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Reactions of Dimesylthymidine with Secondary Amines: Easy Access to 3',5'-Dideoxy-3'-Substituted-5'-Alkylaminothymidines - New Classes of Potential Antiviral Aminonucleosides#.

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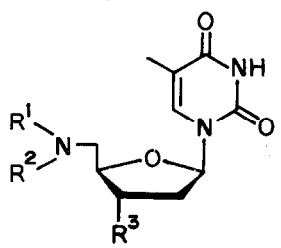
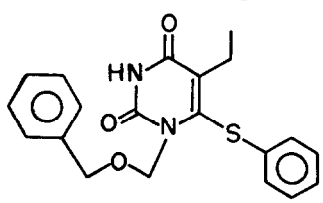
Abstract: *3',5'-Di-O-mesylthymidine* ***4a*** *(DMST) on reaction with secondary amines undergoes hitherto unknown "one-pot-two-steps" transformation to produce 2,3'-O-anhydro-5'-deoxy-5'-alkylaminothymidines* ***5a-h****. Most of the amines used, irrespective of their basicities showed remarkable selectivity towards the 5'-substitution over the 2,3'-O-anhydro ring formation. Compounds* ***5a-h*** *could be used as intermediates for the synthesis of a variety of 3',5'-dideoxy-3'-substituted-5'-alkylaminothymidines of the type* ***9, 10a-b, 11****.*

A variety of aminonucleosides were synthesised to study their biological properties[1]. Among them 5'-deoxy-5'-aminothymidine **1a** was shown to be a good competitive inhibitor of phosphorylation of thymidine kinase and a modest inhibitor of thymidylate kinase[2]. 5'-Deoxy-5'-aminothymidine was also reported[3] to inhibit the replication of HSV-1 selectively in cultured cells. 5'-(Bromoacetamido)-5'-deoxythymidine showed[4] significant activity in the p388 mouse leukemia screen. Polyoxins, a group of antibiotics are pyrimidine nucleoside peptide derivatives[5] with an aminoacyl moiety attached *via* the 5'-amino group of the nucleosides. 5'-Deoxy-5'-alkylammoniumnucleosides[6] were synthesised to study their interactive properties with natural polynucleotides. The 5'-hydroxyl moiety of several nucleoside analogues has been replaced with amino group in an attempt to reduce their toxicity with retention of antiviral activity [3b,7]. Several other 5'-deoxy-5'-N-substituted nucleosides, such as, 5'-azido-5'-deoxythymidine and 5'-azido-2',5'-dideoxy-5-iodouridine showed antiviral activities against Herpes Simplex Virus[8]; Zbiral and co-workers reported[8b] the synthesis and antiretroviral



1

a. $R^1 = R^2 = H$, $R^3 = OH$
b. $R^1, R^2 = C$, $R^3 = N_3$



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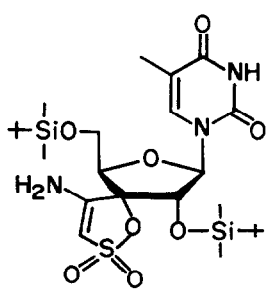


3

properties of 3'-azido-5'-isocyano-3',5'- dideoxythymidine **1b** and related compounds. In another development, very recently, Miyasaka and co-workers have shown[9] that *a modified nucleoside 2 having no free primary hydroxyl group, i.e. a nucleoside which can not be phosphorylated,* inhibits HIV-1 more efficiently than the corresponding nucleoside with free hydroxyl group; compound **2** and related derivatives[9,10] interact, as such, noncompetitively, with a specific allosteric binding site of HIV-1 reverse transcriptase. Another recently reported[11] modified nucleoside, compound **3** with *no free hydroxyl groups* selectively inhibited HIV-1. The last two reports coupled with the aforementioned literature results warrants the synthesis of 3',5'-dideoxy-3',5'-disubstituted thymidine nucleosides.

There are very few reports on the synthesis[8h,12] and antiviral properties[8h,10] of 3',5'-dideoxy-3',5'-disubstituted thymidines, especially when 3'- and 5'-sites are heterosubstituted. *A full evaluation of the biological activity of this type of compounds will be possible only when they are easily accessible.* In order to develop a general methodology for the synthesis of 5'-deoxy-5'-alkylaminothymidines with different substituents at the 3'-sites, we set out to identify versatile intermediates substituted at the 5'-sites and suitably functionalised to undergo further transformations at the 3'-sites. We argued that the ideal reagent should be both basic and moderately nucleophilic in charecter to functionalise the 5'-end of the derivatives of thymidine and form the 2,3'-O-anhydro ring but should stop short of opening the anhydro ring. We report herein, that secondary amines do indeed show such selectivity.

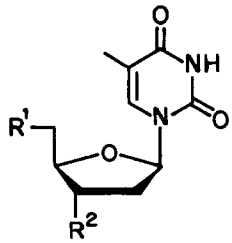
Thus, 3',5'-di-O-mesylthymidine **4a** (DMST)[13] on reaction with secondary amines undergoes a hitherto unknown "one-pot-two-steps" transformation to produce a new class of modified nucleosides **5a-h.** DMST was reacted with neat morpholine, thiomorpholine, piperidine and pyrrolidine at room temperature or directly at 50-60°C to produce compounds **5a-d** respectively. Other bifunctionalised cyclic amines such as 1-methylpiperazine, 1-acetylpiperazine and ethyl *iso*nipecotate reacted with DMST in a similar fashion to produce compounds **5e-g** respectively. In all cases (except for thiomorpholine) the products precipitated out from the reaction mixtures.

DMST reacted with acyclic amine such as diethyl amine in DMF at a much slower rate to furnish a mixture of compounds **5h** and **5j** in a ratio 1.4:1. The ratio was altered in favour of compound **5j** when DMF was substituted with DMSO (**5h**:**5j** = 1:1.2). Use of water as the solvent in the reaction of diethylamine and DMST drastically changed the course of reaction; the only product isolated was compound **5j**.

Reactions of piperidine with DMST in DMSO produced compound **5c** only. Whereas, use of water instead of DMSO produced a mixture of compounds **5c** and **5j** in a ratio 4:1. All these ratios were estimated from the ^{1}H-NMR spectra of the crude products.

In order to establish the structures of the products **5a-h** unambiguously compound **5a**, as a representative example, was synthesised through an independent route. 5'-O-tosylthymidine **4c** (ref. 4a), on reaction with morpholine at room temperature was converted to compound **4d** which on treatment with methanesulfonyl chloride in pyridine produced 3'-O-mesyl-5'-N-morpholino-5'-deoxythymidine **4e**. Compound **4e** on reaction with DBU furnished compound **5a** in good overall yield.

The ^{1}H-NMR of compounds **5a-h** are consistent with the structures assigned. The H-1' resonance appear at @ 5.52-5.77 ppm as a doublet showing small coupling constant ($J_{1',2''}$= @ 3.8 Hz) and the H-3' resonance appears at 5.11-5.22 ppm as broad singlet which are consistent with the literature values[14] for compound **5i**. The H-4' proton couples with H-3', H-5' and H-5'' as evident from the cross peaks observed in the COSY spectrum. In case of all the compounds the H-4' signal appears either as sextet or septet. The carbon signals were assigned on the basis of HET-COSY for the morpholino- and the diethylamino- derivatives **5a** and **5h** respectively. It was

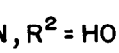


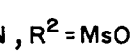
4

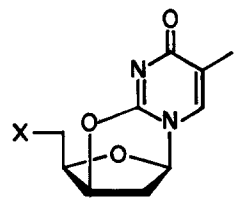
a. $R^1 = R^2 = MsO$

b. $R^1 = R^2 = TsO$

c. $R^1 = TsO$, $R^2 = HO$

d. R^1 =  , $R^2 = HO$

e. R^1 =  , $R^2 = MsO$



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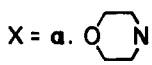
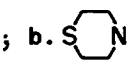
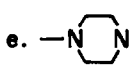
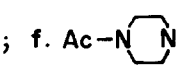
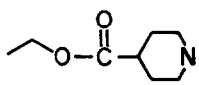
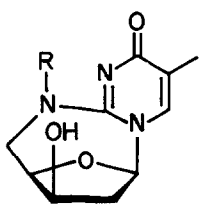
X = a.  ; b. 

c.  ; d. 

e.  ; f. 

g.  ; h. 

i. TsO ; j. MsO

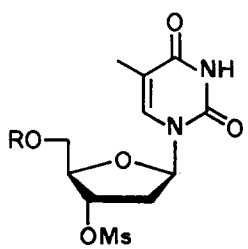


6

a. R = H

b. R = CH_3

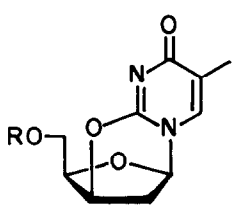
c. R = n-Propyl



7

a. R = Trityl

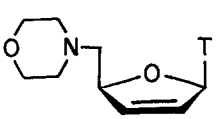
b. R = H



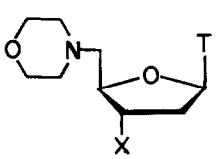
8

a. R = Trityl

b. R = H

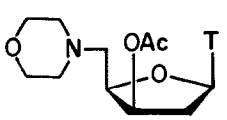


9



10

a. $X = N_3$, b. X = 



11

assumed that the carbon signals of the rest of the compounds followed the same order.

The mechanism of conversion of DMST to compound **5a** is believed to involve formation of compound **4e** by nucleophilic displacement of the 5'-O-mesyl group of DMST, *followed by anhydro ring formation.* In fact, if the reaction mixture of DMST and morpholine was not heated at 50°C the major product isolated was compound **4e**. Prior formation of compound **5j** is also ruled out by the fact that unreacted starting material was recovered when **5j** was reacted with morpholine at 50°C. It is assumed that the same mechanism is operating in case of all the reported compounds **5b-h.** *These observations should be contrasted with the reactions of ammonia and primary amines with 3',5'-di-O-tosylthymidine 4b (DTST)* ; DTST reacted with ammonia and methyl amine to produce[14] 2,5'-imino- and 2,5'-(methylimino)-1-(2-deoxy-β-D-*threo*-pentofuranosyl)-thymines **6a** and **6b** respectively, *via* the formation of 2,3'-O-anhydro-5'-O-tosylthymidine **5i** and subsequent attack on C-2. *The formation of compounds 5a-h from the reactions of DMST and secondary amines was not obvious* as it was expected that piperidine (pKa 11.123)[15] and pyrrolidine (pKa 11.27)[15], which were stronger amines than methylamine (pKa 10.657)[15] and ammonia (pKa 9.247)[15] should have produced the anhydro compound **5j** first, by abstracting the N-3 proton[16]. In fact, as mentioned earlier, diethylamine (pKa 11.09)[15], a less nucleophilic amine because of its "flapping" ethyl groups, produced compound **5j** alongside the desired product **5h**, in a roughly equal ratio. It is highly probable that *reactions of DMST and DTST with secondary and primary amines were controlled by the nucleophilicities of the amines and not by their basicities.* It should also be emphasised that the presence of an amino group at the 5'-position facilitated the anhydro ring formation. This conclusion corroborated from the fact that compounds **7a** and **7b** (ref. 13) required 104h and 140h respectively to get converted to compounds **8a** (ref. 17a) and **8b** (ref. 17b) when treated with neat piperidine at room temperature; DMST was converted to compound **5c** under identical conditions within 70h. Whether the tertiary amino group present at the 5'-end of the intermediate (compound of the structure such as **4e**) abstracts the N-3 proton intramolecularly or alters its pKa through intramolecular H-bonding or through-space interactions[18], remains to be established.

In order to synthesise 3',5'-dideoxy-3'-substituted-5'-morpholinothymidines, compound **5a** was subjected to four different reaction conditions. Thus, compound **5a** on reaction with potassium-*tert*-butoxide, lithium azide, sodium thiophenolate and 0.1N sodium hydroxide solution produced compounds **9, 10a-b** and **11** respectively.

In conclusion, we have demonstrated that DMST reacts with secondary amines to generate a new class of aminonucleosides, ready to undergo further transformations; most of the amines used, irrespective of their basicities showed remarkable selectivity towards the 5'-substitution over the 2,3'-O-anhydro ring formation. Reactions of secondary amines with mesylated uridines and related derivatives follow completely different pathways[19]. The antiviral properties of the compounds reported herein will be published in due course.

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Experimental:

Melting points were uncorrected. All amines were purchased from Aldrich, U.S.A. and were used without further purification. Thymidine 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, solvent chloroform-d or dioxane (in case of D_2O) as internal standards.

3'-O-Mesyl-5'-deoxy-5'-N-morpholinothymidine 4e: 5'-O-Tosylthymidine **4c** (2mmol) was reacted with morpholine (neat, 5ml) at room temperature. After 4d, the amine was removed under reduced pressure. The residue was passed through a basic alumina column. The appropriate fractions were collected and solvent was evaporated. The residue was dried by coevaporation with pyridine and was redissolved in the same solvent (10ml). The solution was cooled at 0°C and methanesulphonyl chloride (10mmol) in pyridine (5ml) was added dropwise to it. After completion of the addition, the solution was left at +4°C overnight. The mixture was then poured in saturated sodium bicarbonate solution (30ml) and was extracted with dichloromethane (3x20ml). Dichloromethane solution was evaporated to dryness and the residual pyridine was coevaporated with toluene. The residue thus obtained, was purified on a silica gel column. Yield: 88% (based on compound **4c**), m.p. 130°C. ^{1}H-NMR ($CDCl_3$): δ 9.49 (bs, 1H) N-H; 7.21 (d, 0.9 Hz, 1H) H-6; 6.18 (t, 6.8 Hz, 1H) H-1'; 5.24 (m, 1H) H-3'; 4.31 (dd, 1H) H-4'; 3.75 (m, 4H) H_2C-O-CH_2; 3.14 (s, 3H) SO_2CH_3; 2.75-2.35 (m, 8H) H-2', H-2'', H-5', H-5'', H_2C-N-CH_2; 1.95 (d, 3H) 5-CH_3. ^{13}C-NMR ($CDCl_3$): δ 164.1, C-4; 150.6, C-2; 135.6, C-6; 111.6, C-5; 85.6, C-1'; 81.5, C-4'; 79.9, C-3'; 66.9, H_2C-O-CH_2; 59.7, C-5'; 54.4, H_2C-N-CH_2; 38.6, SO_2CH_3; 37.5, C-2'; 12.7, 5-CH_3.

2,3'-O-Anhydro-5'-deoxy-5'-N-morpholinothymidine 5a: DMST (1mmol) was reacted with neat morpholine (5ml) at room temperature for 20h and then at 60°C for 40h. The reaction mixture was poured into ether and filtered. The residue was washed thoroughly with ether and was purified by column chromatography on basic alumina to yield compound **5a**. This reaction could also be carried out directly at 50°C for 50h. Yield: 80%, m.p. 229°C (decomp). ^{1}H-NMR ($CDCl_3$): δ 7.06 (d, 1.0 Hz, 1H) H-6; 5.58 (d, 3.8 Hz, 1H) H-1'; 5.19 (bs, 1H) H-3'; 4.44-4.37 (sept, 1H) H-4'; 3.67 (m, 4H) H_2C-O-CH_2; 2.8-2.43 (m, 8H) H-2', H-2'', H-5', H-5'', H_2C-N-CH_2; 1.92 (d, 3H) 5-CH_3. ^{13}C-NMR (D_2O): δ 175.9, C-4; 156.1, C-2; 140.0, C-6; 118.8, C-5; 89.4, C-1'; 84.0, C-4'; 80.6, C-3'; 67.2, H_2C-O-CH_2; 59.1, C-5'; 54.3, H_2C-N-CH_2; 33.8, C-2'; 13.6, CH_3.

Synthesis of compound 5a from compound 4e: A solution of compound **4e** (1.5mmol) and DBU (1.65mmol) in dichloromethane (20ml) was stirred for 6h at room temperature. The solvent was then removed under reduced pressure and the residue was purified on basic alumina column. The product thus obtained was similar in every respect with compound **5a**.

2,3'-O-Anhydro-5'-deoxy-5'-N-thiomorpholinothymidine 5b: DMST (1mmol) was reacted with neat thiomorpholine (3ml) at room temperature for 17h and at 50°C for 48h. The reaction mixture was poured in ether and filtered. Saturated sodium bicarbonate solution was added to the residue and the mixture was stirred for 30min. The compound was then extrated with dichloromethane (3x15ml). Dichloromethane fractions were pooled together, dried on sodium sulphate and filtered. The filtrate was evaporated to dryness and the residue was purified on a basic alumina column. Yield: 76%, m.p. 233°C. ^{1}H-NMR ($CDCl_3$): δ 7.0 (s, 1H) H-6; 5.52 (d, 3.8 Hz, 1H) H-1'; 5.17 (bs, 1H) H-3'; 4.4-4.32 (sex, 1H) H-4'; 2.83-2.41 (m, 12H) H-2', H-2'', H-5', H-5'', H_2C-N-CH_2, H_2C-S-CH_2; 1.94 (s, 3H) 5-CH_3. ^{13}C-NMR (D_2O): δ 175.8, C-4; 156.0, C-2; 139.9, C-6; 118.8, C-5; 89.3, C-1'; 84.2, C-4'; 80.6, C-3'; 59.1, C-5'; 55.5, H_2C-N-CH_2; 33.8, C-2'; 27.3, H_2C-S-CH_2; 13.5, CH_3.

2,3'-O-Anhydro-5'-deoxy-5'-N-piperidinothymidine 5c: DMST (1mmol) was reacted with neat piperidine (5ml) at 50°C for 50h. The product was isolated and purified as described in case of compound **5a**. Yield: 85%, m.p. 223°C (decomp). ^{1}H-NMR ($CDCl_3$): δ 6.99 (d, 1.0 Hz, 1H) H-6; 5.52 (d, 3.8 Hz, 1H) H-1'; 5.14 (bs,

1H) H-3'; 4.4-4.33 (sept, 1H) H-4'; 2.78-2.39 (m, 8H) H-2', H-2'', H-5', H-5'', H_2C-N-CH_2; 1.91 (d, 3H) 5-CH_3; 1.6-1.39 (m, 6H) H_2C-CH_2-CH_2. ^{13}C-NMR ($CDCl_3$+DMSO-d_6): δ 170.6, C-4; 152.5, C-2; 135.0, C-6; 116.0, C-5; 86.1, C-1'; 82.4, C-4'; 76.8, C-3'; 57.4, C-5'; 53.7, H_2C-N-CH_2; 32.3, C-2'; 24.5 and 22.6 H_2C-CH_2-CH_2; 11.9, CH_3.

2,3'-O-Anhydro-5'-deoxy-5'-N-pyrrolidinothymidine 5d: DMST (1mmol) was reacted with neat pyrrolidine (5ml) at room temperature for 72h. The product was isolated and purified as described in case of compound **5a**. Yield: 93%, m.p. 215°C. ^{1}H-NMR (DMSO-d_6): δ 7.55 (s, 1H) H-6; 5.77 (d, 1H) H-1'; 5.2 (bs, 1H) H-3'; 4.3 (sex, 1H) H-4'; 2.8-2.3 (m, 8H) H-2', H-2'', H-5', H-5'', H_2C-N-CH_2; 1.75-1.5 (m, 7H) 5-CH_3, H_2C-CH_2. ^{13}C-NMR (DMSO-d_6+$CDCl_3$): δ 170.9, C-4; 153.5, C-2; 136.5, C-6; 115.8, C-5; 86.6, C-1'; 83.7, C-4'; 77.5, C-3'; 55.1, C-5'; 54.0, H_2C-N-CH_2; 32.7, C-2'; 23.1 H_2C-CH_2; 12.8, CH_3.

2,3'-O-Anhydro-5'-deoxy-5'-N-(1-methylpiperazino)thymidine 5e: DMST (1mmol) was reacted with neat 1-methylpiperizine (3ml) at room temperature for 34h and at 50°C for 24h. The product was isolated and purified as described in case of compound **5a**. Yield: 62%, m.p. 238°C. ^{1}H-NMR ($CDCl_3$): δ 6.98 (s, 1H) H-6; 5.52 (d, 3.7 Hz, 1H) H-1'; 5.11 (bs, 1H) H-3'; 4.34 (sept, 1H) H-4'; 2.77-2.36 (m, 12H) H-2', H-2'', H-5', H-5'', (H_2C-N-CH_2)$_2$; 2.22 (s, 3H) N-CH_3; 1.87 (s, 3H) 5-CH_3. ^{13}C-NMR ($CDCl_3$): δ 171.6, C-4; 153.4, C-2; 135.3, C-6; 118.0, C-5; 87.5, C-1'; 83.6, C-4'; 77.5, C-3'; 57.7, C-5'; 54.7 and 53.5, (H_2C-N-CH_2)$_2$; 45.7, N-CH_3; 33.5, C-2'; 13.1, CH_3.

2,3'-O-Anhydro-5'-deoxy-5'-N-(1-acetylpiperazino)thymidine 5f: DMST (1mmol) was reacted with neat 1-acetylpiperazine (3ml) at room temperature for 96h and at 50°C for 48h. The product was isolated and purified as described in case of compound **5a**. Yield: 70%, m.p. 256°C. ^{1}H-NMR ($CDCl_3$): δ 7.55 (s, 1H) H-6; 5.58 (d, 1H) H-1'; 5.22 (bs, 1H) H-3'; 4.37 (m, 1H) H-4'; 2.75-2.3 (m, 12H) H-2', H-2'', H-5', H-5'', (H_2C-N-CH_2)$_2$; 1.95 (s, 3H) NC(O)CH_3; 1.75 (s, 3H) 5-CH_3. ^{13}C-NMR (D_2O): δ 175.8, acetyl CO; 173.4, C-4; 156.1, C-2; 139.9, C-6; 118.7, C-5; 89.3, C-1'; 84.2, C-4'; 80.5, C-3'; 58.3, C-5'; 53.8, 53.4, 46.8 and 42.2, (H_2C-N-CH_2)$_2$; 33.7, C-2'; 21.3, acetyl CH_3; 13.4, CH_3.

2,3'-O-Anhydro-5'-deoxy-5'-N-(ethyl *iso*nipecotatyl)thymidine 5g: DMST (1mmol) was reacted with neat ethyl *iso*nipecotate (3ml) at room temperature for 48h. The reaction mixture was poured in ether and filtered. Saturated sodium bicarbonate solution was added to the residue and the mixture was stirred for 30min. The compound was then extrated with dichloromethane (3x15ml). Dichloromethane fractions were pooled together, dried over sodium sulphate and filtered. The filtrate was evaporated to dryness and the residue was purified on basic alumina column. Yield: 66%, m.p. 230°C. ^{1}H-NMR ($CDCl_3$): δ 7.0 (d, 0.9 Hz 1H) H-6; 5.52 (d, 3.8 Hz, 1H) H-1'; 5.17 (bs, 1H) H-3'; 4.38 (sept, 1H) H-4'; 4.13 (q, 2H) ethyl CH_2; 2.95-1.65 (m, 16H) H-2', H-2'', H-5', H-5'', HC(H_2C-N-CH_2)$_2$, 5-CH_3; 1.25 (t, 3H) ethyl CH_3. ^{13}C-NMR ($CDCl_3$): δ 174.6, ester CO; 171.7, C-4; 153.4, C-2; 135.5, C-6; 117.7, C-5; 87.4, C-1'; 83.7, C-4'; 77.5, C-3'; 59.9 ethyl CH_2; 57.9, C-5'; 53.28 and 53.19, H_2C-N-CH_2; 40.4 and 27.9 H_2C-CH-CH_2; 33.4, C-2'; 13.9, ethyl CH_3; 12.9, CH_3.

2,3'-O-Anhydro-5'-deoxy-5'-N-diethylaminothymidine 5h: DMST (1mmol) was reacted with diethylamine (3ml) in DMF (2ml) at room temperature for 100h. The precipitate formed was filtered and it was found to be compound **5j**. The filtrate was evaporated to dryness and was purified on a basic alumina column to produce the title compound. Yield: 55%, m.p. 191°C. ^{1}H-NMR ($CDCl_3$): δ 6.97 (d, 1.1 Hz, 1H) H-6; 5.5 (d, 3.8 Hz, 1H) H-1'; 5.15 (bs, 1H) H-3'; 4.31-4.24 (sex, 1H) H-4'; 2.9-2.4 (m, 8H) H-2', H-2'', H-5', H-5'', H_2C-N-CH_2; 1.91 (d, 3H) 5-CH_3; 0.97 (t, 6H) ethyl $(CH_3)_2$. ^{13}C-NMR ($CDCl_3$): δ 172.0, C-4; 153.7, C-2; 135.8, C-6; 117.9, C-5; 87.6, C-1'; 84.9, C-4'; 77.6, C-3'; 53.1, C-5'; 47.5, H_2C-N-CH_2; 33.7, C-2'; 13.3, CH_3; 11.7, ethyl $(CH_3)_2$.

2',3',5'-Trideoxy-2'-ene-5'-N-morpholinothymidine 9: A mixture of compound **5a** (1mmol) and potassium *tert*butoxide (2.2mmol) in DMSO (5ml) was stirred at room temperature. After 1h the mixture was poured in water (10ml). The aqueous solution was extracted with dichloromethane (3x15ml). Organic layers were pooled together and washed with water (3x10ml). Dichloromethane solution was dried over sodium sulphate and filtered. The filtrate was evaporated to dryness and the residue was purified on basic alumina column. Yield: 81%, m.p. 125°C. ^{1}H-NMR ($CDCl_3$): δ 7.15 (s, 1H) H-6; 7.02 (m, 1H) H-1'; 6.32 (m, 1H) H-3'; 5.82 (m, 1H) H-2'; 5.03 (m, 1H) H-4'; 3.74 (t, 4H) H_2C-O-CH_2; 2.63 (m, 6H) H-5', H-5'', H_2C-N-CH_2; 1.92 (d, 3H) CH_3. ^{13}C-NMR ($CDCl_3$): δ 164.3, C-4; 151.0, C-2; 135.63/135.58, C-6/C-3'; 125.9, C-2'; 111.1 C-5; 90.1, C-1'; 84.0, C-4'; 66.6, H_2C-O-CH_2; 62.8, C-5'; 54.1, H_2C-N-CH_2; 12.6, CH_3.

3',5'-Dideoxy-3'-azido-5'-N-morpholinothymidine 10a: A mixture of compound **5a** (1mmol) and lithium azide (3mmol) in DMF (5ml) was heated at 140°C. After 4h the mixture was cooled and poured in water (10ml). The aqueous solution was extracted with ethyl acetate (3x15ml). Organic layers were pooled together and washed with water (3x10ml). Ethyl acetate solution was dried on sodium sulphate and filtered. The filtrate was evaporated to dryness. The white foam thus obtained, was purified on basic alumina column. Yield: 62%, hygroscopic. IR (Nujol): 2100 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 9.87 (bs, 1H) H-3; 7.18 (s, 1H) H-6; 6.06 (t, 6.0 Hz and 6.7 Hz, 1H) H-1'; 4.12 (m, 1H) H-3'; 3.98 (m, 1H) H-4'; 3.76 (t, 4H) H_2C-O-CH_2; 2.83-2.32 (m, 8H) H-2', H-2'', H-5', H-5'', H_2C-N-CH_2; 1.95 (s, 3H) CH_3. ^{13}C-NMR ($CDCl_3$): δ 163.8, C-4; 150.4, C-2; 135.9, C-6; 111.6, C-5; 85.9/82.2, C-1'/C-4'; 67.1, H_2C-O-CH_2; 62.5, C-3'; 60.8, C-5'; 54.9, H_2C-N-CH_2; 37.5, C-2'; 12.7, CH_3.

3',5'-Dideoxy-3'-thiophenyl-5'-N-morpholinothymidine 10b: A mixture of compound **5a** (1mmol) and sodium thiophenolate (5mmol) in DMF (5ml) was heated at 60°C. After 16h the mixture was cooled and poured in water (10ml). The aqueous solution was extracted with dichloromethane (3x15ml). Organic layers were pooled together and washed with water (3x10ml). Dichloromethane solution was dried over sodium sulphate and filtered. The filtrate was evaporated to dryness and the residue was purified on basic alumina column. Yield: 54%, m.p. 43°C. ^{1}H-NMR ($CDCl_3$): δ 9.55 (bs, 1H) H-3; 7.51-7.25 (m, 6H) aromatic, H-6; 6.11 (dd, 6.7 Hz and 5.2 Hz, 1H) H-1'; 4.03 (m, 1H) H-4'; 3.72 (t, 4H) H_2C-O-CH_2; 3.54 (m, 1H) H-3'; 2.67-2.64 (m, 2H) and 2.61-2.40 (m, 6H) H-2', H-2'', H-5', H-5'', H_2C-N-CH_2; 1.95 (d, 1.2 Hz, 3H) CH_3. ^{13}C-NMR ($CDCl_3$): δ 164.1, C-4; 150.5, C-2; 135.6, C-6; 133.3, 133.0, 129.5, 128.4, aromatic; 111.2, C-5; 85.1/83.0, C-1'/C-4'; 66.9, H_2C-O-CH_2; 60.6, C-5'; 54.6, H_2C-N-CH_2; 46.9, C-3'; 39.3, C-2'; 12.8, CH_3.

3'-O-Acetyl-5'-deoxy-5'-N-morpholino-*lyxo*thymidine 11: Compound **5a** (1mmol) was reacted with aqueous sodium hydroxide solution (0.1N, 3ml) at room temperature. After 3h, the reaction mixture was neutralised with aqueous hydrochloric acid solution (0.1N). The solution was evaporated to dryness and the residual water was removed by coevaporation with pyridine (3x5ml). The residue was redissolved in pyridine (5ml) and acetic anhydride (5mmol) was added. After 2h the reaction mixture was poured into saturated sodium bicarbonate solution (15ml) and was extracted with dichloromethane (3x15ml). Dichloromethane solution was evaporated to dryness and the residual pyridine was coevaporated with toluene. The residue thus obtained, was purified on a silica gel column. Yield: 73% (based on compound **5a**), m.p. 95°C. ^{1}H-NMR ($CDCl_3$): δ 7.43 (s, 1H) H-6; 6.26 (dd, 2.9 Hz and 8.0 Hz, 1H) H-1'; 5.41 (m, 1H) H-3'; 4.21 (m, 1H) H-4'; 3.75 (t, 4H) H_2C-O-CH_2; 2.85 - 2.49 (m, 7H) and 2.09 - 1.96 (m, 1H) H-2', H-2'', H-5', H-5'', H_2C-N-CH_2; 2.11 (s, 3H) acetate CH_3; 1.96 (s, 3H) CH_3. ^{13}C-NMR ($CDCl_3$): δ 169.1, acetyl CO; 163.6, C-4; 150.4, C-2; 135.1, C-6; 110.4, C-5; 83.7/79.9, C-1'/C-4'; 72.9, C-3'; 66.5, H_2C-O-CH_2; 57.1, C-5'; 53.9, H_2C-N-CH_2; 39.3, C-2'; 20.5, acetate CH_3; 12.4, CH_3.

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19. This subject will be treated separately in a forthcoming publication. Sakthivel, K.; Bera, S.; Pathak, T. *manuscript in preparation.*