



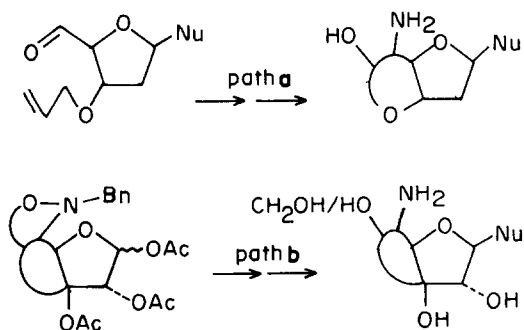
An Entry to Unusual Classes of Nucleoside Analogues

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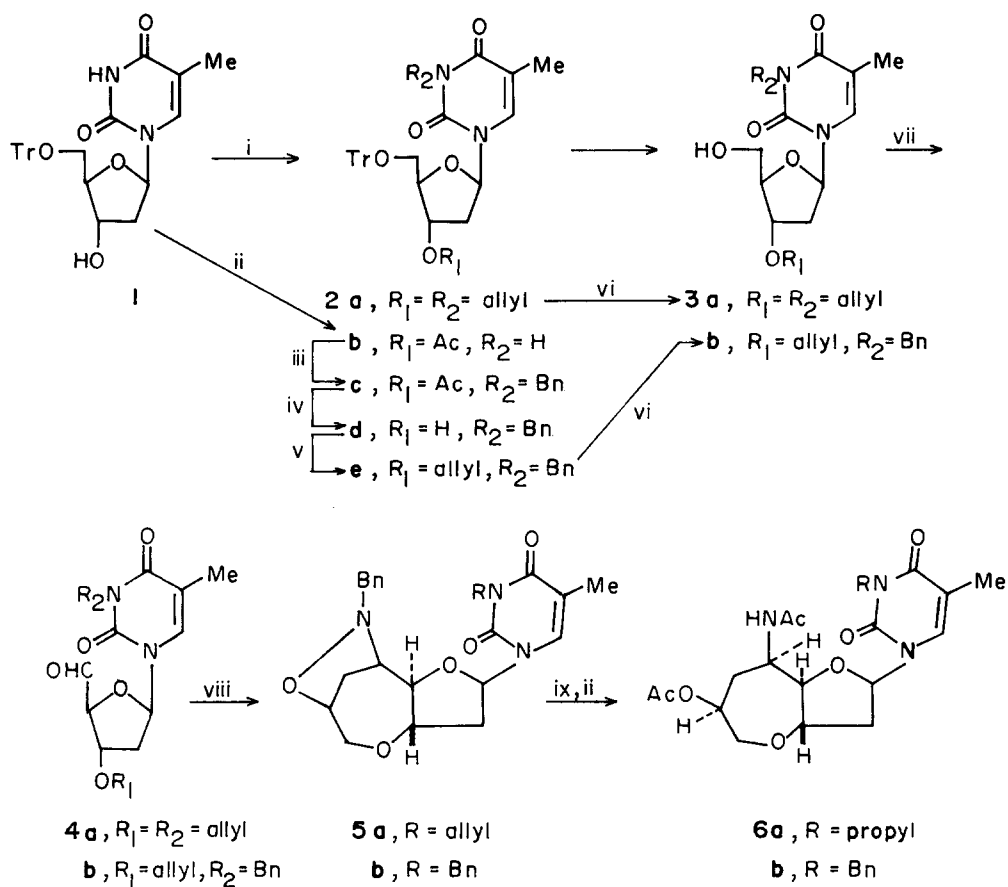
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Abstract : Nucleosides **6a**, **6b** and **16-18** having additional carbocycle or oxygen heterocycle fused to the ribose moiety have been synthesized by two routes. While **6a** and **6b** could be obtained from thymidine using 1, 3-dipolar cycloaddition approach, Vorbrüggen reaction on appropriately preformed carbocyclic derivatives furnished **16-18**. © 1997 Published by Elsevier Science Ltd.

The development of new methodologies enabling the synthesis of unnatural nucleosides plays a significant role in search for new antitumor and antiviral agents. The quest for unusual nucleoside analogues has led to structural alterations in either the heterocyclic ring or the sugar moiety or both, leading to effective inhibitors of HIV, HSV and tumor cells.¹⁻⁶ Nevertheless, synthetic routes to newer classes of nucleosides are in great demand. We have, therefore, taken up a programme to establish methodologies for nucleosides having the furanose ring fused to carbocycles of different ring-sizes or to oxygen heterocycles, towards development of biologically important molecules. We envisaged two approaches (**scheme 1**) for this, both based on the simple and effective nitron cycloaddition route : (i) Building up the carbocycle/heterocycle onto a nucleoside, using 3'- and 5'- hydroxyl groups of the furanose ring, and (ii) Construction of carbocyclic or heterocyclic derivatives from appropriately substituted D-glucose, followed



Scheme 1



Scheme 2 . Reagents and conditions : i , Allyl bromide (2.5 eq), NaH, DMF, 20h ; ii, $\text{Ac}_2\text{O}/\text{Py}$, rt, 12h ; iii, BnBr, NaH, DMF, 5h; iv, NaOMe, MeOH, 10°C , 2h ; v, Allyl bromide (5 eq), $\text{Bu}_4\text{N}^+\text{Br}^-$ (0.1 eq), CH_2Cl_2 , NaOH (50%), rt, 10 h ; vi, 80% HOAc, 80°C , 5h; vii, TFA-Py- DCC (0.5:1:3 molar eq), C_6H_6 -DMSO (1:1), 18h ; viii, BnNH OH , EtOH, NaHCO_3 ,rt, 12h, then reflux, 2h ; ix, $\text{H}_2/\text{Pd-C}$ (10%), EtOH, reflux, 6h .

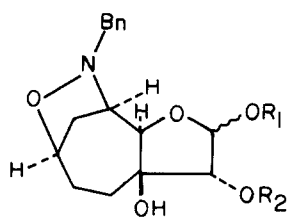
by introduction of nucleoside bases. In this communication, we report the development of the methodologies for the synthesis of unnatural nucleosides **6**, **16**, **17** and **18**.

We originally attempted to prepare the 3'-*O*- allyl derivative of thymidine through initial blocking of the 5'-hydroxyl group by tritylation. Treatment of **1** (scheme 2) with allyl bromide, however, afforded the *N,O*- diallyl derivative **2a** which was detritylated with acetic acid to give **3a** (in 54% overall yield). In another process, **1** was converted to the *N*- benzyl derivative **2d** with the hope that the hydrogenolysis step to be carried out subsequently would remove the benzyl group also. The desired conversion was achieved *via* protection of the hydroxyl group (Ac₂O/Py), reaction with benzyl bromide, and deprotection (NaOMe/MeOH). Allylation furnished **2e** (79% yield based on **1**) which could be easily detritylated to furnish **3b**. Both **3a** and **3b** were separately oxidized to the corresponding aldehydes **4a** and **4b** with Moffatt's reagent⁷ and treated with *N*- benzyl hydroxylamine⁸ for *in situ* cyclization of the corresponding nitrones to furnish isoxazolidine derivatives **5a** and **5b** in 65% and 57% overall yields respectively. Reductive hydrogenolysis (10% Pd/C, dry EtOH, cyclohexene, reflux, 3-6h)⁹ of the isoxazolidines gave the corresponding nucleoside analogues identified as their diacetyl derivatives **6a** and **6b**; the anticipated imide *N*-debenzylation of **5b** failed to occur, whereas *N*-allyl group of **5a** was reduced to *N*-propyl group.

In the alternative approach, the isoxazolidine derivatives **7**, **8** and **9**, which could be conveniently prepared¹⁰ from D-glucose and characterized adequately, were converted to **10**, **11** and **12** respectively through acid hydrolysis followed by acetylation. Treatment with bis-*O*-(trimethylsilyl) uracil in dichloroethane under the conditions reported by Vorbrüggen¹¹ [TMS-OTf, at 25° C (for **11** and **12**) or reflux temperature (for **10**)] thereafter afforded **13**, **14** and **15** respectively in fairly good yields (42-81%). The isoxazolidine rings in the products were then cleaved by hydrogenolysis to the corresponding amino carbocyclic nucleoside derivatives which were fully characterized as their tetracetate derivatives **16**, **17** and **18**.

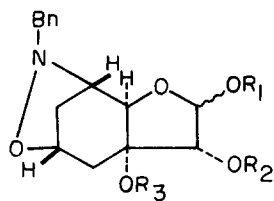
The introduction of the heterocyclic ring in the products was evident from the typical signals for H-5 and H-6 (or 5-Me and H-6) observed in the ¹H NMR spectra. Regarding the stereochemistry, those in the products **16**, **17** and **18** must be the same (except perhaps for C-1') as in the compounds **7**, **8** and **9** already established by us.¹⁰ In the ¹H NMR spectrum of **16**, the doublets (*J*=5Hz) at δ 5.28 and 5.76 were attributed to the protons H-2' and H-1'. Similarly, the *J*_{1',2'} was found to be 7Hz in **17** and 8Hz in **18**, close to those reported for analogous system.¹²

A bridged isoxazolidine ring for **5a** was clearly evident from the appearance of three upfield multiplets at δ 2.11 (2H), 2.31 (1H) and 2.53 (1H) in the ¹H NMR spectrum and two upfield triplets



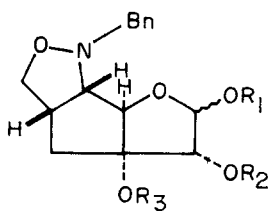
7 $R_1 + R_2 = -CMe_2-$

10 $R_1 = R_2 = Ac$



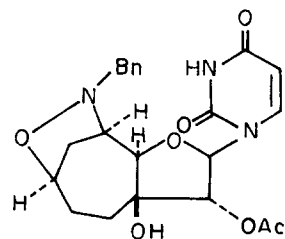
8 $R_1 + R_2 = -CMe_2-$, $R_3 = H$

11 $R_1 = R_2 = R_3 = Ac$

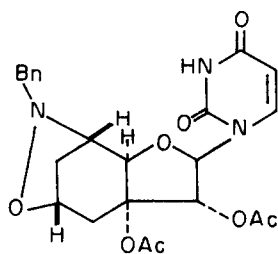


9 $R_1 + R_2 = -CMe_2-$, $R_3 = H$

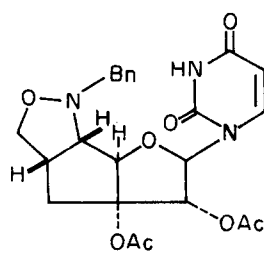
12 $R_1 = R_2 = R_3 = Ac$



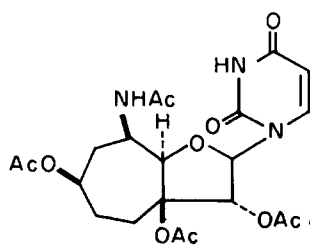
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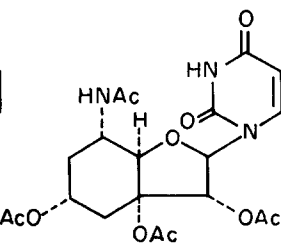
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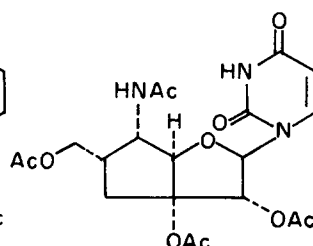
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16



17



18

at δ 29.3 and 38.3 in its ^{13}C NMR due to the methylene groups at the bridge-head and in the 2'-deoxy furanose ring. Similar results were obtained with **5b** also. Formation of compound **6a** was concluded from the two singlets at δ 2.30 (OAc) and 2.19 (NHAc, 5-Me) observed in the ^1H NMR spectrum, the triplet at δ 1.21 clearly proving that the olefinic double bond of *N*-allyl group in **5a** was reduced during hydrogenolysis. The quintet at δ 4.69 and a quartet at δ 4.85 were assigned to H-5' and H-3' protons respectively based on D_2O exchange experiments which transformed the δ 4.69 signal into a quartet ($J=8\text{Hz}$) and eliminated the δ 7.56 (d, $J=5.4\text{ Hz}$) signal which could be ascribed to the -NH- proton. The peak at δ 5.19 (brdt, $J= 2.4, 8.7, 8.7\text{ Hz}$) conceivably belongs to H-7'. In the ^{13}C NMR spectrum of **6a**, signals for four methyl carbons at δ 11.3, 12.9, 20.8, 23.0 and for four carbonyl carbons at δ 151.2, 163.2, 169.3, 170.2 were noted. Similar results were observed in ^1H and ^{13}C NMR spectra of **6b** also.

From these results, we feel that between the two synthetic approaches, the second one is clearly preferable. No solubility problem was encountered, and the product had the heterocyclic ring unencumbered with additional substituents. It is also more flexible, reliable and easier to carry out to prepare these unusual kinds of nucleosides.

EXPERIMENTAL

Melting points taken in open capillaries are uncorrected. IR spectra were measured on a JASCO 700 spectrophotometer. ^1H and ^{13}C NMR spectra were measured either on a JEOL FX-100 or on a Bruker AM 300L spectrometer using TMS as internal standard. Mass spectra were obtained using a JEOL AX-500 spectrometer operating at 70eV. Optical rotations were measured in a JASCO DIP 360 polarimeter.

3'-O-, N³-Diallyl- 5'-O-trityl thymidine (2a)

Sodium hydride (600mg, 25 mmol) was added portionwise to a solution of 5'-O-trityl thymidine (**1**) (4.35g, 10 mmol) in dry DMF (50ml) at 0-5 $^\circ\text{C}$, stirred for 1h, then a solution of allyl bromide (3.05g, 25mmol) in the same solvent (10ml) added and stirring continued for 20h. Excess hydride was decomposed, the solvent evaporated and the residue extracted with CHCl_3 (3x50ml). The combined extracts were washed with water, dried (Na_2SO_4) and the solvent evaporated in vacuo to a material which was purified by column chromatography. Petroleum ether- CHCl_3 (1:3) eluents furnished **2a** as a foam (4.12g, 75%):

IR (KBr): 1687 (NCO), 1645 (C=C), 732, 690 cm^{-1} ; ^1H NMR (CDCl_3) : δ 1.41 (d, 3H, $J=1\text{Hz}$), 2.16-2.39 (m, 2H), 3.72-4.32(m, 6H), 4.52 (d, 2H, $J=6\text{Hz}$), 5.08-5.38 (m, 4H), 5.60-6.01(m, 2H), 6.12 (t, 1H, $J=7\text{Hz}$), 7.36 (m, 15H), 7.48 (d, 1H, $J=1\text{Hz}$).

3'-O-Acetyl- 5'-O-trityl thymidine (2b)

Compound **1** (2.75g, 5 mmol) was acetylated with pyridine (30ml) and acetic anhydride (5ml) at 10°C for 14h. Usual work-up afforded a gummy material **2b** (2.48g, 95%) : IR (neat): 3380 (NH), 1740 (OCO), 1683 (NCO), 1641 (C=C), 1275, 730, 680 cm^{-1} ; ^1H NMR (CDCl_3) : δ 1.40 (brs, 3H), 2.08 (s, 3H), 2.32-2.56 (m, 2H), 3.48 (d, 2H, $J=2\text{Hz}$), 4.14 (m, 1H), 5.46 (m, 1H), 6.44 (dd, 1H, $J=6, 8\text{Hz}$), 7.44 (m, 15H), 7.62 (brs, 1H), 8.72 (brs, 1H).

3'-O-Acetyl- N^3 -benzyl- 5'-O-trityl thymidine (2c)

Oil-free sodium hydride (100 mg, 4.20 mmol) was added portionwise to **2b** (1.60g, 3 mmol) in dry DMF (40ml) at 0°C , stirred for 1h, benzyl bromide (684 mg, 4 mmol) was added and kept at rt for 5h with stirring. Usual work -up (as described for **2a**) followed by column chromatography using petroleum ether- CHCl_3 (1:2) furnished pure **2c** (1.69g, 92%): IR (KBr): 1745 (OCO), 1685 (NCO), 1280, 732, 685 cm^{-1} ; ^1H NMR (CDCl_3) : δ 1.44 (s, 3H), 2.04 (s, 3H), 2.32-2.56 (m, 2H), 3.46 (d, 2H, $J=2\text{Hz}$), 4.12 (m, 1H), 5.14 (s, 2H), 5.44 (m, 1H), 6.48 (dd, 1H, $J=6.8\text{Hz}$), 7.16-7.72 (m, 21H).

N^3 -Benzyl- 5'-O-trityl thymidine (2d)

Compound **2c** (1.23g, 2 mmol) in dry MeOH (5ml) was added to a solution (10ml) of sodium methoxide (300 mM) and stirred at 0°C for 5h. The solvent was evaporated and the residue extracted with CHCl_3 which was then washed (H_2O), dried (Na_2SO_4) and evaporated in vacuo to furnish **2d** (1.12g, 98%) : IR (neat): 3500 (OH), 1678 (NCO), 1645, 728, 675 cm^{-1} ; ^1H NMR (CDCl_3) : δ 1.52 (d, 3H, $J=1\text{Hz}$), 2.20-2.44 (m, 2H), 3.44 (t, 2H, $J=3\text{Hz}$), 4.02 (m, 1H), 4.52 (m, 1H), 5.14 (s, 2H), 6.42 (t, 1H, $J=6\text{Hz}$), 7.20-7.64 (m, 21H).

3'-O-Allyl- N^3 -benzyl- 5'-O-trityl thymidine (2e)

To a mixture of the compound **2d** (1.0g, 1.75 mmol) and allyl bromide (1.1g, 8.75 mmol) in dichloromethane (25ml) was added 50% NaOH solution (25ml) and tetrabutyl ammonium bromide (156mg, 0.87 mmol) and stirred vigorously for 20h at rt. The organic layer was separated, washed with water, dried (Na_2SO_4) and evaporated to a thick liquid which was purified by chromatography. Elution was performed with petroleum ether- CHCl_3 (1:2) to afford **2e** (985 mg, 92%) as a gum: IR (neat): 1673 (NCO), 1642 (C=C), 1272, 735, 673 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.43 (d, 3H, $J=1\text{Hz}$), 2.10-2.34 (m, 2H), 3.42-4.30 (m, 6H), 5.00 -5.40 (m, 4H), 5.66-6.02 (m, 1H), 6-14 (dd, 1H, $J=6, 8\text{Hz}$), 7.30-7.50 (m, 21H).

3'-O-, N³ -Diallyl thymidine (3a) ; 3'-O-Allyl-N³-benzyl thymidine (3b)

Compound **2a** (2.75g, 5 mmol) was dissolved in 80% HOAc (20ml) and heated at 80⁰ C for 5h. The solvent was evaporated, and the crude product was purified by chromatography using CHCl₃ - MeOH (49:1) to yield a glassy material **3a** (1.16g, 72%). IR (KBr): 3480 (OH), 1681 (NCO), 1070, 728, 678 cm⁻¹; ¹H NMR (CDCl₃) : δ 1.94 (d, 3H, J=1Hz), 2.24-2.48 (m, 2H), 3.76-4.36 (m, 6H), 4.56 (d, 2H, J=6Hz), 5.12-5.44 (m, 4H), 5.68-6.04 (m, 2H), 6.16 (t, 1H, J=7Hz), 7.38 (d, 1H, J=1Hz); FABMS, *m/z*: 313 (M+H)⁺.

Compound **2e** (1.24g, 2 mmol) was converted to **3b** (520 mg, 70%) following the procedure described for **3a**. **3b**: IR (KBr): 3490 (OH), 1675 (NCO), 1640, 1070, 735, 672 cm⁻¹; ¹H NMR (CDCl₃): δ 1.92 (d, 3H, J=1Hz), 2.20-2.44 (m, 2H), 3.48-4.36 (m, 6H), 5.04-5.44 (m, 4H), 5.72-6.4 (m, 1H), 6.14 (dd, 1H, J=6,8 Hz), 7.20-7.60 (m, 5H); FABMS, *m/z* : 373 (M+H)⁺.

3-Allyloxy 2-formyl - 5-(N³ -allyl thymine-1-yl)-tetrahydrofuran (4a); 3-Allyloxy-2 formyl-5-(N³ -benzyl thymine-1-yl)-tetrahydrofuran (4b)

To a solution of the alcohol **3a** (500 mg, 1.55 mmol) in a mixture of dry DMSO (2.5ml) and dry C₆H₆ (2.5ml) were added pyridine (124μl, 1.55 mmol), trifluoroacetic acid (62μl, 0.775 mmol) and DCC (958 mg, 4.65 mmol) and the mixture stirred at rt for 18h. A solution of oxalic acid (418mg, 4.65 mmol) in MeOH (4ml) was added and the mixture kept for 30 min. After neutralization with solid NaHCO₃, CHCl₃ (40ml) was added and the solution filtered. The filtrate was evaporated in vacuo, the residue extracted with diethyl ether (3x100ml) and the solvent removed to an oil which was purified quickly through a short column using CHCl₃ as the eluent to furnish **4a** (377mg, 76%) : IR (neat): 1730 (CHO), 1685 (NCO) cm⁻¹.

Following the procedure described for **4a**, **3b** (1 mmol) was converted to **4b** (255mg, 69%): IR (neat): 1733 (CHO), 1680 (NCO), 1605, 680 cm⁻¹.

9-Benzyl-2-[N³-allyl-5-methyl-2,4 (1H,3H)-pyrimidinedione-1-yl] -perhydro-6,8-(epoxyimino) furo [3,2-b] oxepin (5a) ; 9-Benzyl-2-(N³ -benzyl-5-methyl-2,4 (1H,3H)-pyrimidinedione-1-yl)-perhydro-6,8-(epoxyimino) furo [3,2-b] oxepin (5b).

To a solution of the aldehyde **4a** (370mg, 1.16mmol) in dry EtOH(10ml) was added *N*-benzyl hydroxylamine (185mg, 1.50 mmol) and NaHCO₃ (5mg). It was stirred (12h, rt) and then heated at reflux (2h). The solvent was evaporated to furnish a crude material which was chromatographed over silica gel. Elution with petroleum ether-CHCl₃ (1:4) afforded the compound **5a** as a shiny glassy material (423 mg, 86%) : [α]_D²⁷ + 158.6⁰ (c 0.7, CHCl₃); IR (KBr): 1670 (NCO), 1645(C=C), 1380, 732, 691 cm⁻¹; ¹H NMR (CDCl₃) (300 MHz): δ 1.92 (s, 3H), 2.11 (m, 2H), 2.31 (m, 1H), 2.53 (m, 1H), 3.46 (d, 1H, J=7Hz),

3.58 (d, 1H, $J=10.8$ Hz), 3.85 (m, 3H), 4.09 (d, 1H, $J=13$ Hz), 4.40 (q-like, 1H), 4.53 (d, 2H, $J=5.4$ Hz), 4.60 (d, 1H, $J=9$ Hz), 5.19 (d, 2H, $J=10,16$ Hz), 5.84 (m, 1H), 6.16 (d, 1H, $J=7$ Hz), 7.31 (m, 5H), 8.02(s, 1H); ^{13}C NMR (CDCl_3) (75 MHz): δ 13.2 (q), 29.4, 38.3, 43.1, 63.2, 73.0, 109.6 (6xt), 61.6, 72.8, 78.3, 84.0, 84.7, 127.7, 131.9, 134.3 (8xd), 128.5 (2xd), 129.0 (2xd), 117.8, 136.9, 150.4, 163.1 (4xs); FABMS, m/z : 448 ($\text{M}+\text{Na}$) $^+$, 426 ($\text{M}+\text{H}$) $^+$; Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_5$: C, 64.92; H, 6.40; N, 9.88. Found : C, 64.88; H, 6.43; N, 9.53.

The compound **4b** (370mg, 1mmol) was converted to **5b** (394mg, 83%) according to the procedure described (for **5a**). **5b**: $[\alpha]_{\text{D}}^{27} +145.0^0$ (c 0.65, CHCl_3); IR (neat): 1673 (NCO), 1370, 928, 685 cm^{-1} ; ^1H NMR(CDCl_3) (100 MHz): δ 1.92 (s, 3H), 2.02-2.60 (m, 4H), 3.40-4.76 (m, 8H), 5.12 (s,2H), 6.32 (dd, 1H, $J=1$, 7Hz), 7.20-7.72 (m, 10H), 8.04 (s, 1H); FABMS, m/z : 476 ($\text{M}+\text{H}$) $^+$.

8-Acetamido-6-acetoxy-2-[3-propyl-5-methyl-2,4 (1H, 3H)-Pyrimidinedion-1-yl]-perhydro-furo[3,2-*b*]oxepin (6a); 8-Acetamido-6-acetoxy-2-[3-benzyl-5-methyl-2,4 (1H,3H)-pyrimidinedion-1-yl]-perhydro-furo [3,2-*b*]oxepin (6b)

For **6a**: To a solution of the compound **5a** (300mg, 0.71 mmol) in dry EtOH (20ml) was added Pd/C (10%) (200mg) and cyclohexene (1ml) and heated at reflux (6h) under N_2 atmosphere. The solution was filtered, the solvent evaporated and the crude product dried under vacuum to afford a solid material. Without further purification, it was treated with pyridine (5ml) and Ac_2O (2ml) at rt for 12h. Usual work-up followed by chromatography [solvent : CHCl_3 -MeOH (49:1)] afforded a crystalline compound **6a** (234mg, 78%): mp 210-211 0 C; $[\alpha]_{\text{D}}^{27} +30.4^0$ (c 0.5, CHCl_3); IR (KBr): 3340 (NH), 1665 (NCO), 1375, 730, 690 cm^{-1} ; ^1H NMR (CDCl_3) (300 MHz): δ 1.21 (t, 3H, $J=7.5$ Hz), 1.91 (m,2H), 2.19 (1xs+m, 7H), 2.30 (s, 3H), 2.75 (m, 1H), 3.03 (m, 2H), 3.71 (dd, 1H, $J=8.7,11.7$ Hz), 4.15 (m, 4H), 4.69 (qnt, 1H), 4.85 (q, 1H, $J=8$ Hz), 5.20 (dt, 1H, $J=2.4,8.7$, 8.7 Hz), 5.75 (dd, 1H, $J=3.9,6$ Hz), 7.25 (s, 1H), 7.56 (d, 1H, $J=5.4$ Hz); ^{13}C NMR (CDCl_3) (75) MHz): δ 11.3, 12.9, 20.8, 23.0 (4xq), 21.0, 37.8, 38.1, 42.8, 73.7 (5xt), 45.2, 69.3, 76.6, 84.8, 92.2, 137.8 (6xd), 110.4, 151.2, 163.1, 169.3, 170.2 (5xs); FABMS, m/z : 446 ($\text{M}+\text{Na}$) $^+$, 424 ($\text{M}+\text{H}$) $^+$.

Anal. Calcd for $\text{C}_{20}\text{H}_{29}\text{N}_3\text{O}_7 \cdot \text{H}_2\text{O}$: C, 54.42; H, 7.07 N, 9.52 found : C, 54.48; H, 7.11; N, 9.55. Following the method (as described for **6a**) **5b** (400mg, 0.84 mmol) was converted to **6b** (138mg, 61%): mp 225-227 0 C; $[\alpha]_{\text{D}}^{27} + 45.5^0$ (c 0.41, CHCl_3); IR(KBr): 3350 (NH), 1670 (NCO), 1601, 728, 680 cm^{-1} ; ^1H NMR (CDCl_3) (300 MHz): δ 1.88 (s, 3H), 2.32 (s,3H), 2.56 (s, 3H), 3.75 (dd, 1H, $J=8.4$, 11.7Hz), 4.21 (m, 2H), 4.56 (q, 1H) 4.69 (qnt, 1H), 5.20 (dt-like, 1H, $J=1.8,9.9$ Hz), 5.28 (d, 1H, $J=14$ Hz), 5.49 (d, 1H, $J=14$ Hz), 5.79 (dd, 1H, $J=2.7$, 9.3 Hz), 7.31 (s, 1H), 7.34 (brd, 1H, $J=5.4$ Hz), 7.60 (m, 5H); ^{13}C NMR (CDCl_3) (75MHz): δ 13.0, 21.0, 22.8 (3xq), 37.5, 37.8, 44.5, 73.6 (4xt), 45.2, 69.5, 76.5, 84.8, 92.2,

127.7, 138.1 (7xd), 128.1 (2xd), 128.6 (2xd), 110.5, 136.4, 151.3, 163.2, 169.0, 170.2(6xs); FABMS, m/z : 472 (M+H)+.

Anal. Calcd for $C_{24}H_{29}N_3O_7$: C, 61.13; H, 6.20; N, 8.92. found: C, 61.09; H, 6.18; N, 8.59.

9-Benzyl-2,3-diacetoxy-3a-hydroxy-perhydro-6,8-(epoxyimino) cyclohepta[b] furan (10); 8-Benzyl-2,3,3a-triacetoxy-perhydro-5,7-(epoxyimino) benzo[b] furan (11); 1-Benzyl-4a,5,6-triacetoxy-perhydro-furo [2',3':2,1] cyclopent [3,4-c] isoxazole (12)

Compound **7**¹⁰ (700mg, 2.02 mmol) was treated with 4% H_2SO_4 (30ml) in CH_3CN-H_2O (3:1), stirred (rt, 24h) and then heated (60°C, 2h). The reaction mixture was neutralized with solid $CaCO_3$, filtered and the solvent evaporated in vacuo to furnish a crude product which after drying (over P_2O_5), was treated with pyridine (5ml) and Ac_2O (1ml) at rt for 12h. Usual work up and column chromatography furnished **10**¹³ (689mg, 87%). Compound **8**¹⁰ (350mg, 1.05 mmol) afforded **11**¹³ (340mg, 77%) and compound **9**¹⁰ (690mg, 2.07mmol) yielded **12**¹³ (730mg, 84%). **10**: IR (KBr): 3378, 1742, 1380, 1255, 1006, 740, 696 cm^{-1} ; ¹H NMR ($CDCl_3$): δ 1.20-2.56 (m, 6H+ 2xs, 3H each at 2.04 and 2.12), 2.58-4.24 (m, 4H), 4.56-4.80 (m, 1H), 5.00 & 5.92 (2xs), 5.10 & 6.66 (2xd, $J=4Hz$), 5.88 & 6.00 (2xs), 7.34 (m, 5H); EIMS, m/z : 391 (M^+), 349, 153, 91. **11**: IR (KBr): 1740, 1438, 1365, 748 cm^{-1} ; ¹H NMR ($CDCl_3$): δ 2.04, 2.09, 2.11, 2.13 (4xs), 3.60-4.24 (m), 4.36 (d), 4.48-4.80 (m), 4.92 (s), 5.42 (s), 6.04 (s), 7.32 (m); EIMS, m/z : 419 (M^+), 377, 360, 168, 149, 91. **12**: IR (neat): 1740, 1435, 1370, 747 cm^{-1} ; ¹H NMR ($CDCl_3$): δ 2.04, 2.10 (2xs), 2.24-2.88 (m), 3.24-4.28 (m), 4.63 (s), 4.66 (s), 5.46 (d), 5.48(s), 6.07 (s), 6.36 (d), 7.36 (m); FABMS, m/z : 420 (M+H)+.

3-Acetoxy-9-benzyl-3a-hydroxy-2-[2,4 (1H, 3H)-pyrimidinedion-1-yl]-perhydro-6,8-(epoxyimino) cyclohepta [b] furan (13); 8-Benzyl-3, 3a- diacetoxy-2-[2,4 (1 H, 3H)- pyrimidinedion-1y-l]- perhydro-5,7-(epoxyimino) benzo [b] furan (14); 1-Benzyl-4a, 5-diacetoxy-[6-[2,4 (1H, 3H)-pyrimidinedion-1y-l]-perhydro-furo [2',3': 2,1] cyclopent [3,4-c] isoxazole (15).

A mixture of uracil (300mg, 2.67 mmol), hexamethyldisilazane (10ml) and Me_3SiCl (2drops) was heated at 135-140°C for 12h under N_2 . The solvent was evaporated in vacuo, the residue dissolved in dichloroethane (3ml), added to a mixture of the diacetate **10** (370mg, 0.95mmol) and TMS.OTf (0.4ml, 2mmol) in the same solvent (3ml) under N_2 and the mixture heated at 80°C for 3h. The reaction was quenched by solid $NaHCO_3$, the product extracted with $CHCl_3$ -MeOH mixture (99.8:0.2 v/v, 3x20ml), the solvent dried (Na_2SO_4) and evaporated in vacuo to obtain a crude product, purified by column chromatography using $CHCl_3$ as the solvent to afford a pure foamy material **13** (340mg, 81%). $[\alpha]_D^{27} + 80.8^\circ$ (c 0.23, $CHCl_3$); IR (KBr): 3376, 1745, 1687, 1375, 1228, 1067, 734, 697 cm^{-1} ; ¹H NMR ($CDCl_3$) (100MHz): δ 2.12

(s, 3H), 3.60 (d, 1H, $J=2$ Hz), 3.84 and 4.12 (2xd, 1H each, $J=13$ Hz), 3.98 (dd, 1H, $J=2,7$ Hz), 4.80 (dd, 1H, $J=4,9$ Hz), 5.04 (s, 1H), 5.74 (s, 1H +dd, 1H, $J=2,88$ Hz), 5.84 (s, 1H), 7.33 (s, 5H), 8.24 (dd, 1H, $J=8$ Hz), 8.64 (brs, 1H); FABMS, m/z : 466 (M+Na)⁺, 444 (M+H)⁺.

Similarly, **11** (340mg, 0.81 mmol) was converted to **14** (310mg, 81%), and **12** (419 mg, 1.23 mmol) to **15** (242 mg, 42%). The protocol used was similar to that described for **13**, except that the reaction mixtures were stirred (rt, 20h) in both the cases. **14**: foam; $[\alpha]_D^{27} - 16.7^\circ$ (c 0.3 CHCl₃); IR (KBr): 3458, 1740, 1720, 1698, 1460, 1376, 1107 cm⁻¹; ¹H NMR (CDCl₃) (100 MHz) δ 2.04 (s, 3H), 2.14 (s, 3H), 3.60 (m, 1H), 3.78 and 4.14 (2xd, 1H each, $J=14$ Hz), 4.38 (d, 1H, $J=2$ Hz), 4.62 (m, 1H), 5.40 (d, 1H, $J=6$ Hz), 5.68 (d, 1H, $J=6$ Hz), 5.78 (d, 1H, $J=8$ Hz), 7.16 (d, 1H, $J=8$ Hz), 7.34 (m, 5H), 8.86 (brs, 1H); FABMS, m/z : 494 (M+Na)⁺, 472 (M+H)⁺. **15**: foam.; $[\alpha]_D^{27} - 10.7^\circ$ (c 0.41, CHCl₃); IR (KBr): 3240, 1752, 1695, 1458, 1377, 1238, 1053, 750, 697 cm⁻¹; ¹H NMR (CDCl₃) (100 MHz) : δ 2.06, 2.12 (2xs, 3H each), 3.40-3.60 (m, 3H), 3.92 and 4.08 (2xd, 1H each, $J=13$ Hz), 4.20 (dd, 1H, $J=6,8$ Hz), 5.56 (d, 1H, $J=6$ Hz), 5.80-5.90 (t-like, 2H), 7.14 (d, 1H, $J=8$ Hz), 7.36 (m, 5H), 9.00 (brs, 1H); FABMS, m/z : 494 (M+Na)⁺, 472 (M+H)⁺.

8-Acetamido-3,3a, 6-triacetoxy-2-[2,4 (1H, 3H)-pyrimidinedion-1-yl]-perhydro-cyclohepta[b] furan (16), 7-Acetamido-3, 3a, 5-triacetoxy-2-[2,4 (1H, 3H)-pyrimidinedion -1-yl]-perhydro-benzo[b]furan (17) and 6-Acetamido-5-acetoxymethyl-3,3a-diacetoxy-2-[2,4 (1H, 3H)-pyrimidinedion-1-yl]- perhydro-cyclopenta [b] furan (18)

Conversion of **13** (170mg, 0.38 mmol) to **16** (81mg, 44%), **14** (170mg, 0.36 mmol) to **17** (81mg, 48%) and **15** (145mg, 0.31 mmol) to **18** (71mg, 50%) were performed following the procedure described for **6a**.

16 : mp 178-180^o C (dec.); $[\alpha]_D^{27} +51.0^\circ$ (c 0.45, CHCl₃); IR (KBr): 3438, 1745, 1721, 1705, 1690, 1375, 1236, 1027 cm⁻¹; ¹H NMR (DMSO-d₆) (300 MHz) : δ 1.39 (m, 1H), 1.70 (m, 2H), 1.83, 1.94, 2.03, 2.16 (4xs, 3H each), 2.20 (m2H), 2.46 (m, 1H), 4.17 (d, 1H, $J=7$ Hz), 4.60 (m, 1H), 4.73 (t-like, 1H, $J= 7.5, 8$ Hz), 5.35 (d, 1H, $J=5$ Hz), 5.69 (brd, 2H), 7.10 (d, 1H, $J=8$ Hz), 7.77 (d, 1H, $J=8$ Hz), 11.37 (brs, 1H); ¹³C NMR (75 MHz): δ 20.3, 21.1, 21.8, 22.8 (4xq), 25.5, 30.4, 39.2 (3xt), 43.1, 69.7, 70.0, 82.3, 86.6, 102.3, 140.5 (7xd), 87.7, 150.3, 162.9, 168.3, 169.1, 169.3, 169.8 (7xs); FABMS, m/z : 482 (M+H)⁺.

Anal. Calcd for C₂₁H₂₇N₃O₁₀ · 0.5H₂O : C, 51.43; H, 5.75; N, 8.57. Found : C, 51.28; H, 5.68; N, 8.32.

17; mp 214-215^o C (dec.); $[\alpha]_D^{27} +9.7^\circ$ (c 0.33, CHCl₃); IR (KBr): 3362, 1741, 1695, 1549, 1389, 1239, 1040 cm⁻¹; ¹H NMR (DMSO-d₆) (100 MHz): δ 1.85, 1.98, 2.02, 2.12 (4xs, 3H each), 4.38 (d, 1H, $J=9$ Hz), 4.00-4.41 (m, 1H), 5.12 (m, 1H), 5.48 (d, 1H, $J=7$ Hz), 5.72 (d, 1H, $J=8$ Hz), 5.96 (d, 1H, $J=8$ Hz), 7.92

(d, 1H, $J=8\text{Hz}$), 11.36 (brs, 1H); ^{13}C NMR (DMSO- d_6): δ 20.3, 20.8, 21.8, 22.7, 31.9, 32.8, 47.4, 66.6, 73.9, 82.1, 83.6, 85.6, 85.7, 102.2, 141.5, 150.6, 162.8, 168.8, 169.5, 169.5, 169.6; FABMS, m/z : 468 (M+H) $^+$.

Anal. Calcd for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_{10} \cdot \text{H}_2\text{O}$: C, 49.48; H, 5.61; N, 8.65. Found: C, 49.43; H, 5.53; N, 8.31.

18: mp 123-125 $^\circ\text{C}$ (dec.); $[\alpha]_D^{27} +6.1^\circ$ (c 0.46, CHCl_3); IR (KBr): 3446, 1745, 1721, 1710, 1695, 1376, 1239, 1043 cm^{-1} ; ^1H NMR (CDCl_3) (300 MHz): δ 1.99, 2.03, 2.09, 2.12 (4xs, 3H each), 2.24 (t, 1H, $J=13\text{Hz}$), 2.53 (dd, 1H, $J=6, 13\text{Hz}$), 2.71 (m, 1H), 4.01 (dd, 1H, $J=6, 11\text{Hz}$), 4.24 (dd, 1H, $J=7, 11\text{Hz}$), 4.53 (s, 1H), 4.56 (dd, 1H, $J=6.9\text{Hz}$), 5.03 (d, 1H, $J=8\text{Hz}$), 5.80 (d, 1H, $J=8\text{Hz}$), 5.97 (d, 1H, $J=8\text{Hz}$), 6.87 (d, 1H, $J=9\text{Hz}$), 7.27 (d, 1H, $J=8\text{Hz}$), 9.71 (brs, 1H); ^{13}C NMR (CDCl_3): δ 20.4, 20.8, 21.5, 23.2 (4xq), 36.2, 62.4 (2xt), 40.4, 54.1, 77.0, 84.9, 90.7, 103.8, 140.0 (7xd), 87.5, 150.4, 162.7, 169.9, 170.0, 170.4, 170.9 (7xs); FABMS, m/z : 468 (M+H) $^+$.

Anal. Calcd for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_{10}$: C, 49.69; H, 5.21; N, 8.69. Found: C, 49.48; H, 5.19; N, 8.36.

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13. Each of the compounds **10,11** and **12** proved to be a mixture of anomers from the ^1H NMR spectra.

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