Pergamon

Tetrahedron Vol. 51, No. 5, pp. 1459-1470, 1995

0040-4020/95 $9.50+0.00

0040-4020(94)01040-4

Opening of 2',3'-O-Anhydro-ring of 2',3'-O- Anhydro-*lyxo*-uridine by Alkyl- and Arylamines. Easy Syntheses and Preparative Uses of 2'- Deoxy-2'-alkylamino-*xylo*- and 3'-Deoxy-3'-alkylamino-*ara*-uridines#.

Sanjib Bera and Tanmaya Pathak*
Organic Chemistry Division (Synthesis), National Chemical Laboratory, Pune 411008, India

Graham J. Langley
Department of Chemistry, The University, Southampton SO9 5NH, UK

Abstract: *Contrary to the previous report (ref. 8), under controlled conditions alkylamines, both primary and secondary and arylamines, opened the epoxide ring of 1-(5-O-trityl-2,3-O-anhydro-β-D-lyxo-furanosyl)-uracil to produce 2'-deoxy-2'-alkylamino-xylo- and 3'-deoxy-3'-alkylamino-ara- uridines without causing any significant deglycosylation. To show the utility of these products, several modified uridine derivatives were synthesised.*

INTRODUCTION

3'-Azido-3'-deoxythymidine (AZT)[1], 2',3'-dideoxyinosine (DDI)[2], 2',3'-dideoxycytidine (DDC)[2] and 2',3'-didehydro-3'-deoxythymidine (D_4T)[3] are, so far, the only nucleoside based drugs approved for the clinical treatment of Acquired Immuno Deficiency Syndrome (AIDS); the usefulness of these compounds, however, is limited because of their toxic side effects[4]. A plethora of 3'-substituted-3'-deoxy compounds have been synthesised and their biological properties were studied[5]. Attempts are currently underway to introduce novel functional groups[6,7] at the 2'- and/or 3'- sites which includes the functionalisation of 2'- and/or 3'- sites by primary and secondary amines[8,9]. In fact, 3'-amino-3'-deoxythymidine has been found to exhibit wide ranging biological activities[10] and recently reported two other aminonucleosides, compounds **A** and **B** have shown weak inhibitory effects against HIV replication[8]. *However, a full evaluation of the biological activity of this type of compounds will be possible only when they are easily accessible.* In continuation of our interest in the area of aminonucleosides[11], we decided to develop a general strategy leading to the synthesis of 2'-deoxy-2'-alkylamino- and 3'-deoxy-3'-alkylaminopyrimidine nucleosides as AZT contains a pyrimidine base, thymine.

Alkylamino-substituted nucleosides were synthesised by reacting 3'-deoxy-3'-amino nucleosides with an appropriate aldehyde and ketone to give the corresponding Schiff base which was then reduced with sodium borohydride[12a,b]. Attempted displacement of the 3'-O-mesyl group of 1-(2-deoxy-3-O-methanesulphonyl-β-D-*threo*-pentofuranosyl)thymine with alkylamines was unsuccessful as the desired products were obtained in very poor yield[8,12b]. Chattopadhyaya and co-workers made use of Michael addition reactions of amines to ene-sulfone[9a] or ene-selenone[9b,c] uridines. However, apart from the facts that the preparation of the starting materials involved multiple steps and in the latter case use of toxic selenium compounds, both the methodologies suffered from certain serious drawbacks: i) the reductive removal of sulfone group after amination caused extensive deglycosylation as was evident from the yield of the products[9a] and ii) 2'- and 3'-ene selenones, because

of their very special kind of reactivities produced 2,2'-O-anhydro-3'-deoxy-3'-aminouridines or 2',3'-dideoxy-2',3'-epiminouridines [9b,c] (depending on the amine used) in uncontrolled fashion. In another development, Wengel and co-workers reacted[13] an α,β-unsaturatd aldehyde, 4,6-di-O-acetyl-2,3-dideoxy-*aldehydo*-D-erythro-trans-hex-2-enose with amines in Michael fashion; the product was converted to 2',3'-dideoxy-3'-alkylamino-D-ribohexofuranosyl pyrimidines through multiple steps. However, the synthesis was restricted only to piperidino, pyrrolidino and N-acetylpiperazino derivatives as other amines did not react with the starting α,β-unsaturated aldehyde.

RESULTS AND DISCUSSION

Since, nucleophilic ring opening of 2',3'-O-anhydro nucleoside in general is one of the most efficient ways of functionalising nucleosides[9, 14] and in view of the fact that 3'-amino-3'-deoxy-*ara*-uridine was indeed synthesised[15] by the reactions of 2',3'-O-anhydro-*lyxo*-uridine with ethanolic ammonia, we decided to reinvestigate the reactions between alkyl- and arylamines and 1-(5-O-trityl-2,3-O-anhydro-β-D-*lyxo*-furanosyl)-uracil **1a** under controlled conditions, *although previous attempts to open 2',3'-O-anhydro-lyxo-uridine with pyrrolidine[8] failed as it "led only to cleavage of the glycosidic bond".* We report, herein, for the first time that contrary to the previous report[8], under the right conditions, alkylamines, both primary and secondary and arylamines, do indeed open the epoxide ring of compound **1a** to produce the desired products without causing significant, if any, deglycosylation.

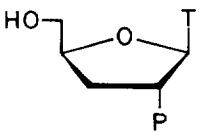
In general, a solution of compound **1a** (1mmol) and amine (5-10mmol) in DMSO (3ml) was heated at 90-95°C. After completion of the reaction (tlc), the reaction mixture was worked up and the compounds were purified by column chromatography. The reaction temperatures varied slightly from amine to amine but the reaction times varied widely (see experimental). In general more basic amines reacted faster than the less basic amines. The aromatic amines were the slowest; the reaction mixtures had to be heated for longer times at higher temperatures.

Isobutylamine, benzylamine, cyclohexylamine, piperidine, pyrrolidine, morpholine, ethyl *iso*nipecotate, aniline and p-methoxyaniline, all reacted in similar fashion to produce compounds **2a-g** and **3a-i**. Only 3'-deoxy-3'-arylamino compounds could be obtained in pure form from the reaction between aniline or p-methoxyaniline and **1a**. N-Methylpiperazine, N-acetylpiperazine, N-methylethanolamine, N,N'-dimethylethylenediamine, diethanolamine, 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane also opened the epoxide in varying yields; however, all attempts to separate the isomers failed. The major product (2':3' 1:2.4) obtained from the reaction between **1a** and 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane was separated as the diacetate **4j**; as far as our knowledge goes into literature, **4j** is the first reported compound of its kind. It should be noted that in case of isobutylamine, compound **1a** was reacted with neat amine to give the desired products in moderate yields. This observation indicated that the use of neat amine had caused deglycosylation. Nevertheless, use of 7 equivalents of isobutylamine in DMSO (70°C, 20h) produced the mixture of **2a/3a** in 80% yield.

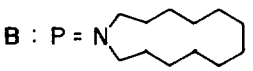
That the presence of the trityl protecting group at the 5'-position did influence the product distribution was evident from the fact that compound **1b** on treatment with piperidine produced the 3'-piperidino- derivative **4e** and the corresponding 2'-substituted derivative in a ratio 3.2:1 (mixture isolated as the diacetates) which is significantly different from the ratio of 3' and 2'isomers, 2.7:1 obtained from the reaction of compound **1a** and piperidine.

Compounds **2a-f**, **3a-f**, **3h-i** were deprotected using Amberlite IR-120 H^+ in water. The deprotected compounds were eluted out of the column using ammonia solution. It was important to neutralise the medium with ammonia as soon as possible to avoid degradation. It was interesting to note that compounds **2a-f** were more stable under the conditions than compounds **3a-f**. However, compounds **2g** and **3g** could not be deprotected using the general deprotection conditions as elution with ammonia caused partial deprotection of the nipecotyl ester group. Compounds **2g/3g**, were deprotectrd using 80% acetic acid and the deprotected compounds were collected as their diacetyl derivatives. The deprotected compounds **8a-f**, **4g**, **10g**, **9a** were highly hygroscopic.

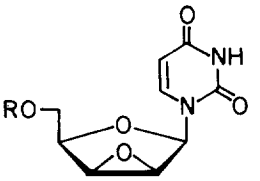
To show the usefullness of products **2** and **3** as versatile intermediates, we synthesised various derivatives



A : P = N

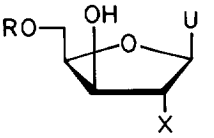


B : P = N



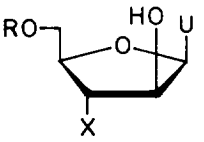
1a : R = Tr

1b : R = H



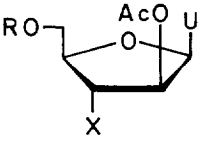
2a-g : R = Tr ; X = a-g

8a-f : R = H ; X = a-f



3a-i : R = Tr ; X = a-i

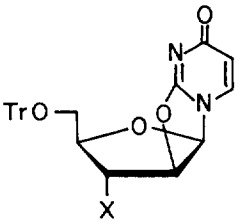
9a-f,h,i : R = H ; X = a-f,h,i



4e : R = Ac ; X = e

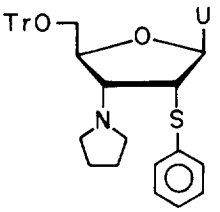
4g : R = Ac ; X = g

4j : R = Tr ; X = j

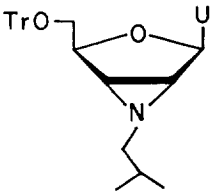


5d : X = d

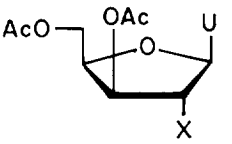
5e : X = e



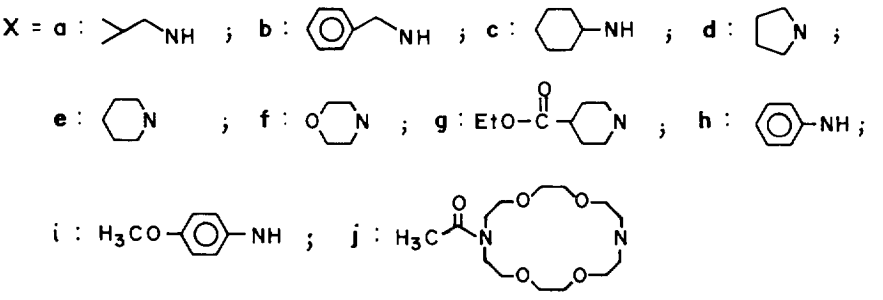
6



7



10g : X = g



from selected compounds. A mixture of compounds **2d** and **3d** was mesylated in pyridine at +4°C. The purified mixture was redissolved in pyridine and the solution was heated under reflux for 6 hours to produce the known[9b] 3'-deoxy-3'-pyrrolidino-2,2'-O-anhydro-5'-O-trityluridine **5d**. Similarly compounds **2e** and **3e** were converted to 3'-deoxy-3'-piperidino-2,2'-O-anhydro-5'-O-trityluridine **5e**. It is obvious that the formation of a reactive aziridinium ion intermediate has led to the conversion to the more stable anhydro derivatives. Compound **5e** on treatment with 1N aqueous sodium hydroxide produced 2,2'-O-anhydro ring opened compound which was identical to the major isomer **3e** obtained from the reaction between piperidine and compound **1a**. This method is useful for converting a mixture of *ara-* and *xylo-* isomers to pure *ara-* compound if only 3'-deoxy-3'-substituted compound is required. Compound **5d** on treatment with thiophenol in presence of tetramethylguanidine produced the 2',3'-dideoxy-2',3'-disubstituted derivative **6**.

The compounds derived from primary amines were converted smoothly to the epimino derivatives in good yields. Thus, a mixture of compounds **2a** and **3a** on treatment with triphenyl phosphine and diisopropyl azodicarboxylate produced 1-(5-O-trityl-2,3-dideoxy-2,3-N-isobutylepimino-β-D-ribofuranosyl)- uracil **7** in 65% yield. Mixture of compounds **2b/3b** and compounds **2c/3c** could also be converted to the corresponding epimino derivatives as was evident from ^{1}H-NMR spectrum of the products; however, the products could not be obtained in pure form as they were always contaminated with triphenyl phosphonium oxide.

The structures of all new compounds were assigned unambiguously by chemical as well as spectroscopic means. That the amines were indeed connected to the 2'- or 3'- carbons was proved by the preparation of compounds **5d**, **5e** and **7**. Although it was well known in the literature[8, 15, 16] that the major product of the epoxide ring opening reactions was always the 3'-deoxy-3'-substituted compound, the identity of at least one isomer was established as the 3'-deoxy-3'-substituted compound by converting **5e** to the known compound **3e**. However, the preparation of compound **5e** from a mixture of compounds also proved, albeit indirectly, the presence of 2'-deoxy-2'-substituted compound **2e** which was converted to the final product **5e** through a common aziridinium intermediate.

The ^{1}H-NMR of compounds **2a-g** and **3a-i** are consistent with the structures assigned. The H-1' resonances of compounds **2a-c** always appeared more upfield than the resonances of compounds **3a-c**; the coupling constants ($J_{1',2'}$= > 1.4 Hz) of **2a-c** were always much smaller than **3a-c** ($J_{1',2'}$= > 4.6 Hz). The H-2' resonances of compounds **2a-c** were always shielded by almost 1ppm than the H-3' resonances. In case of compounds **3a-c**, as expected, the H-2' resonances were always deshielded than the H-3' resonances. The H-4' resonances of 2'-deoxy-2'-substituted compounds **2a-c** were always deshielded than the same resonances of the 3'-deoxy-3'substituted compounds **3a-c**; this was, most probably due to the presence of more electronegative functionality OH (as opposed to NHR) at C-3' position in compounds **2a-c**. The pattern was more or less similar in case of compounds **2d-g** and **3d-g**. However, in case of H-1' and H-4'-resonances the differences were less pronounced and except for **2d/3d** pair, the $J_{1',2'}$ coupling constant values were very close. The proton signals of compounds **2a/3a**, **2d/3d** and **6** were assigned on the basis of COSY analysis. The structure of almost all the compounds were established unambiguously with the help of high resolution mass spectrum.

In conclusion, we have developed a general methodology for the synthesis of a great number and wide variety of 2'-deoxy-2'-alkylamino-*xylo-* and 3'-deoxy-3'-alkylamino-*ara-*uridines **2a-g** and **3a-i** respectively. We have also demonstrated that these compounds could be converted to various derivatives in controlled fashion.

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

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. All mass spectrometric experiments were carried out on a VG Analytical 70-250-SE normal geometry double focussing mass spectrometer. Accurate mass measurements were carried out at 10 000 resolution using mixtures of polyethylene glycols as mass calibrants.

5'-O-Trityl-2'-deoxy-2'-N-isobutylamino-*xylo*- uridine 2a and 5'-O-trityl-3'-deoxy-3'-N-isobutylamino-*ara*-uridine 3a: A mixture of compound **1a** (1mmol) and neat isobutylamine (4ml)) was heated at 80°C for 10h. The excess amine was removed under reduced pressure. The residue was dissolved in ethyl acetate (50ml) and the solution was washed with water (3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on silica gel column. Compound **2a**: Yield: 20%; m.p. 101°C; ^{1}H-NMR ($CDCl_3$): δ 7.84 (d, 8.2 Hz, 1H) H-6; 7.47-7.24 (m, 15H) trityl; 5.72 (d, 1.4 Hz, 1H) H-1'; 5.59 (d, 8.2 Hz, 1H) H-5; 4.38 (m, 1H) H-4'; 4.11 (d, 1H) H-3'; 3.62 (d, 2H) H-5', H-5''; 3.24 (s, 1H) H-2'; 2.59, 2.43 (m, 2H) isobutyl -CH_2-; 1.71 (m, 1H) isobutyl -CH-; 0.95 (d, 6H) isobutyl (-CH_3)$_2$. ^{13}C-NMR ($CDCl_3$): δ 164.1, C-4; 150.7, C-2; 143.4, trityl; 141.4, C-6; 128.8, 128.3, 127.6, trityl; 101.5, C-5; 91.4 C-1'; 87.9, trityl; 82.1, C-4'; 76.0/72.3, C-2'/C-3'; 62.5, C-5'; 56.1, isobutyl -CH_2-; 28.6 isobutyl -CH-; 20.7, isobutyl (-CH_3)$_2$. MS (FAB$^+$): (M+H)$^+$ calc. for $C_{32}H_{35}N_3O_5$: 542.2655, found 542.2707. Compound **3a**: Yield: 37%; m.p. 99-100°C; ^{1}H-NMR ($CDCl_3$): δ 7.93 (d, 8.0 Hz, 1H) H-6; 7.47-7.22 (m, 15H) trityl; 6.12 (d, 4.7 Hz, 1H) H-1'; 5.38 (d, 8.0 Hz, 1H) H-5; 4.37 (m, 1H) H-2'; 3.82 (m, 1H) H-4'; 3.50 (m, 2H) H-5', H-5''; 3.30 (t, 1H) H-3'; 2.52, 2.35 (m, 2H) isobutyl -CH_2-; 1.64 (m, 1H) isobutyl -CH-; 0.85 (d, 6H) isobutyl (-CH_3)$_2$. ^{13}C-NMR ($CDCl_3$): δ 165.0, C-4; 151.3, C-2; 143.6, trityl; 142.7, C-6; 128.9, 128.1, 127.5, trityl; 101.1, C-5; 87.5, trityl; 86.1, C-1'; 82.2, C-4'; 75.8/64.5, C-2'/C-3'; 63.7, C-5'; 56.1, isobutyl -CH_2-; 28.6 isobutyl -CH-; 20.7, isobutyl (-CH_3)$_2$. MS (FAB$^+$): (M+H)$^+$ calc. for $C_{32}H_{35}N_3O_5$: 542.2655, found 542.2689.

5'-O-Trityl-2'-deoxy-2'-N-benzylamino-*xylo*- uridine 2b and 5'-O-trityl-3'-deoxy-3'-N-benzylamino-*ara*-uridine 3b: A mixture of compound **1a** (1mmol) and benzylamine (5mmol) in DMSO (3ml) was heated at 95°C for 19h. The reaction mixture was diluted with ethyl acetate (50ml) and washed with water (3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column. Compound **2b**: Yield: 18%; m.p. 105°C; ^{1}H-NMR ($CDCl_3$): δ 7.79 (d, 8.2 Hz, 1H) H-6; 7.69-7.29 (m, 20H) trityl and aromatic; 5.83 (d, 1.4 Hz, 1H) H-1'; 5.56 (d, 8.2 Hz, 1H) H-5; 4.44 (m, 1H) H-4'; 4.15 (m, 1H) H-3'; 3.93 (2xd, 2H) benzyl -CH_2-, 3.64 (m, 2H) H-5', H-5''; 3.35 (s, 1H) H-2'. ^{13}C-NMR ($CDCl_3$): δ 164.3, C-4; 150.8, C-2; 143.5, trityl; 141.4, C-6; 139.7, 128.8, 128.6, 128.2, 127.4, 127.3, trityl and benzyl; 101.4, C-5; 91.2, C-1'; 87.6, trityl; 82.5, C-4'; 75.6/71.6, C-2'/C-3'; 62.4, C-5'; 52.1, benzyl -CH_2-. MS (FAB$^+$): (M+H)$^+$ calc. for $C_{35}H_{33}N_3O_5$: 576.2498, found 576.2559. Compound **3b**: Yield: 62%; m.p. 99°C; ^{1}H-NMR ($CDCl_3$): δ 7.86 (d, 8.1 Hz, 1H) H-6; 7.41-7.20 (m, 20H) trityl and aromatic; 6.11 (d, 4.8 Hz, 1H) H-1'; 5.34 (d, 8.1 Hz, 1H) H-5; 4.37 (t, 1H) H-2'; 3.81 (m, 3H) H-4'and benzyl -CH_2-, 3.43 (m, 3H) H-3', H-5', H-5''. ^{13}C-NMR ($CDCl_3$): δ 165.0, C-4; 151.3, C-2; 143.6, trityl; 142.7, C-6; 139.8, 128.9, 128.6, 128.4, 128.1, 127.5, 127.3, trityl and benzyl; 101.1, C-5; 87.5, trityl; 86.0, C-1'; 81.8, C-4'; 76.0/63.6, C-2'/C-3'; 63.6, C-5'; 51.9, benzyl -CH_2-. MS (FAB$^+$): (M+H)$^+$ calc. for $C_{35}H_{33}N_3O_5$: 576.2498, found 576.2510.

5'-O-Trityl-2'-deoxy-2'-N-cyclohexylamino-*xylo*- uridine 2c and 5'-O-trityl-3'-deoxy-3'-N-cyclohexylamino-*ara*-uridine 3c: A mixture of compound **1a** (1mmol) and cyclohexylamine (5mmol) in DMSO (3ml) was heated at 95°C for 23h. The reaction mixture was diluted with ethyl acetate (50ml) and washed with water (3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column. Compound **2c**: Yield: 14%; m.p. 91°C; ^{1}H-NMR ($CDCl_3$): δ 7.86 (d, 8.2 Hz, 1H) H-6; 7.50-7.26 (m, 15H) trityl; 5.73 (d, 1.8 Hz, 1H) H-1'; 5.61 (d, 8.2 Hz, 1H) H-5; 4.42 (m, 1H) H-4'; 4.13 (d, 1H) H-3'; 3.63 (d, 2H) H-5', H-5''; 3.48 (bs, 1H) H-2'; 2.62 (m, 1H) cyclohexyl -CH-; 1.77 (m, 4H) and 1.18 (m, 6H) -(CH_2)$_5$-. ^{13}C-NMR ($CDCl_3$): δ 164.2, C-4; 150.8, C-2; 143.5, trityl; 141.4, C-6; 128.8, 128.2, 127.5, trityl; 101.5, C-5; 91.7, C-1'; 87.8, trityl; 82.0, C-4'; 76.4/68.9,

C-2'/C-3'; 62.5, C-5'; 54.7, cyclohexyl -CH-; 34.1, 33.7, 26.1 and 25.2, -$(CH_2)_5$-. MS (FAB^+): $(M+H)^+$ calc. for $C_{34}H_{37}N_3O_5$: 568.2811, found 568.2849. Compound **3c**: Yield: 61%; m.p. 114-115°C; ^{1}H-NMR ($CDCl_3$): δ7.92 (d, 8.1 Hz, 1H) H-6; 7.45-7.17 (m, 15H) trityl; 6.11 (d, 4.7 Hz, 1H) H-1'; 5.37, (d, 8.2 Hz, 1H) H-5; 4.35 (m, 1H) H-2'; 3.81 (m, 1H) H-4'; 3.49 (m, 3H) H-3', H-5', H-5''; 2.48 (m, 1H) cyclohexyl -CH-; 1.81 (m, 4H) and 1.00 (m, 6H) -$(CH_2)_5$-. ^{13}C-NMR ($CDCl_3$): δ 164.8, C-4; 151.3, C-2; 143.6, trityl; 142.6, C-6; 129.0, 128.2, 127.5, trityl; 101.3, C-5; 87.5, trityl; 85.9, C-1'; 82.3, C-4'; 76.3/61.1, C-2'/C-3'; 63.4, C-5'; 55.0, cyclohexyl -CH-; 33.8, 26.1 and 25.2, -$(CH_2)_5$-. MS (FAB^+): $(M+H)^+$ calc. for $C_{34}H_{37}N_3O_5$: 568.2811, found 568.2878.

5'-O-Trityl-2'-deoxy-2'-N-pyrrolidino-*xylo*- uridine 2d and 5'-O-trityl-3'-deoxy-3'-N-pyrrolidino-*ara*-uridine 3d: A mixture of compound **1a** (1mmol) and pyrrolidine (5mmol) in DMSO (3ml) was heated at 95°C for 5h. The reaction mixture was diluted with ethyl acetate (50ml) and washed with water (3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column. Compound **2d**: Yield: 27%; m.p. 112-113°C; ^{1}H-NMR ($CDCl_3$): δ 7.83 (d, 8.2 Hz, 1H) H-6; 7.49-7.26 (m, 15H) trityl; 6.15 (d, 2.7 Hz, 1H) H-1'; 5.66 (d, 8.2 Hz, 1H) H-5; 4.44 (d, 3.3Hz, 1H) H-3'; 4.31 (m, 1H) H-4'; 3.56 (m, 2H) H-5', H-5''; 2.91 (d, 2.7 Hz, 1H) H-2'; 2.68 (m, 4H) -CH_2-N-CH_2-; 1.82 (bs, 4H) -CH_2-CH_2-. ^{13}C-NMR ($CDCl_3$): δ 164.2, C-4; 150.5, C-2; 143.5, trityl; 142.1, C-6; 128.7, 128.2, 127.5, trityl; 102.2, C-5; 88.3, C-1'; 87.7, trityl; 81.1, C-4'; 78.2/74.8, C-2'/C-3'; 62.4, C-5'; 52.6, -CH_2-N-CH_2-; 23.4, -CH_2-CH_2-. MS (FAB^+): $(M+H)^+$ calc. for $C_{32}H_{33}N_3O_5$: 540.2498, found 540.2460. Compound **3d**: Yield: 52%; m.p. 112-113°C; ^{1}H-NMR ($CDCl_3$): δ 7.76 (d, 8.1 Hz, 1H) H-6; 7.5-7.2 (m, 15H) trityl; 6.11 (d, 3.6 Hz, 1H) H-1'; 5.39 (d, 8.1 Hz, 1H) H-5; 4.67 (bs, 1H) H-2'; 4.2 (m, 1H) H-4'; 3.46 (m, 2H) H-5', H-5''; 2.95 (m, 1H) H-3'; 2.58 (m, 4H) -CH_2-N-CH_2-; 1.74 (bs, 4H) -CH_2-CH_2-. ^{13}C-NMR ($CDCl_3$): δ 165.5, C-4; 150.9, C-2; 143.9, trityl; 143.4, C-6; 129.0, 128.1, 127.4, trityl; 100.7, C-5; 87.3/86.9, trityl/ C-1'; 80.9, C-4'; 73.3/71.7, C-2'/C-3'; 64.9, C-5'; 52.0, -CH_2-N-CH_2-; 23.5 -CH_2-CH_2-. MS (FAB^+): $(M+H)^+$ calc. for $C_{32}H_{33}N_3O_5$: 540.2498, found 540.2436.

5'-O-Trityl-2'-deoxy-2'-N-piperidino-*xylo*- uridine 2e and 5'-O-trityl-3'-deoxy-3'-N-piperidino-*ara*-uridine 3e: A mixture of compound **1a** (1mmol) and piperidine (5mmol) in DMSO (3ml) was heated at 90°C for 4h. The reaction mixture was diluted with ethyl acetate (50ml) and washed with water (3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column. Compound **2e**: Yield: 18%; m.p. 126-127°C; ^{1}H-NMR ($CDCl_3$): δ 7.71 (d, 8.2 Hz, 1H) H-6; 7.49-7.29 (m, 15H) trityl; 6.14 (d, 4.4 Hz, 1H) H-1'; 5.67 (d, 8.2 Hz, 1H) H-5; 4.48 (m, 1H) H-3'; 4.13 (m, 1H) H-4'; 3.51 (m, 2H) H-5', H-5''; 3.05 (m, 1H) H-2'; 2.56 (m, 4H) -CH_2-N-CH_2-; 1.60 and 1.50 (m, 6H) -CH_2-CH_2-CH_2-. ^{13}C-NMR ($CDCl_3$): δ 163.9, C-4; 150.5, C-2; 143.5, trityl; 142.0, C-6; 128.7, 128.2, 127.5, trityl; 102.9, C-5; 87.7, trityl; 85.8, C-1'; 81.1, C-4'; 79.2/72.8, C-2'/C-3'; 62.5, C-5'; 51.9, -CH_2-N-CH_2-; 25.9 and 24.3, -CH_2-CH_2-CH_2-. MS (FAB^+): $(M+H)^+$ calc. for $C_{33}H_{35}N_3O_5$: 554.2655, found 554.2643. Compound **3e**: Yield: 50%; m.p. 118°C; ^{1}H-NMR ($CDCl_3$): δ 7.82 (d, 8.0 Hz, 1H) H-6; 7.54-7.23 (m, 15H) trityl; 6.07 (d, 4.0 Hz, 1H) H-1'; 5.39 (d, 8.0 Hz, 1H) H-5; 4.81 (m, 1H) H-2'; 4.16 (m, 1H) H-4'; 3.45 (m, 2H) H-5', H-5''; 3.07 (m, 1H) H-3'; 2.56 (m, 4H) -CH_2-N-CH_2-; 1.56 (m, 6H) -CH_2-CH_2-CH_2- ^{13}C-NMR ($CDCl_3$): δ 165.4, C-4; 150.4, C-2; 143.6, trityl; 143.3, C-6; 128.7, 127.7, 127.0, trityl; 100.1, C-5; 86.8, trityl and C-1'; 78.4, C-4'; 73.4/70.0, C-2'/C-3'; 65.0, C-5'; 51.3, -CH_2-N-CH_2-; 26.0 and 24.3, -CH_2-CH_2-CH_2-. MS (FAB^+): $(M+H)^+$ calc. for $C_{33}H_{35}N_3O_5$: 554.2655, found 554.2561.

5'-O-Trityl-2'-deoxy-2'-N-morpholino-*xylo*- uridine 2f and 5'-O-trityl-3'-deoxy-3'-N-morpholino-*ara*-uridine 3f: A mixture compound **1a** (1mmol) and morpholine (5mmol) in DMSO (3ml) was heated at 90°C for 15h. The reaction mixture was diluted with ethyl acetate (50ml) and washed with water (3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column. Compound **2f**: Yield: 27%; m.p. 100-101°C; ^{1}H-NMR ($CDCl_3$): δ 7.74 (d, 8.1 Hz, 1H) H-6; 7.48-7.26 (m, 15H) trityl; 6.13 (d, 3.9 Hz, 1H) H-1'; 5.68 (d, 8.1 Hz, 1H) H-5; 4.49 (bs, 1H) H-3'; 4.16 (m, 1H) H-4'; 3.75 (m, 4H) -CH_2-O-CH_2-, 3.58 (ddd, 2H) H-5', H-5''; 2.95 (m,

1H) H-2'; 2.63 (m, 4H) -CH_2-N-CH_2-. ^{13}C-NMR ($CDCl_3$): δ 164.0, C-4; 150.6, C-2; 143.5, trityl; 141.9, C-6; 128.8, 128.3, 127.6, trityl; 102.8, C-5; 87.9, trityl; 86.7, C-1'; 81.1, C-4'; 78.8/72.4, C-2'/C-3'; 66.9, -CH_2-O-CH_2-; 62.4, C-5'; 51.8, -CH_2-N-CH_2-. MS (FAB^+): $(M+H)^+$ calc. for $C_{32}H_{33}N_3O_6$: 556.2448, found 556.2473. Compound **3f**: Yield: 52%; m.p. 126°C; ^{1}H-NMR ($CDCl_3$): δ 7.84 (d, 8.1 Hz, 1H) H-6; 7.53-7.23 (m ,15H) trityl; 6.06 (d, 4.0 Hz, 1H) H-1'; 5.42 (d, 8.1 Hz, 1H) H-5; 4.82 (bs, 1H) H-2'; 4.15 (m, 1H) H-4'; 3.70 (bs, 4H) -CH_2-O-CH_2-, 3.48 (m, 2H) H-5', H-5''; 3.07 (m, 1H) H-3'; 2.63 (m, 4H) -CH_2-N-CH_2-. ^{13}C-NMR ($CDCl_3$): δ 165.3, C-4; 150.9, C-2; 143.9, trityl; 143.2, C-6; 128.9, 128.1, 127.4, trityl; 100.8, C-5; 87.4, trityl; 86.5, C-1'; 78.1, C-4'; 72.4/70.9, C-2'/C-3'; 67.2, -CH_2-O-CH_2-; 64.5, C-5'; 51.2, -CH_2-N-CH_2-. MS (FAB^+): $(M+H)^+$ calc. for $C_{32}H_{33}N_3O_6$: 556.2448, found 556.2369.

5'-O-Trityl-2'-deoxy-2'-N-(ethyl *iso*nipecotatyl)-*xylo*-uridine 2g and 5'-O-trityl-3'-deoxy-3'-N-(ethyl *iso*nipecotatyl)-*ara*-uridine 3g: A mixture of compound **1a** (1mmol) and ethyl *iso*nipecotate (5mmol) in DMSO (3ml) was heated at 95°C for 7h. The reaction mixture was diluted with ethyl acetate (50ml) and washed with water (3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column. Compound **2g**: Yield: 26%; m.p. 105°C; ^{1}H-NMR ($CDCl_3$): δ 7.70 (d, 8.1 Hz, 1H) H-6; 7.47-7.24 (m, 15H) trityl; 6.09 (d, 4.2 Hz, 1H) H-1'; 5.65 (d, 8.1 Hz, 1H) H-5; 4.44 (bs, 1H) H-3'; 4.12 (m, 3H) ethyl -CH_2- and H-4'; 3.53 (m, 2H) H-5', H-5''; 3.18 (m, 1H) H-2'; 3.04-1.67 (m, 9H) -CH_2-N-CH_2-, -CH_2-CH-CH_2-; 1.26 (t, 3H) ethyl CH_3. ^{13}C-NMR ($CDCl_3$): δ 174.9 ethyl CO; 163.9, C-4; 150.4, C-2; 143.5, trityl; 141.8, C-6; 128.7, 128.2, 127.5, trityl; 102.8, C-5; 87.8, trityl; 86.1, C-1'; 81.0, C-4'; 78.6/72.7, C-2'/C-3'; 62.5, C-5'; 60.6, ethyl CH_2; 50.7 and 50.2, -CH_2-N-CH_2-; 40.9, nipecotyl -CH-; 28.2, nipecotyl -CH_2-; 14.3, ethyl -CH_3. MS (FAB^+): $(M+H)^+$ calc. for $C_{36}H_{39}N_3O_7$: 626.2866, found 626.2812. Compound **3g**: Yield: 52%; m.p. 105°C; ^{1}H-NMR ($CDCl_3$): δ 7.90 (d, 8.1 Hz, 1H) H-6; 7.50-7.25 (m, 15H) trityl; 6.04 (d, 4.7 Hz, 1H) H-1'; 5.39 (d, 8.1 Hz, 1H) H-5; 4.77 (m, 1H) H-2'; 4.14 (q, 2H) ethyl -CH_2-; 4.05 (m, 1H) H-4'; 3.45 (m, 2H) H-5', H-5''; 3.21 (m, 1H) H-3'; 2.96-1.69 (m, 9H) -CH_2-N-CH_2-, -CH_2-CH-CH_2-; 1.26 (t, 3H) ethyl CH_3. ^{13}C-NMR ($CDCl_3$): δ 175.1, ethyl CO; 165.4, C-4; 150.9, C-2; 143.8, trityl; 143.3, C-6; 128.9, 128.1, 127.4, trityl; 100.7, C-5; 87.2, trityl; 86.2, C-1'; 77.9, C-4'; 71.9/70.5, C-2'/C-3'; 64.5, C-5'; 60.5, ethyl -CH_2-; 51.9 and 48.5, -CH_2-N-CH_2-; 41.3, nipecotyl -CH-; 28.9 and 28.6, nipecotyl -CH_2-; 14.4, ethyl -CH_3. MS (FAB^+): $(M+H)^+$ calc. for $C_{36}H_{39}N_3O_7$: 626.2866, found 626.2793.

5'-O-Trityl-3'-deoxy-3'-N-anilino-*ara*-uridine 3h: A mixture of compound **1a** (1mmol) and aniline (10mmol) in DMSO (2ml) was heated at 95°C for 42h and then at 110°C for 26h. The reaction mixture was diluted with ethyl acetate (50ml) and washed with water (3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column. Yield: 50%; m.p. 121-122°C; ^{1}H-NMR ($CDCl_3$): δ 7.83 (d, 8.1 Hz, 1H) H-6; 7.79-7.23 (m, 15H) trityl; 7.15 (m, 2H) and 6.75 (m, 3H), anilino; 6.12 (d, 4.0 Hz, 1H) H-1'; 5.41 (d, 8.1 Hz, 1H) H-5; 4.40 (t, 1H) H-2'; 3.91 (m, 2H) H-3', H-4'; 3.56 (m, 2H) H-5', H-5''. ^{13}C-NMR ($CDCl_3$): δ 165.1, C-4; 151.2, C-2; 146.9, anilino; 143.7, trityl; 142.9, C-6; 129.6, 129.1, 128.3, 127.6, trityl; 118.5, 113.9, anilino; 101.2, C-5; 87.7, trityl; 86.5, C-1'; 82.8, C-4'; 75.7/61.3, C-2'/C-3'; 64.1, C-5'. MS (FAB^+): $(M+H)^+$ calc. for $C_{34}H_{31}N_3O_5$: 562.2342, found 562.2320.

5'-O-Trityl-3'-deoxy-3'-N-(*p*-methoxyanilino)-*ara*-uridine 3i: A mixture of compound **1a** (1mmol) and p-methoxyaniline (7mmol) in DMSO (3ml) was heated at 90°C for 29h and then at 110°C for 26h. The reaction mixture was diluted with ethyl acetate (50ml) and washed with water (3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column. Yield: 74%; m.p. 118-119°C; ^{1}H-NMR ($CDCl_3$): δ 7.80 (d, 8.1 Hz, 1H) H-6; 7.49-7.26 (m, 15H) trityl; 6.72 (m, 4H), anilino; 6.08 (d, 3.8 Hz, 1H) H-1'; 5.37 (d, 8.1 Hz, 1H) H-5; 4.42 (bs, 1H) H-2'; 3.88 (m, 2H) H-3' and H-4'; 3.74 (s, 3H) OCH_3; 3.56 (m, 2H) H-5', H-5''. ^{13}C-NMR ($CDCl_3$): δ 165.1, C-4; 152.8, anilino; 151.0, C-2; 143.7, trityl; 142.9, C-6; 140.9, anilino; 129.0, 128.1, 127.5, trityl; 115.4, 115.2, anilino; 101.0, C-5; 87.6, trityl; 86.5, C-1'; 82.8, C-4'; 75.4/62.1, C-2'/C-3'; 64.1, C-5'; 55.9, -OCH_3. MS (FAB^+):

$(M)^+$ calc. for $C_{35}H_{33}N_3O_6$: 591.2369, (peak overlaps with mass reference compound, PEG).

5'-O-Trityl-2'-O-acetyl-3'-deoxy-3'-N-(N-acetyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecanyl)-*ara*-uridine 4j: A mixture of compound **1a** (0.5mmol) and 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (1.5mmol) in DMSO (2ml) was heated at 120°C for 12h. The reaction mixture was diluted with ethyl acetate (30ml) and washed with water (3x10 ml). The ethylacetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column. The mixture of products was dissolved in pyridine (10ml) and acetic anhydride (3mmol) was added dropwise at room temperature. After 24h pyridine was removed under reduced pressure by coevaporation with toluene. The solid residue was dissolved in ethyl acetate (25ml) and the organic layer was washed with saturated aqueous sodium bicarbonate followed by water (3x10ml each). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on silica gel column. Yield: 28%; m.p. 95°C; ^{1}H-NMR ($CDCl_3$): δ 7.78 (d, 8.1 Hz, 1H) H-6; 7.47-7.27 (m, 15H) trityl; 6.21 (d, 5.5 Hz, 1H) H-1'; 5.62 (m, 1H) H-2'; 5.43 (d, 8.1 Hz, 1H) H-5; 3.96 (m, 1H) H-4'; 3.74-3.40 and 2.87 (m, 27H) H-3', H-5', H-5'' and diazacyclooctadecanyl; 2.11 (s, 3H) ester -CH_3; 2.0 (s, 3H) amide -CH_3. ^{13}C-NMR ($CDCl_3$): δ 171.0, ester CO; 169.1, amide CO; 163.5, C-4; 150.1, C-2; 143.5, trityl; 141.3, C-6; 128.8, 128.1, 127.5, trityl; 101.3, C-5; 87.2, trityl; 83.7, C-1'; 78.5, C-4'; 72.6, C-2'; 71.3, 71.2, 71.0, 70.7, 70.4, 69.8, diazacyclooctadecanyl; 68.2, C-3'; 62.5, C-5'; 52.3, 49.9, 47.0, diazacyclooctadecanyl; 21.7, ester -CH_3; 20.7, amide -CH_3. MS (FAB^+): $(M+H)^+$ calc. for $C_{44}H_{54}N_4O_{11}$: 815.3867, found 815.3795.

General procedure for the deprotection: Compounds **2a-f, 3a-f, 3h-i** (approx. 0.5 mmol each) were dissolved in a mixture of methanol-water (10ml, 4:1v/v). The solution was applied to a column made of Amberlite IR-120 H+ (7cmx2.5cm settled volume) in water. In order to remove tritanol that was generated after deprotection, the column was eluted with methanol. Once all tritanol was eluted (tlc), the column was further eluted either with aqueous ammonia solution (3%; for compounds **2a-d, 2f, 3a-b**) or with a mixture of methanol-aqueous ammonia [30% aq. ammonia (10ml) and methanol (90ml); for compounds **2e, 3c-f, 3h-i**]. *Ammonia solution must be added within 15min of loading the compounds on the column.*

2'-Deoxy-2'-N-isobutylamino-*xylo*- uridine 8a and 3'-deoxy-3'-N-isobutylamino-*ara*-uridine 9a: Compound **8a**: Yield: 73%; hygroscopic; ^{1}H-NMR (D_2O): δ 7.93 (d, 8.1 Hz, 1H) H-6; 5.87 (d, 8.1 Hz, 1H) H-5'; 5.84 (d, 3.2 Hz, 1H) H-1'; 4.33 (m, 2H) H-3', H-4'; 3.91 (m, 2H) H-5', H-5"; 3.33 (m, 1H) H-2'; 2.53 (d, 2H) isobutyl -CH_2-; 1.79 (m, 1H) isobutyl -CH-; 0.88 (d, 6H) isobutyl (-CH_3)$_2$. ^{13}C-NMR (D_2O): δ 166.8, C-4; 152.1, C-2; 142.9, C-6; 102.5, C-5; 90.3, C-1'; 83.8, C-4'; 74.5/71.6, C-2'/C-3'; 60.5, C-5'; 55.7, isobutyl -CH_2-; 27.7, isobutyl -CH-; 20.5, isobutyl (-CH_3)$_2$. Compound **9a**: Yield: 64%; hygroscopic; ^{1}H-NMR (D_20): δ 7.85 (d, 8.0 Hz, 1H) H-6; 6.12 (d, 4.8 Hz, 1H) H-1'; 5.85 (d, 8.1 Hz, 1H) H-5; 4.42 (m, 1H) H-2'; 3.89 (m, 3H) H-4', H-5', H-5" ; 3.12 (m, 1H) H-3'; 2.53 (m, 2H) isobutyl -CH_2-; 1.77 (m, 1H) isobutyl -CH-; 0.90 (d, 6H) isobutyl (-CH_3)$_2$. ^{13}C-NMR (D_2O+DMSO-d_6): δ 167.3, C-4; 152.7, C-2; 144.9, C-6; 102.3, C-5; 87.4, C-1'; 84.1, C-4'; 76.0/66.4, C-2'/C-3'; 63.3, C-5'; 56.9, isobutyl -CH_2-; 29.1, isobutyl -CH-; 22.1, 21.95, isobutyl (-CH_3)$_2$.

2'-Deoxy-2'-N-benzylamino-*xylo*- uridine 8b and 3'-deoxy-3'-N-benzylamino-*ara*-uridine 9b: Compound **8b**: Yield: 75%; hygroscopic; ^{1}H-NMR (D_2O): δ 7.76 (d, 8.1 Hz, 1H) H-6; 7.33 (m, 5H), aromatic; 5.83 (d, 3.5 Hz, 1H) H-1'; 5.74 (d, 8.1 Hz, 1H) H-5; 4.30 (m, 2H) H-3', H-4'; 3.88 (m, 4H) benzyl -CH_2-, H-5', H-5''; 3.30 (m, 1H) H-2'. ^{13}C-NMR (D_2O+DMSO-d_6): δ 166.6, C-4; 151.9, C-2; 142.8, C-6; 138.9, 129.6, 129.2, 128.4, aromatic; 102.6, C-5; 90.1, C-1'; 83.7, C-4'; 74.9/70.2, C-2'/C-3'; 60.6, C-5'; 51.6, benzyl -CH_2-. Compound **9b**: Yield: 65%; m.p. 182-183°C; ^{1}H-NMR (D_2O+DMSO-d_6): δ 7.91 (d, 8.1 Hz, 1H) H-6; 7.46 (m, 5H) aromatic; 6.20 (d, 4.6 Hz, 1H) H-1'; 5.78 (d, 8.1 Hz, 1H) H-5; 4.50 (t, 1H) H-2'; 4.00 (m, 5H) H-4', H-5', H-5''and benzyl -CH_2-; 3.27 (m, 1H) H-3'. ^{13}C-NMR (D_2O+DMSO-d_6): δ 166.3, C-4; 152.1, C-2; 144.6, C-6; 140.8, 130.0, 129.9, 128.7, aromatic; 101.6, C-5; 87.2, C-1'; 84.3, C-4'; 75.6/65.8, C-2'/C-3'; 63.1, C-5'; 52.3, benzyl -CH_2-. MS (FAB^+): $(M+H)^+$ calc. for $C_{16}H_{19}N_3O_5$: 334.1403, found 334.1429.

2'-Deoxy-2'-N-cyclohexylamino-*xylo*-uridine 8c and 3'-deoxy-3'-N-cyclohexyl-amino-*ara*-uridine 9c: Compound **8c**: Yield: 79%; hygroscopic; ^{1}H-NMR (D_2O): δ 7.94 (d, 8.1 Hz, 1H) H-6; 5.87 (m, 2H) H-1', H-5; 4.32 (m, 2H) H-4', H-3'; 3.93 (d, 2H) H-5', H-5''; 3.59 (d, 1H) H-2'; 2.73 (m, 1H) cyclohexyl -CH-; 1.70 and 1.18 (m, 10H) -$(CH_2)_5$-. ^{13}C-NMR (D_2O): δ 166.9, C-4; 152.2, C-2; 142.9, C-6; 102.8, C-5; 90.3, C-1'; 83.7, C-4'; 74.9/67.9, C-2'/C-3'; 60.6, C-5'; 55.5, cyclohexyl -CH-; 32.8, 32.4, 26.1 and 25.4, -$(CH_2)_5$-. Compound **9c**: Yield: 66%; m.p. 191-193°C; ^{1}H-NMR (D_2O+DMSO-d_6): δ 7.70 (d, 8.1 Hz, 1H) H-6; 5.92 (d, 4.7 Hz, 1H) H-1'; 5.63, (d, 8.1 Hz, 1H) H-5; 4.12 (m, 1H) H-2'; 3.65 (m, 3H) H-4', H-5', H-5''; 3.11 (m, 1H) H-3'; 2.49 (m, 1H) cyclohexyl -CH-; 1.60 and 0.96 (m, 10H) -$(CH_2)_5$-. ^{13}C-NMR (D_2O+DMSO-d_6): δ 166.2, C-4; 152.1, C-2; 144.5, C-6; 101.6, C-5; 86.8, C-1'; 84.3, C-4'; 76.3/62.7, C-2'/C-3'; 62.7, C-5'; 55.6, cyclohexyl -CH-; 34.4, 33.6, 27.1, 26.2 and 26.0, -$(CH_2)_5$-. MS (FAB$^+$): $(M+H)^+$ calc. for $C_{15}H_{23}N_3O_5$: 326.1716, found 326.1731.

2'-Deoxy-2'-N-pyrrolidino-*xylo*- uridine 8d and 3'-deoxy-3'-N-pyrrolidino-*ara*-uridine 9d: Compound **8d**: Yield: 80%; hygroscopic; ^{1}H-NMR (D_2O): δ 7.91 (d, 8.1 Hz, 1H) H-6; 6.06 (d, 4.1 Hz, 1H) H-1'; 5.91 (d, 8.1 Hz, 1H) H-5; 4.53 (m, 1H) H-3'; 4.23 (m, 1H) H-4'; 3.90 (m, 2H) H-5', H-5''; 3.06 (m, 1H) H-2'; 2.70 (m, 4H) -CH_2-N-CH_2-; 1.80 (bs, 4H) -CH_2-CH_2-. ^{13}C-NMR (D_2O): δ 166.9, C-4; 152.1, C-2; 143.2, C-6; 103.4, C-5; 88.0, C-1'; 82.9, C-4'; 77.8/73.9, C-2'/C-3'; 60.6, C-5'; 52.9, -CH_2-N-CH_2-; 23.3, -CH_2-CH_2-. Compound **9d**: Yield: 73%; m.p. 218-220°C; ^{1}H-NMR (D_2O+DMSO-d_6): δ 7.70 (d, 8.1 Hz, 1H) H-6; 5.88 (d, 4.5 Hz, 1H) H-1'; 5.64 (d, 8.1 Hz, 1H) H-5; 4.39 (m, 1H) H-2'; 3.91 (m, 1H) H-4'; 3.63 (m, 2H) H-5', H-5''; 2.74 (m, 1H) H-3'; 2.53 (m, 4H) -CH_2-N-CH_2-; 1.67 (m, 4H) -CH_2-CH_2-. ^{13}C-NMR (D_2O+DMSO-d_6): δ 165.3, C-4; 151.7, C-2; 144.2, C-6; 101.1, C-5; 86.5, C-1'; 82.5, C-4'; 73.8/72.0, C-2'/C-3'; 63.1, C-5'; 52.8, -CH_2-N-CH_2-; 23.9, -CH_2-CH_2-. MS (FAB$^+$): $(M+H)^+$ calc. for $C_{13}H_{19}N_3O_5$: 298.1403, found 298.1377.

2'-Deoxy-2'-N-piperidino-*xylo*-uridine 8e and 3'-deoxy-3'-N-piperidino-*ara*-uridine 9e: Compound **8e**: Yield: 77%; hygroscopic; ^{1}H-NMR (D_2O+DMSO-d_6): δ 7.87 (d, 8.2 Hz, 1H) H-6; 6.12 (d, 5.4 Hz, 1H) H-1'; 5.93 (d, 8.2 Hz, 1H) H-5; 4.57 (m, 1H) H-3'; 4.14 (m, 1H) H-4'; 3.87 (m, 2H) H-5', H-5''; 3.11 (m, 1H) H-2'; 2.56 (m, 4H) -CH_2-N-CH_2-; 1.52 (m, 6H) -CH_2-CH_2-CH_2-. ^{13}C-NMR (D_2O+DMSO-d_6): δ 165.5, C-4; 151.8, C-2; 143.3, C-6; 103.9, C-5; 85.9, C-1'; 83.6, C-4'; 79.9/72.4, C-2'/C-3'; 61.1, C-5'; 52.8, -CH_2-N-CH_2-; 26.4 and 25.0, -CH_2-CH_2-CH_2- . Compound **9e**: Yield: 71%; m.p. 213-214°C; ^{1}H-NMR (D_2O+DMSO-d_6): δ 7.94 (d, 8.2 Hz, 1H) H-6; 6.05 (d, 4.3 Hz, 1H) H-1'; 5.90 (d, 8.2 Hz, 1H) H-5; 4.63 (m, 1H) H-2'; 4.22 (m, 1H) H-4'; 3.89 (m, 2H) H-5', H-5''; 2.98 (m, 1H) H-3'; 2.70 (m, 4H) -CH_2-N-CH_2-; 1.66 (m, 6H) -CH_2-CH_2-CH_2- ^{13}C-NMR (D_2O+DMSO-d_6): δ 165.6, C-4; 151.8, C-2; 144.3, C-6; 101.2, C-5; 87.1, C-1'; 80.4, C-4'; 73.9/71.3, C-2'/C-3'; 63.7, C-5'; 52.4, -CH_2-N-CH_2-; 26.6 and 25.1, -CH_2-CH_2-CH_2-. MS (FAB$^+$): $(M+H)^+$ calc. for $C_{14}H_{21}N_3O_5$: 312.1559, found 312.1540.

2'-Deoxy-2'-N-morpholino-*xylo*- uridine 8f and 3'-deoxy-3'-N-morpholino-*ara*-uridine 9f: Compound **8f**: Yield: 83%; hygroscopic; ^{1}H-NMR (D_2O): δ 7.90 (d, 8.2 Hz, 1H) H-6; 6.13 (d, 5.2 Hz, 1H) H-1'; 5.95 (d, 8.2 Hz, 1H) H-5; 4.62 (m, 1H) H-3'; 4.18 (m, 1H) H-4'; 3.89 (m, 2H) H-5', H-5''; 3.77 (m, 4H) -CH_2-O-CH_2-; 3.14 (m, 1H) H-2'; 2.76 (m, 4H) -CH_2-N-CH_2-. ^{13}C-NMR (D_2O): δ 166.5, C-4; 151.9, C-2; 143.0, C-6; 103.7, C-5; 85.7, C-1'; 82.7, C-4'; 78.3/71.6, C-2'/C-3'; 66.7, -CH_2-O-CH_2-; 60.6, C-5'; 51.4, -CH_2-N-CH_2-. Compound **9f**: Yield: 75%; m.p. 212-214°C; ^{1}H-NMR (DMSO-d_6+D_2O): δ 7.69 (d, 8.1 Hz, 1H) H-6; 5.82 (d, 4.9 Hz, 1H) H-1'; 5.57 (d, 8.1 Hz, 1H) H-5; 4.33 (t, 1H) H-2'; 3.87 (m, 1H) H-4'; 3.55 (m, 6H) -CH_2-O-CH_2-, H-5', H-5''; 2.77 (m, 1H) H-3'; 2.49 (m, 4H) -CH_2-N-CH_2-. ^{13}C-NMR (DMSO-d_6+D_2O): δ 165.0, C-4; 151.5, C-2; 143.9, C-6; 101.0, C-5; 86.1, C-1'; 79.6, C-4'; 72.6/70.9, C-2'/C-3'; 67.4, -CH_2-O-CH_2-; 62.9, C-5'; 51.7, -CH_2-N-CH_2-. MS (FAB$^+$): $(M+H)^+$ calc. for $C_{13}H_{19}N_3O_6$: 314.1352, found 314.1341.

3', 5'-Di-O-acetyl-2'-deoxy-2'-N-(ethyl *iso*nipecotatyl)-*xylo*-uridine 10g and 2', 5'-Di-O-acetyl-3'-deoxy-3'-N-(ethyl *iso*nipecotatyl)-*ara*-uridine 4g: A solution of compound **2g** (0.56 mmol) in aqueous acetic acid (80%, 10 ml) was heated at 100°C for 0.5h. Acetic acid was removed under reduced pressure and coevaporated twice with ethanol. The solid residue was triturated with ether to remove tritanol. The compound thus obtained

was dissolved in dry pyridine (15 ml) and acetic anhydride (3mmol) was added dropwise at ambient temperature. The solution was stirred at room temperature overnight. After adding ice-cold water to the reaction mixture, pyridine was removed under reduced pressure and coevaporated twice with toluene. The oily material was partitioned between ethyl acetate and saturated sodium hydrogencarbonate solution. The organic layer was separated, dried over sodium sulphate and evaporated to dryness. The residue was purified by column chromatography on silica gel. Compound **10g**: Yield: 60%; hygroscopic; ^{1}H-NMR ($CDCl_3$): δ 7.47 (d, 8.2 Hz, 1H) H-6; 6.19 (d, 4.6 Hz, 1H) H-1'; 5.80 (d, 8.2 Hz, 1H) H-5; 5.55 (m, 1H) H-3'; 4.35 (t, 1H) H-4'; 4.28 (d, 2H) and 4.11 (m, 2H) ethyl -CH_2-, H-5', H-5''; 3.02-1.82 (m, 10H) H-2', -CH_2-N-CH_2-, -CH_2-CH-CH_2-; 2.11 and 2.09 (2xs, 6H) 2xacetyl -CH_3; 1.23 (t, 3H) ethyl CH_3. ^{13}C-NMR ($CDCl_3$): δ 174.7 ethyl CO; 170.5, 169.4 2xacetyl CO; 163.5, C-4; 150.3, C-2; 139.8, C-6; 103.3, C-5; 85.2, C-1'; 78.1, C-4'; 76.4/72.7, C-2'/C-3'; 61.5/60.4, C-5'/ethyl CH_2; 50.7 and 50.2, -CH_2-N-CH_2-; 40.6, nipecotyl -CH-; 28.0, nipecotyl -CH_2-; 20.8, 2xacetyl -CH_3; 14.2, ethyl -CH_3. Compound **3g** (0.7 mmol) was deprotected and acetylated as above. Compound **4g**: Yield: 77%; hygroscopic; ^{1}H-NMR ($CDCl_3$): δ 7.48 (d, 8.2 Hz, 1H) H-6; 6.10 (d, 4.6 Hz, 1H) H-1'; 5.72 (d, 8.2 Hz, 1H) H-5; 5.57 (m, 1H) H-2'; 4.34 (m, 2H) and 4.17 (m, 3H), ethyl -CH_2-, H-4', H-5', H-5''; 3.05 (m, 1H) H-3'; 2.90-1.74 (m, 9H) -CH_2-N-CH_2-, -CH_2-CH-CH_2-; 2.12 and 1.99 (2xs, 6H) 2xacetyl -CH_3; 1.24 (t, 3H) ethyl CH_3. ^{13}C-NMR ($CDCl_3$): δ 174.6, ethyl CO; 170.7, 168.9, 2xacetyl CO; 163.5, C-4; 150.1, C-2; 140.8, C-6; 101.5, C-5; 84.7, C-1'; 76.6, C-4'; 71.6/71.2, C-2'/C-3'; 64.6/60.5, C-5'/ethyl -CH_2-; 51.7 and 48.4, -CH_2-N-CH_2-; 40.7, nipecotyl -CH-; 28.3 and 28.1, nipecotyl -CH_2-; 20.8 and 20.6, 2xacetyl -CH_3; 14.2, ethyl -CH_3.

3'-Deoxy-3'-N-anilino-*ara*-uridine 9h: Yield: 53%; m.p. >230°C; ^{1}H-NMR (DMSO-d_6+D_2O): δ 7.73 (d, 8.1 Hz, 1H) H-6; 7.08 (t, 2H) and 6.59 (m, 3H), anilino; 5.97 (d, 4.2 Hz, 1H) H-1'; 5.59 (d, 8.1 Hz, 1H) H-5; 4.01 (m, 1H) H-2'; 3.85 (m, 1H) H-4'; 3.64 (m, 3H) H-3', H-5', H-5''. ^{13}C-NMR (DMSO-d_6+D_2O): δ 164.7, C-4; 151.3, C-2; 148.4, anilino; 143.5, C-6; 130.0, 117.7, 113.6, anilino; 100.9, C-5; 86.3, C-1'; 83.7, C-4'; 74.7/61.1, C-2'/C-3'; 62.3, C-5'. MS (FAB$^+$): $(M+H)^+$ calc. for $C_{15}H_{17}N_3O_5$: 320.1246, found 320.1277.

3'-Deoxy-3'-N-(*p*-methoxyanilino)-*ara*-uridine 9i: Yield: 64%; m.p. >230°C; ^{1}H-NMR (DMSO-d_6): δ 7.70 (d, 8.1 Hz, 1H) H-6; 6.67 (m, 4H), anilino; 5.99 (d, 4.0 Hz, 1H) H-1'; 5.58 (d, 8.1 Hz, 1H) H-5; 3.99 (bs, 1H) H-2'; 3.85 (m, 1H) H-4'; 3.63 (bs, 6H) OCH_3, H-3', H-5', H-5''. ^{13}C-NMR (DMSO-d_6+D_2O): δ 164.5, C-4; 152.2, anilino; 151.2, C-2; 143.5, anilino; 142.5, C-6; 115.6, 114.8, anilino; 100.8, C-5; 86.4, C-1'; 83.9, C-4'; 74.6/61.9, C-2'/C-3'; 62.4, C-5'; 56.3, -OCH_3. MS (FAB$^+$): $(M+H)^+$ calc. for $C_{16}H_{19}N_3O_6$: 350.1352, found 350.1359.

5'-O-Trityl-2,2'-O-anhydro-3'-deoxy-3'-N-pyrrolidinouridine 5d: To a solution of compounds **2d** and **3d** (2mmol) in dry pyridine (10ml), methanesulphonyl chloride (10mmol) in dry pyridine (10ml) was added dropwise at 0°C. The reaction mixture was left at +4°C overnight. Pyridine was removed in vacuuo and residual pyridine was removed by coevaporation with toluene. The oily residue was dissolved in dichloromethane (100ml) and washed with saturated aqueous sodium bicarbonate solution (3x25ml). The organic layer was dried over sodium suphate, filtered and evaporated to dryness. The dark brown residue was dissolved in dry pyridine (20ml) and the solution was heated under reflux for 6h. The reaction mixture was cooled and pyridine was removed by co-evaporation with toluene. The product was purified by column chromatography on silica gel. Yield: 64%; m.p. 85°C; ^{1}H-NMR ($CDCl_3$): δ 7.44-7.21 (m, 16H) H-6 and trityl; 6.1 (d, 5.9 Hz, 1H) H-1'; 5.98 (d, 7.4 Hz, 1H) H-5; 5.28 (dd, 6.2 Hz and 1.8 Hz, 1H) H-2'; 4.48 (m, 1H) H-4'; 3.35 (m, 1H) H-3'; 3.07 (d, 2H) H-5', H-5''; 2.56 (m, 4H) -CH_2-N-CH_2-; 1.81 (bs, 4H) -CH_2-CH_2-. ^{13}C-NMR ($CDCl_3$): δ 171.8, C-4; 159.4, C-2; 143.4, trityl; 134.8, C-6; 128.5, 128.1, 127.4, trityl; 110.2, C-5; 90.4, C-1'; 87.1, trityl; 86.1, C-2'; 83.9, C-4'; 70.1, C-3'; 64.0, C-5'; 51.5, -CH_2-N-CH_2-; 23.5 -CH_2-CH_2-. MS (FAB$^+$): $(M+H)^+$ calc. for $C_{32}H_{31}N_3O_4$: 522.2393, found 522.2382.

5'-O-Trityl-2,2'-O-anhydro-3'-deoxy-3'-N-piperidinouridine 5e: The product was synthesised and purified as described in case of compound **5d**. Yield: 53%; m.p. 109°C; ^{1}H-NMR ($CDCl_3$): δ 7.43-7.20 (m, 16H) H-6 and trityl; 6.05 (d, 5.9 Hz, 1H) H-1'; 5.94 (d, 7.4 Hz, 1H) H-5; 5.32 (dd, 5.9 Hz, 1H) H-2'; 4.47 (m, 1H) H-4'; 3.37

(m, 1H) H-3'; 3.05 (m, 2H) H-5', H-5''; 2.43 (m, 4H) -CH_2-N-CH_2-; 1.60 and 1.44 (m, 4H) -CH_2-CH_2-CH_2-. ^{13}C-NMR ($CDCl_3$): δ 171.9, C-4; 159.5, C-2; 143.4, trityl; 134.8, C-6; 128.6, 128.1, 127.5, trityl; 110.3, C-5; 90.6, C-1'; 87.2, trityl; 84.7, C-2'; 81.8, C-4'; 72.1, C-3'; 64.4, C-5'; 51.2, -CH_2-N-CH_2-; 25.7 and 23.8 -CH_2-CH_2-CH_2-. MS (FAB$^+$): $(M+H)^+$ calc. for $C_{33}H_{33}N_3O_4$: 536.2549, found 536.2501.

1-(5-O-Trityl-2,3-dideoxy-2-S-thiophenyl-3-N-pyrrolidino-β-D-ribofuranosyl)-uracil 6: To a solution of thiophenol (10mmol) in DMSO, tetramethylguanidine (12mmol) was added. After 15m at room temperature, compound **5d** (1mmol) was added to the solution. The reaction mixture was heated at 100°C for 30h. The dark brown solution was cooled to room tempture and ethyl acetate (25ml) was added. The organic layer was washed with water (3x10ml), separated and dried over sodium suphate, filtered and evaporated to dryness. The product was purified by column chromatography on silica gel. Yield: 27%; m.p. 104°C; ^{1}H-NMR ($CDCl_3$): δ 7.71 (d, 8.2 Hz) H-6; 7.55-7.23 (m, 20H) trityl and thiophenyl; 6.24 (d, 6.2 Hz, 1H) H-1'; 5.02 (d, 8.1 Hz, 1H) H-5; 4.37 (m, 1H) H-4'; 4.11 (t, 1H) H-2'; 3.85 (m, 1H) H-3'; 3.63 (dd, 1H) and 3.39 (dd, 1H) H-5', H-5''; 2.69 (m, 4H) -CH_2-N-CH_2-; 1.80 (bs, 4H) -CH_2-CH_2-. ^{13}C-NMR ($CDCl_3$): δ 163.1, C-4; 150.2, C-2; 143.2, trityl; 140.1, C-6; 133.7, 133,1, 129.2, thiophenyl; 128.9, 128.2, 127.7, trityl; 102.3, C-5; 90.4, C-1'; 87.9, trityl; 79.5, C-4'; 66.0, C-5'; 63.5/57.0 C-2'/C-3'; 50.9, -CH_2-N-CH_2-; 23.7 -CH_2-CH_2-. MS (FAB$^+$): $(M+H)^+$ calc. for $C_{38}H_{37}N_3O_4S$: 632.2583, found 632.2481.

1-(5-O-Trityl-2,3-dideoxy-2,3-N-*iso*butylepimino-β-D-*ribo*furanosyl)- uracil 7: A mixture of compounds **2a** and **3a** (1mmol), triphenylphosphine (1.5mmol) and diisopropyl azodicarboxylate (2mmol) in dichloromethane (10ml) was stirred at room temperature for 8h under nitrogen. Dicholoromethane was removed under reduced pressure and the compound was purified by column chromatography on silica gel. Yield: 65%; m.p. 89-90°C; ^{1}H-NMR ($CDCl_3$): δ 7.63 (d, 8.1 Hz, 1H) H-6; 7.47-7.24 (m, 15H) trityl; 5.9 (s, 1H) H-1'; 5.13 (d, 8.1 Hz, 1H) H-5; 4.34 (t, 1H) H-4'; 3.35 (ddd, 2H) H-5', H-5''; 2.7 (d, 4.7Hz, 1H)/2.58 (d, 4.7Hz, 1H) H-2'/H-3'; 2.22 (m, 2H) -N-CH_2-; 1.9 (m, 1H) amino -CH-; 0.99 (d, 6H) amino $(CH_3)_2$. ^{13}C-NMR ($CDCl_3$): δ 163.9, C-4; 150.7, C-2; 143.2, trityl; 140.9, C-6; 128.7, 128.1, 127.5, trityl; 101.8, C-5; 87.5, trityl; 86.8, C-1'; 81.9, C-4'; 65.9/64.4, C-5'/-N-CH_2-; 48.8/46.2, C-2'/C-3'; 29.1, amino -CH-; 20.9, amino -$(CH_3)_2$. MS (FAB$^+$): $(M+H)^+$ calc. for $C_{32}H_{33}N_3O_4$: 524.2549, found 524.2499.

REFERENCES AND NOTES

NCL Communication No. 5899.

1. Mitsuya, H; Weinhold, K.J.; Furman, P.A.; St. Clair, M.H.; Lehrman, S.N.; Gallo, R.C.; Bolognesi, D.; Barry, D.W.; Broder, S., *Proc. Natl. Acad. Sci. U.S.A.* **1985**, 82, 7096- 100.
2. Mitsuya, H; Broder, S., *Proc. Natl. Acad. Sci. U.S.A.* **1986**, 83, 1911-5.
3. a) Balzarini, J.; Kang, G.-J.; Dalal, M.; Herdewijn, P.; De Clercq, E.; Broder, S.; Johns, D.G., *Mol. Pharmacol.*, **1987**, 32, 162-7. b) Hamamoto, Y.; Nakashima, H.; Matsui, T.; Matsuda, A.; Ueda, T.; Yamamoto, N., *Antimicrob. Agents Chemother.*, **1987**, 31, 907-10.
4. a) De Clercq, E. *Aids Research Human Retroviruses*, **1992**, 8, 119-34.; b) Balzarini, J. *Pharm. World Sci.* **1994**, 16, 113-26.; c) De Clercq, E. *Nucleoside Nucleotide*, **1994**, 13, 1271-95.
5. a) Huryn, D.M.; Okabe, M. *Chem. Rev.* **1992**, 92, 1745-68 *and the references cited therein.* b) Herdewijn, P.; De Bruyn, A.; Wigerinck, P.; Hendrix, C.; Kerremans, L.; Rozenski, J.; Busson, R. *J. Chem. Soc. PT 1*, **1994**, 249-55.
6. a) Wigerinck, P.; Van Aerschot, A.; Janssen, G.; Glaes, P.; Balzarini, J.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **1990**, 33, 868-73. b) Ariza, X.; Garces, J.; Vilarrasa, J. *Tetrahedron Lett.* **1992**, 33, 4069-72.
7. Balzarini, J.; Perez-Perez, M.-J.; San-Felix, A.; Scholas, D.; Perno, C.-F.; Vandamme, A.-M.; Camarasa, M.-J.; De Clercq, E. *Proc. Natl. Acad. Sci. USA* **1992**, 89, 4392-6.
8. Vial, J.-M.; Johansson, N.G.; Vrang, L.; Chattopadhyaya, *J. Antiv. Chem. Chemother.* **1990**, 1, 183-202.

9. a) Wu, J-C.; Pathak, T.; Tong, W.; Vial, J-M.; Remaud, G.; Chattopadhyaya, J. *Tetrahedron*, **1988**, 44, 6705-22. b) Wu, J-C.; Chattopadhyaya, J. *Tetrahedron*, **1989**, 45, 4507-22. c) Tong, W.; Xi, Z.; Gioeli, C.; Chattopadhyaya, J. *Tetrahedron*, **1991**, 47, 3431-50.
10. a) Cheng, Y.-C.; Dutschman, G.E.; Bastow, K.F.; Sarngadharan, M.G.; Ting, R.Y.C. *J. Biol. Chem.*, **1987**, 262, 2187-9. b) Lin, T.-S.; Chen, M.-S.; McLaren, C.; Gao, Y.-S.; Ghazzouli, I.; Prusoff, W.H. *J. Med. Chem.*, **1987**, 30, 440-4. c) Lin, T.-S.; Prusoff, W.H. *J. Med. Chem.*, **1978**, 21, 109-12. d) Matsuda, A.; Watanabe, K.A.; Fox, J.J. *J. Org. Chem.*, **1980**, 45, 3274-8.
11. a) Sakthivel, K.; Krishna Kumar, R.; Pathak, T. *Tetrahedron*, **1993**, 49, 4365-72. b) Sakthivel, K.; Bera, S.; Pathak, T. *Tetrahedron*, **1993**, 49, 10387-92. c) Sakthivel, K.; Suresh, C. G.; Pathak, T. *Tetrahedron*, in press.
12. a) Morr, M.; Ernst, L. *Chem. Ber.*, **1979**, 112, 2815-28. b) Celewicz, L.; Urjasz, W.; Golankiewicz, K. *Nucleosides Nucleotides*, **1993**, 12, 951-6.
13. a) Wengel, J.; Pedersen, E.B.; Vestergaard, B.F. *Synthesis*, **1992**, 319-22. b) Petersen, G.V.; Platz, J.; Nielsen, C.; Wengel, J. *Synthesis*, **1994**, 823-6.
14. Mofatt, J.G. In *Nucleoside Analogues: Chemistry, Biology and Medical Applications*; Walker, R.T.; De Clercq, E.; Ecstein, F. Eds.; Plenum Press, New York, **1979**, pp 71-164.
15. Codington, J.F.; Fecher, R.; Fox, J.J. *J. Org. Chem.* **1962**, 27, 163-7.
16. a) Kowollik, G.; Langen, P. *Z. Chem.* **1975**, 15, 147-8. b) Reichman, U.; Hollenberg, D.H.; Chu, C.K.; Watanabe, K.A.; Fox, J.J. *J. Org. Chem.* **1976**, 41, 2042-3. c) Hollenberg, D.H.; Watanabe, K.A.; Fox, J.J. *J. Med. Chem.* **1977**, 20, 113-6. d) Mete, A.; Hobbs, J.B.; Scopes, D.I.C.; Newton, R.F. *Tetrahedron Lett.* **1985**, 26, 97-100. e) Nyilas, A.; Chattopadhyaya, J. *Synthesis* **1986**, 196-8.

(*Received in UK* 19 *April* 1994; *revised* 22 *November* 1994; *accepted* 25 *November* 1994)