**. The hydrolysed product obtained from the enamine present in the mother liquor was similar to the authentic compound (mixed ^{1}H-NMR). The crystallized enamine was established to be the α-anomer with the help of crystal structure analysis (**Fig. 1**) of a representative example **3d**.

In order to complete the study we decided to probe into the formation of various intermediates leading to the final products. The first step of the study was to eliminate the possibility of the involvement of the intermediates such as 2'-O-mesyl-3'-deoxy-3'-morpholino-5'-O-trityl-*ara*- and 2'-deoxy-2'-morpholino-3'-O-mesyl-5'-O-trityl-*xylo*-uridines **9a** and **10a** respectively, which could have been formed by the direct nucleophilic attack of the amines at the 2'- or 3'-site of compound **1**. We converted compounds **7a** and **8a** (obtained from the reactions between compound **6** and morpholine[11]) separately to the mesylated derivatives **9a** and **10a** (Mesyl chloride; Pyridine; +4°C); a mixture of **9a** and **10a** was then heated under reflux with neat morpholine. The reaction did not furnish the enamines **2a** and **3a**; instead, the starting materials underwent extensive degradation as was evident from tlc.

As it was well known that under basic or even nucleophilic conditions, 1-(2, 3-di-O-mesyl-5-O-benzoyl-β-**D**-*lyxo*furanosyl)uracil undergoes an elimination reaction to form the 1-(2,3-dideoxy-2-O-mesyl-5-O-benzoyl-**D**-glycero-pent-2-enofuranosyl)uracil[12] it could be assumed that similar type of ene-mesylate derivative was also an intermediate formed in the present case. To prove that point unambiguously, we synthesised 1-(2,3-dideoxy-2-O-mesyl-5-O-trityl-β-**D**-glycero-pent-2-enofuranosyl)-uracil **11** from compound **1** (*t*BuOK, DMSO). It was extremely difficult to obtain compound **11** in pure form as in solution some of it got converted into the corresponding keto derivative **4** as was evident from the ^{13}C-NMR. Compound **11** was then reacted with


MsO
OMs
TrO
U
1
2a-d
3a-d
X : a = ; b = ;
c = ; d = N—CH3
4
2a + 3a
2a
i) H+
ii) BzCl, Py
BzO
5
RO
OR
6
7a : R=H
9a : R=Ms
8a : R=H
10a : R=Ms
OMs
11
2a +3a

morpholine (neat; reflux; 1h). The reaction did furnish compounds **2a** and **3a**.

As the formation of the ene-mesylate as intermediates alone did not explain the formation of the anomers **2a** and **3a**, formation of the 2'-ketonucleoside was thought to be prerequisite for the anomerisation to take place. It is not illogical to assume the formation of the 2'-ketonucleosides as it was well known in the literature that the conversion of the ene-mesylates to the 2'-ketonucleoside was a facile reaction under basic conditions[12]. The assumption was further supported by the fact that the pure 2'-ketonucleoside **4** could be converted to the mixture of anomers **2a** and **3a** very easily as described above. Whether the 2'-ketonucleoside was formed directly from compound **1** through 1,2-hydride shift[13] remains to be established; however, all reports of 1,2-hydride shift in case of nucleosides involved the presence of metal ions[13].

The spectral data are consistent with the structures assigned. A discussion on the ^{1}H-NMR will be pertinent here. The H-1' signals of both the sets of anomers appeared at around 7.0 ppm as doublets; however, H-1' of **2a-d** were always more deshielded than the same of **3a-d**. A perusal of the COSY spectrum of compound **3a** revealed that H-1' was coupled with H-4' showing a coupling constant of 4.2 Hz. It was also evident that H-1' was weakly coupled with H-3'. The H-1' of compound **2a**, on the other hand showed a very small coupling constant of 1.7 Hz. H-3' of both the anomers carrying a particular amine appeared at the same ppm values as singlets showing that the difference in anomeric configuration had no bearing on H-3'. It is worth mentioning here that the chemical shift values of the vinyl protons of all the enamines (H-3') followed the expected and reported[14] order, i.e. H-3' protons of pyrrolidine enamines (**2c/3c**, 4.48/4.49 ppm) were shielded most and the same protons of morpholine enamine pair (**2a/3a**, 4.93/4.92 ppm) was least shielded. The H-4' of the α-anomer **3a** was deshielded than that of the β-anomer **2a** but the multiplet arising from the 5'-methylene protons were more upfield in case of compound **2a**. It may be concluded that the difference in the stereochemistry around C-1' affected both C-4' and C-5' centers. The most striking difference was noted when the chemical shift values of H-5 and H-6 protons of compounds **2a** and **3a** were compared. H-6 of **3a** was shielded by 0.46 ppm and H-5 was deshielded by 0.65 ppm when compared with the same sets of signals of compound **2a**. The drastic changes in the positions of H-5 and H-6 signals indicated the difference in the anomeric configurations of compounds **2a** and **3a**. A further comparison of the positions of H-5/H-6 and the splitting pattern of H-5'/H-5'' of compounds **2a-d** and 1-(5-O-trityl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl) uracil[15] revealed the similarities in the configurations of the C-1' and C-4' centers. In general, the α- and β-enamines could be readily identified by the characteristic positions and coupling patterns of the respective peaks arising from H-1'/H-4' and H-5/H-6 protons.

Elucidation of the crystal structure of a representative example, compound **3d** (**Fig.1**) confirmed unambiguously our assertion that compounds **3a-d** were indeed of α-configuration. A perusal of the selected bond lengths and angles in and around the pentofuranose ring (**Tables 1a** and **1b**) revealed that C2'-C3' was a double bond. The shortening of the neighbouring bonds indicated the presence of double bond character in them, presumably due to delocalisation of the electron density in C2'-C3' bond. The five membered sugar ring was planar with the piperazine nitrogen lying in the plane. The glycosidic torsional angle [O4'-C1'-N1-C2] (**Table 1c**), showed that uracil was present in *syn-* conformation; this was in contrast with the *anti-* conformation of thymine in AZT[16]. However, the mutual orientations of the base and the sugar were orthogonal and resembeled those of molecule A in AZT crystal structure. The orientation of O5' (**Table 1c**) was also identical to that in molecule A of AZT and in turn same as that in thymidine 3'-phosphate moiety of 5'-phosphothymidyl(3'-5')thymidine[17]. The piperazine ring assumed a chair conformation with the four carbons lying approximately in one plane. The N-methyl group of piperazine was oriented in equatorial fashion.

The planar ring of the sugar, the base and one of the phenyl rings were disposed approximately perpendicular to each other with interplanar angles 87, 86 and 81° (**Fig. 2**, the piperazine ring and the two phenyl rings of trityl group were omitted for clarity). This arrangement has provided an interesting packing mode in the crystal with each of these planes being grossly parallel to one of the crystallographic faces. The base being parallel to crystallographic a-b plane, sugar assumed orientation approximately parallel to b-c plane while the relevant phenyl ring of the trityl group was parallel to a-c plane. Except for the one hydrogen bond between N3 of uracil as donor and the nitogen atom of piperazine connected to C2' as acceptor [D....A=2.83(2)Å, ∠H-D...A=17.9(b)°] of a symmetry related molecule there was no other explicit intermolecular interactions in the crystal. It may be

Table 1a
Selected bond lengths (Å)

O4'-C1'	1.44(3)
O4'-C4'	1.41(2)
C1'-N1	1.46(2)
C1'-C2'	1.48(3)
C2'-C3'	1.34(3)
C2'-Np*	1.37(2)
C3'-C4'	1.48(3)
C4'-C5'	1.53(3)
C5'-O5'	1.42(2)

Table 1b
Selected bond angles (°)

O4'-C1'-C2'	106(1)
C1'-O4'-C4'	109(1)
O4'-C1'-N1	111(3)
C2'-C1'-N1	112(3)
C1'-C2'-C3'	109(2)
C1'-C2'-Np*	122(2)
C3'-C2'-Np*	129(2)
C2'-C3'-C4'	109(1)
C3'-C4'-O4'	107(2)
C3'-C4'-C5'	118(1)
O4'-C4'-C5'	111(2)
C4'-C5'-O5'	104(1)

Table 1c
Selected torsion angles (°)

O4'-C1'-N1-C2	98(2)
O4'-C1'-C2'-C3'	5(2)
C1'-C2'-C3'-C4'	-2(2)
C2'-C3'-C4'-O4'	-3(2)
C3'-C4'-O4'-C1'	6(2)
C4'-O4'-C1'-C2'	-7(2)
O4'-C4'-C5'-O5'	-66(2)
O4'-C1'-C2'-Np*	179(1)

Np: Piperazine nitrogen connected to C2'.*

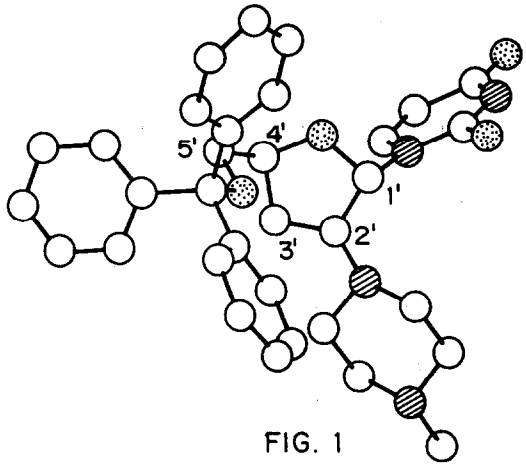


FIG. 1

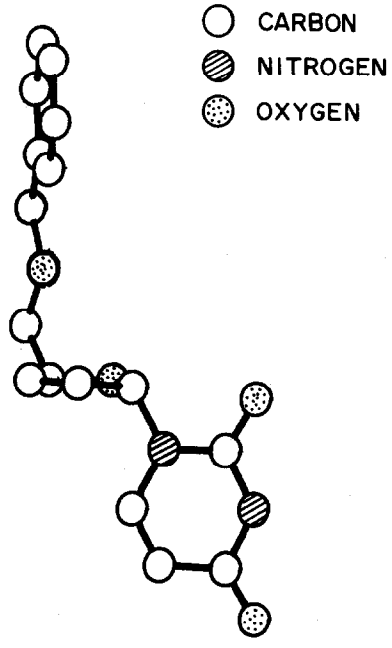


FIG. 2

presumed that the crystal structure had been stabilized through the mixed packing of the three perpendicularly disposed rings mentioned above parallel to crystallographic planes.

In conclusion, we have shown that the mode of reactions of 2',3'-di-O-mesyl-5'-O-trityl-*lyxo*-uridine **1** with secondary amines was completely different than that of 2',3'-di-O-mesyl-5'-O-trityl-*ribo*-uridine. This manuscript also reports an interesting and distinct difference in behaviour of 2',3'-di-O-mesyl-*lyxo*-uridine towards basic nucleophiles (amines) as compared to other nucleophiles such as thiols; the amines reacted as bases first to modulate the course of reactions whereas the thiols produced the expected[8] substitution products. Work is currently in progress to study the reactivities of the enaminonucleosides towards various electrophiles.

EXPERIMENTAL

Melting points were uncorrected. Uridine was purchased from Pharma Waldhof GmbH, Germany and used as received. Thin Layer Chromatography was performed on Merk precoated 60 F_{254} plates. Compounds were visualised on TLC plate under UV light. Column chromatographic separations were done using silica gel (Silica gel 60, 230-400 mesh, E. Merck) or basic alumina (Brockmann Grade I for Chromatography, S.D. Fine Chem. Ltd., India). ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) spectra were recorded on Bruker ACF200 NMR spectrometer (δ scale) using TMS or solvent chloroform-d as internal standards. Mass spectra were recorded on Finnigan MAT 1020B GC/MS.

1-(2,3-Di-O-mesyl-5-O-trityl-β-D-*lyxo*furanosyl) uracil 1: *Lyxo*uridine (10mmol) was dried by coevaporation with dry pyridine and redissolved in same solvent (60ml). Trityl chloride (13 mmol) was added and the solution was kept for overnight at room temperature. The reaction mixture was then heated at 100°C for 3 hours. After completion of the tritylation (tlc), the reaction mixture was cooled to 0°C. Methanesulphonyl chloride (30 mmol) in pyridine (20ml) was added dropwise to it. After completion of the addition, the reaction mixture was allowed to warm up to room temperature and left at that temperature for 20 hours. The reaction mixture was then poured in to the saturated sodium bicarbonate solution (500ml) and was extracted with ethyl acetate (3x200ml). Ethyl acetate solution was evaporated to dryness and the residual pyridine was coevaporated with toluene. The residue thus obtained was purified on silica gel column. The product was crystalised from methanol. Yield: 75%, m.p. 227°C(lit[8]: 229°C). ^{1}H-NMR ($CDCl_3$): δ 9.3 (bs, 1H) NH; 7.48-7.24 (m, 16H) trityl, H-6; 6.38 (d, 6.3 Hz, 1H) H-1'; 5.7 (d, 8 Hz, 1H) H-5; 5.41 (m, 1H) / 5.33 (m, 1H) H-2'/H-3'; 4.28 (m, 1H) H-4'; 3.71-3.44 (m, 2H) H5', 5''; 3.09 (s, 3H) / 2.95 (s, 3H) 2',3', mesyl CH_3. ^{13}C-NMR ($CDCl_3$): δ 163.7, C-4; 150.9, C-2; 143.3, trityl; 140.3, C-6; 128.8, 128.2, 127.6, trityl; 102.4, C-5; 87.8, trityl; 82.0, C-1'; 77.9/77.1, C-2'/C-3'; 74.9, C-4'; 61.7, C-5'; 38.9, 38.6, 2'/3'mesyl CH_3.

1-(2,3-dideoxy-2-N-morpholino-5-O-trityl-β-D-glycero-pent-2- enofuranosyl) uracil 2a and 1-(2,3-dideoxy-2-N-morpholino-5-O-trityl-α-D-glycero-pent-2-enofuranosyl) uracil 3a: A solution of compound **1** (1mmol) in neat morpholine (2ml) was heated under reflux for 12h. After the completion of the reaction, the amine was evaporated under reduced pressure. The oily residue was purified by column chromatography on basic alumina. Total yield: 75%. Compound **3a** was crystallised from methanol[21]. **Compound 2a:** ^{1}H-NMR ($CDCl_3$): δ 7.63 (d, 8 Hz, 1H) H-6; 7.49-7.22 (m, 15H) trityl; 6.99 (d, 1.7 Hz, 1H) H-1'; 5.18 (d, 8 Hz, 1H) H-5; 4.95-4.93 (m, 2H) H-4', H-3'; 3.72 (t, 4H) H_2C-O-CH_2; 3.4-3.23 (m, 2H) H-5', 5''; 3.06-2.94 (m, 4H) H_2C-N-CH_2. ^{13}C-NMR ($CDCl_3$): δ 163.9, C-4; 151.3, C-2; 145.1, C-2'; 143.5, trityl; 141.4, C-6; 128.9, 127.9, 127.4, trityl; 102.8/101.3, C-5/C-3'; 87.2/86.1/84.1, trityl/C-1'/C-4'; 66.2, C-5'and H_2C-O-CH_2; 48.7, H_2C-N-CH_2. **Compound 3a**: Yield: 26%; m.p. 193°C; ^{1}H-NMR ($CDCl_3$): δ 7.49-7.22 (m, 15H) trityl; 7.17 (d, 8 Hz, 1H) H-6; 7.06 (d, 4.2 Hz, 1H) H-1'; 5.83 (d, 8 Hz, 1H) H-5; 5.14 (m, 1H) H-4'; 4.92 (s, 1H) H-3'; 3.7 (t, 4H) H_2C-O-CH_2; 3.25-3.09 (m, 2H) H-5', 5''; 3.03-2.81 (m, 4H) H_2C-N-CH_2. ^{13}C-NMR ($CDCl_3$): δ 163.9, C-4; 151.2, C-2; 145.7, C-2'; 144.1, trityl; 140.2, C-6; 128.9, 128.1, 127.3, trityl; 103.6/103.1, C-5/C-3'; 86.9/86.5/84.8, trityl/C-1'/C-4'; 67.4, C-5'; 66.3, H_2C-O-CH_2; 48.8, H_2C-N-CH_2. MS(EI): m/z 426 (M^+-uracil, 20%); 264 (M^+-Ph_3COCH_2, 40%).

1-(2,3-dideoxy-2-N-piperidino-5-O-trityl-β-D-glycero-pent-2-enofuranosyl) uracil 2b and 1-(2,3-dideoxy-2-N-piperidino-5-O-trityl-α-D-glycero-pent-2-enofuranosyl) uracil 3b: A solution of compound **1** (1mmol) in neat piperidine (2ml) was heated at 80°C for 12h. After the completion of the reaction, the amine was evaporated under reduced pressure. The oily residue was purified by column chromatography on basic alumina. Total yield: 71%. Compound **3b** was crystallised from methanol[21]. **Compound 2b:** ^{1}H-NMR ($CDCl_3$): δ7.55-7.25 (m, 16H) trityl, H-6; 6.90 (bs, 1H) H-1'; 5.16 (d, 8 Hz, 1H) H-5; 4.95 (m, 1H) H-4'; 4.81 (s, 1H) H-3'; 3.40-3.10 (m, 2H) H-5', 5''; 2.95 (bs, 4H) H_2C-N-CH_2; 1.55 (bs, 6H) H_2C-CH_2-CH_2. ^{13}C-NMR ($CDCl_3$): δ 164.1, C-4; 151.3, C-2; 145.0, C-2'; 143.5, trityl; 141.7, C-6; 128.6, 127.9, 127.2, trityl; 102.4/99.3, C-5/C-3'; 87.0/86.4/84.0, trityl/C-1'/C-4'; 66.7, C-5'; 49.3, H_2C-N-CH_2; 25.1, 24.0, H_2C-CH_2-CH_2. **Compound 3b:** Yield: 20%; m.p. 193°C; ^{1}H-NMR ($CDCl_3$): δ 7.48-7.22 (m, 15H) trityl; 7.20 (d, 8 Hz, 1H) H-6; 7.00 (d, 4.0Hz, 1H) H-1'; 5.75 (d, 8 Hz, 1H) H-5; 5.08 (m, 1H) H-4'; 4.81 (s, 1H) H-3'; 3.20-3.04 (m, 2H) H-5', 5''; 2.88 (bs, 4H) H_2C-N-CH_2; 1.53 (bs, 6H) H_2C-CH_2-CH_2. ^{13}C-NMR (DMSO-d_6): δ 163.4, C-4; 151.2, C-2; 144.9, C-2'; 144.1, trityl; 140.8, C-6; 128.7, 128.3, 127.4, trityl; 103.2/99.0, C-5/C-3'; 86.2/84.3, trityl/C-1'/C-4'; 67.4, C-5'; 49.0, H_2C-N-CH_2; 24.9, 23.9, H_2C-CH_2-CH_2. MS(EI): m/z 423 (M^+-uracil, 10%); 262 (M^+-Ph_3COCH_2, 10%).

1-(2,3-dideoxy-2-N-pyrrolidino-5-O-trityl-β-D-glycero-pent-2-enofuranosyl) uracil 2c and 1-(2,3-dideoxy-2-N-pyrrolidino-5-O-trityl-α-D-glycero-pent-2-enofuranosyl) uracil 3c: A solution of compound **1** (1mmol) in neat pyrrolidine (2ml) was heated at 60°C for 10h. After the completion of the reaction, the amine was evaporated under reduced pressure. The oily residue was purified by column chromatography on basic alumina. Total yield: 65%. Compound **3c** was crystallised from methanol[21]. **Compound 2c:** ^{1}H-NMR ($CDCl_3$): δ7.53 (d, 8 Hz, 1H) H-6; 7.48-7.22 (m, 15H) trityl; 6.94 (d, 1.1 Hz, 1H) H-1'; 5.24 (d, 8 Hz, 1H) H-5; 4.98 (m, 1H) H-4'; 4.48 (s, 1H) H-3'; 2.94-3.11 (m, 6H) H_2C-N-CH_2, H-5', 5''; 1.87 (m, 4H) H_2C-CH_2. ^{13}C-NMR ($CDCl_3$): δ 164.0, C-4; 151.1, C-2; 143.6, C-2'; 141.7, trityl; 141.2, C-6; 128.8, 127.9, 127.2, trityl; 102.8/93.7, C-5/C-3'; 87.0/85.2/84.7, trityl/C-1'/C-4'; 66.9, C-5'; 48.6, H_2C-N-CH_2; 25.2, H_2C-CH_2. **Compound 3c:** Yield: 20%; m.p. 158°C; ^{1}H-NMR ($CDCl_3$): δ 7.51-7.22 (m, 16H) trityl; H-6; 7.0 (d, 4.1 Hz, 1H) H-1'; 5.78 (d, 8 Hz, 1H) H-5; 5.19 (m, 1H) H-4'; 4.49 (s, 1H) H-3'; 3.20-2.94 (m, 6H) H-5', 5''; H_2C-N-CH_2; 1.86 (m, 4H) H_2C-CH_2. ^{13}C-NMR (DMSO-d_6+$CDCl_3$): δ 163.43, C-4; 151.22, C-2; 144.1, C-2'; 142.0, trityl; 140.2, C-6; 128.66, 128.1, 127.3, trityl; 103.37/93.55, C-5/C-3'; 86.84/86.27/84.78, trityl/C-1'/C-4'; 68.28, C-5'; 48.46, H_2C-N-CH_2; 25.08, H_2C-CH_2. MS(EI): m/z 248 (M^+-Ph_3COCH_2, 5%).

1-[2,3-dideoxy-2-N-(N-methylpiperazino)-5-O-trityl-β-D-glycero-pent-2-enofuranosyl] uracil 2d and 1-[2,3-dideoxy-2-N-(N-methylpiperazino)-5-O-trityl-α-D-glycero-pent-2-enofuranosyl] uracil 3d: A solution of compound **1** (1mmol) in neat N-methylpiperazine (2ml) was heated at 80°C for 24h. After the completion of the reaction, the amine was evaporated under reduced pressure. The oily residue was purified by column chromatography on basic alumina. Total yield: 70%. Compound **3d** was crystallised from methanol[21]. **Compound 2d:** ^{1}H-NMR ($CDCl_3$): δ 7.53 (d, 8 Hz, 1H) H-6; 7.47-7.20 (m, 15H) trityl; 6.96 (d, 1.3 Hz, 1H) H-1'; 5.14 (d, 8 Hz, 1H) H-5; 4.94 (m, 1H) H-4'; 4.87 (s, 1H) H-3'; 3.37-3.20 (m, 2H) H-5', 5''; 3.10-2.94 (m, 4H) H_2C-N-CH_2; 2.43-2.32 (m, 4H) H_2C-N(CH_3)-CH_2; 2.29 (s, 3H) N-CH_3. ^{13}C-NMR ($CDCl_3$): δ 163.1, C-4; 151.4, C-2; 144.7, C-2'; 143.5, trityl; 141.3, C-6; 128.8, 127.9, 127.3, trityl; 102.6/100.7, C-5/C-3'; 87.1/86.2/84.0, trityl/C-1'/C-4'; 66.5, C-5'; 54.7, H_2C-N(CH_3)-CH_2; 48.0, H_2C-N-CH_2; 45.8, N-CH_3. **Compound 3d:** Yield: 22%; m.p. 220°C; ^{1}H-NMR ($CDCl_3$): δ 9.25 (bs, 1H) N3-H; 7.48-7.22 (m, 15H) trityl; 7.12 (d, 8 Hz, 1H) H-6; 7.02 (d, 4.3 Hz, 1H) H-1'; 5.76 (d, 8 Hz, 1H) H-5; 5.20-5.07 (m, 1H) H-4'; 4.86 (s, 1H) H-3'; 3.23-3.08 (m, 2H) H-5', 5''; 3.02-2.88 (m, 4H) H_2C-N-CH_2; 2.42-2.37 (m, 4H) H_2C-N(CH_3)-CH_2; 2.84 (bs, 3H) N-CH_3. ^{13}C-NMR (DMSO-d_6): δ 163.4, C-4; 151.1, C-2; 144.7, C-2'; 144.0, trityl; 140.4, C-6; 128.6, 128.1, 127.3, trityl; 103.1/100.0, C-5/C-3'; 86.2/85.9/84.2, trityl/C-1'/C-4'; 67.5, C-5'; 54.1, H_2C-N(CH_3)-CH_2; 47.9, H_2C-N-CH_2; 46.1, N-CH_3.

5'-O-Benzoyl-3'-deoxy-2'-ketouridine 5 from from compound 2a: A solution of compound **2a** (0.5mmol) and conc. HCl (1.5mmol) in THF/H_2O (6ml, 5:1) was heated under reflux for 12 h. After completion of the

reaction, solvents were evaporated under reduced pressure. The oily residue was coevaporated with pyridine and redissolved in the same solvent (6ml). the solution was cooled at 0°C and benzoyl chloride in pyridine was added to it . After the addition, the reaction mixture was stirred at RT for 2 h. the reaction mixture was poured into the saturated sodium bicarbonate solution and was extracted with ethyl acetate. Organic layer was dried over sodium sulphate and evaporated under reduced pressure. The oily residue was purified on silica gel column. Yield: 65 %.

Authentic 5'-O-Benzoyl-3'-deoxy-2'-ketouridine 5 from compound 4: A solution of compound 4 (1mmol) and conc. HCl (3mmol) in THF (5ml) was heated under reflux. After completion of the reaction, solvents were evaporated under reduced pressure. The oily residue was coevaporated with pyridine and redissolved in the same solvent (6ml). The solution was cooled at 0°C and benzoyl chloride in pyridine was added to it . After the addition, the reaction mixture was stirred at RT for 2 h. The reaction mixture was poured into the saturated sodium bicarbonate solution and was extracted with ethyl acetate. Organic layer was dried over sodium sulphate and evaporated under reduced pressure. The oily residue was purified on silica gel column. Yield: 70 %. ^{1}H-NMR (DMSO-d_6): δ 11.57 (bs, H) N-H; 8.02-7.49 (m, 6H) benzoyl, H-6 ; 5.65 (d, 7.9 Hz 1H) H-5; 5.52 (s, 1H) H-1'; 4.75 (m, 1H) H-4'; 4.49 (m, 2H) H-5', 5''; 2.77 (d, 7.9 Hz, 2H) H-3', 3''. ^{13}C-NMR (DMSO-d_6): δ 207.4, C-2'; 166.1, benzoyl keto; 163.7, C-4; 150.6, C-2; 145.2, C-6; 133.9, 129.8, 129.2, phenyl; 102.6, C-5; 86.5, C-1'; 73.7, C-4'; 66.4, C-5'; 36.7, C-3'.

2'-O-Mesyl-3'-deoxy-3'-morpholino-5'-O-trityl-ara-uridine 9a: Compound **7a** (0.5mmol) was dried by coevaporation with dry pyridine and redissolved in the same solvent (10ml). The solution was cooled at 0°C and methanesulphonyl chloride (1.5mmol) in pyridine (5ml) was added dropwise to it. After completion of the addition, the solution was left at +4°C overnight. The reaction mixture was then poured in to the ice-cold water. The white precipitate was filtered and the residue was washed thoroughly with water. The residue was redissolved in ethyl acetate, dried over sodium sulphate and filtered. The filtrate was evaporated to dryness. The residue thus obtained was purified on silica gel column[22]. Yield: 68%, m.p. 155°C. ^{1}H-NMR ($CDCl_3$): δ 9.18 (bs, 1H) NH; 7.69 (d, 8 Hz, 1H) H-6; 7.47-7.24 (m, 15H) trityl; 6.14 (d, 4.6 Hz, 1H) H-1'; 5.68 (d, 8 Hz, 1H) H-5; 5.38 (m, 1H) H-2'; 4.13 (m, 1H) H-4'; 3.67 (m, 4H) H_2C-O-CH_2; 3.59-3.36, (m, 3H) H-5', 5'', H-3'; 2.95 (s, 3H) 2'-mesyl CH_3; 2.71-2.58, H_2C-N-CH_2. ^{13}C-NMR: ($CDCl_3$): δ 163.5, C-4; 150.5, C-2; 143.4, trityl; 140.8, C-6; 128.7, 128.1, 127.5, trityl; 102.7, C-5; 87.3, trityl; 83.7, C-1'; 77.4/76.9, C-2'/C-4'; 70.8, C-3'; 66.9, H_2C-O-CH_2; 63.2, C-5'; 50.6, H_2C-N-CH_2; 38.5, 2'-mesyl CH_3.

2'-Deoxy-2'-morpholino-3'-O-mesyl-5'-O-trityl-*xylo*-uridine 10a: Compound **10a** was prepared[22] from **8a** and purified as described in case of compound **9a**. Yield: 70%, m.p. 134°C. ^{1}H-NMR ($CDCl_3$): δ 9.1 (bs, 1H) NH; 7.45-7.25 (m, 16H) trityl, H-6; 6.19 (d, 4.4 Hz, 1H) H-1'; 5.63 (d, 8 Hz, 1H) H-5; 5.29 (m, 1H) H-3'; 4.32 (m, 1H) H-4'; 3.75 (m, 4H) H_2C-O-CH_2; 3.67-3.6, 3.38-3.26 (m, 3H) H-5', 5'', H-2'; 2.83 (s, 3H) 3'-mesyl CH_3; 2.72 (m, 4H) H_2C-O-CH. ^{13}C-NMR ($CDCl_3$): δ 162.3, C-4; 149.4, C-2; 142.3, trityl; 138.7, C-6; 127.6, 127.0, 126.4, trityl; 102.2, C-5; 86.5, trityl; 83.2, C-1'; 77.9, 77.2, 74.7, C-2'/C-3'/C-4'; 65.6, H_2C-O-CH_2; 60.6, C-5'; 50.3, H_2C-N-CH_2; 37.5, 3'-mesyl CH_3.

1-(5-O-Trityl-3-deoxy-2-O-mesyl-β-D-glycero-pent-2-enofuranosyl) uracil 11: A solution of compound (1mmol) in DMSO (3ml) was treated with pottassium t-butoxide (2mmol). After 12h, the reaction mixture was poured in to the water which was substiquently extracted with ethyl acetate. The organic layer was dried over sodium sulphate and evaporated to dryness. The product obtained was purified on silica gel column. Yield: 30 % (25 % starting material was recovred). ^{1}H-NMR ($CDCl_3$): δ 9.00 (bs, 1H) NH; 8.05 (d, 8 Hz, 1H) H-6; 7.4-7.28 (m, 15H) trityl; 6.93-6.9 (m, 1H) H-1'; 6.17 (t, 1H) H-3'; 5.03-4.97 (m, 2H) H-5, H-4'; 3.6-3.4 (m, 2H) H-5', 5''; 3.24 (s, 3H) mesyl CH_3. ^{13}C-NMR ($CDCl_3$): δ 163.6, C-4; 151.2, C-2; 143.0, trityl; 140.82/140.73, C-6/C-2'; 128.9, 128.7, 128.2, trityl; 115.7, C-3'; 103.1, C-5; 87.8, trityl; 84.9/82.9, C-1'/C-4'; 64.4, C-5'; 38.7, CH_3.

Reaction of morpholine with compound 11. A solution of compound **11** (0.28mmol) in neat morpholine (2ml) was heated under reflux for 1h. After the completion of the reaction, the amine was evaporated under reduced pressure. The oily residue was purified by column chromatography on basic alumina to produce a mixture of compounds **2a** and **3a**. Yield 60 %.

Reaction of morpholine with 5'-O-trityl-3'-deoxy-2'-ketouridine 4: A solutiun of compound **4** (1mmol) in neat morpholine (2ml) was heated under reflux. After 1 h, the amine was evaporated under reduced pressure. The oily residue was purified by column chromatography on basic alumina to produce a mixture of compounds **2a** and **3a**. Yield. 70 %.

Reaction of pyrrolidine with 5'-O-trityl-3'-deoxy-2'-ketouridine 4: A mixture compound **4** (1mmol) and pyrrolidine (10 mmol) in toluene and acetonitrile (1:1, 20 ml) was heated under reflux for 20 hours. The reaction mixture was evaporated to dryness and the residue was purified on basic alumina column to produce a mixture of enamines **2c** and **3c**. Yield: 63%.

Reactions of morpholine with compounds 9a and 10a: A solution of a mixture of compounds **9a** and **10a** (1mmol, 0.5mmol each) in neat morpholine (5ml) was heated under reflux for 6h. The reaction did not produce any isolable compounds; instead the starting materials underwent extensive degradation (tlc).

Crystal structure determination[18] of compound 3d: Compound **3d** was crystallised from methanol as colourless rectangular parellelopipeds. Diffraction quality of the crystals were poor. X-ray data were collected using a crystal of size 0.15x0.20x0.45 mm on an EnrafNonius CAD4 p.c. controlled diffractometer. Unit cell determined from "SEARCH" reflections were subsequently refined using 25 well centered reflections in the range $17<2\theta<25°$. Data were collected employing $\omega/2\theta$ scan mode. 3 reflections were monitered at regular intervals of 3600 X-ray seconds and found the variations in intensities to be negligible. Lorentz and polarizations corrections were applied during data reduction. However, no absorbtion corrections were applied. Structure was solved by direct methods using SHELXS-86(ref.19) and the atom parameters were refined using full matrix least squares method in SHELX-76(ref. 20). Out of 2591 unique eeflections 1120 with $F>5\sigma(F)$ were used in refinement.Thermal parameters of non-hydrogen atoms were treated anisotropic. Hydrogens were fixed at ideal geometry with the help of a difference Fourier map and were not refined.

Acknowledgement: K.S. thanks CSIR, New Delhi for a fellowship. T.P. is grateful to the Department of Science and Technology, Government of India for financial support (Grant no. SR/OY/C03/92).

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NCL Communication No. 4966.

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(*Received in UK* 15 *August* 1994; *revised* 23 *September* 1994; *accepted* 30 *September* 1994)