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3′-Selective modification of a 4′,5′-didehydro-5′-deoxy-2′,3′-epoxyuridine using nucleophiles

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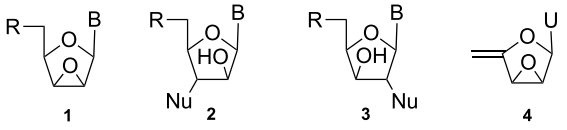
Abstract—1-(2,3-Anhydro-5-deoxy-4,5-didehydro-α-L-*erythro*-pent-4-enofuranosyl)uracil **4** was obtained by the treatment of 5′-iodo-2′,3′-epoxyuridine **5** with LiHMDS in excellent yield. The pyrimidine nucleoside **4** possesses quite unique vinyl epoxide moiety within the molecules. The reactions of **4** with a variety of nucleophiles gave 3′-substituted pyrimidine nucleosides without the formation of the corresponding 2′-substituted isomers. In the case of NaN_3 or PhSH, the corresponding 5′-adduct was obtained as a minor product together with the expected 3′-adduct.

1. Introduction

Chemical modification of nucleosides has been very important for the synthesis of biologically active compounds such as anti-viral agents[1] and synthetic oligonucleotide probes.[2] A number of modifications of the sugar moiety in nucleosides have been carried out up to now. Especially, a wide variety of attempts have been made to devise novel methodologies to functionalize the 2′- and 3′-sites of nucleosides in connection with AZT, a potent anti-HIV agent. 2′,3′-Anhydro-β-D-lyxofuranosyl pyrimidine nucleosides (**1**) first synthesized by Fox et al.,[3] are useful key intermediates for the 2′- or 3′-modified pyrimidine nucleoside analogues. A large number of reactions of **1** with a variety of nucleophiles have been investigated.[4,5] However, a limitation to these methods is the poor regio-control of 2′- or 3′-addition of nucleophiles. Usually, 3′-adducts (**2**) were obtained as major products together with minor 2′-adducts (**3**). Although a few reports indicated that 3′-adducts (**2**) were obtained selectively[5], the yields of the 3′-adducts were very low and the existence of unisolable 2′-adducts (**3**) was suspected. Previously, we have reported the reaction of **1** (R = OH, or OR′) with $AlMe_3$ with a view to the regioselective 2′-attack of the methyl group by the cyclic coordination effect of $AlMe_3$ between 5′- and epoxide-oxygen, while a mixture of the 3′- and 2′-adduct (**2** and **3**) was obtained[6] as well as other reported results.[4]

In order to develop an entirely regioselective nucleophilic attack toward the epoxide moiety of 2′,3′-anhydro nucleosides, we expected the use of a conjugated epoxide with a double bond such as **4** would lead to a better result. Here we would like to report the synthesis of 1-(2,3-anhydro-5-deoxy-4,5-didehydro-α-L-*erythro*-pent-4-enofuranosyl)uracil (**4**) and its application to the regioselective synthesis of 3′-adducts (**2**).[7]



2. Results and discussion

The synthesis of 4′,5′-didehydro-5′-deoxy-2′,3′-epoxyuridine (**4**) was achieved by treatment of 5′-iodo-2′,3′-epoxyuridine (**5**)[3c] with *t*-BuOK, an appropriate non-nucleophilic base, at room temperature (64%), while the use of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as a base gave a complex mixture. After optimization of the reaction conditions, we finally found the use of LiHMDS, a bulky and totally non-nucleophilic base, in DMF at 0 °C gave **4** in 92% yield (Scheme 1).

Therefore, the reaction of **4** using a variety of nucleophiles was investigated. We first carried out the reaction of **4** with

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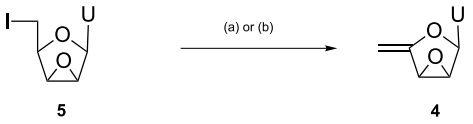
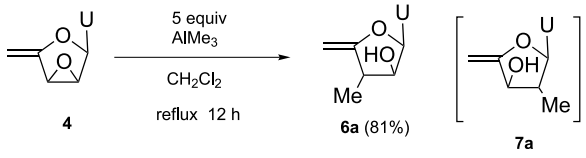


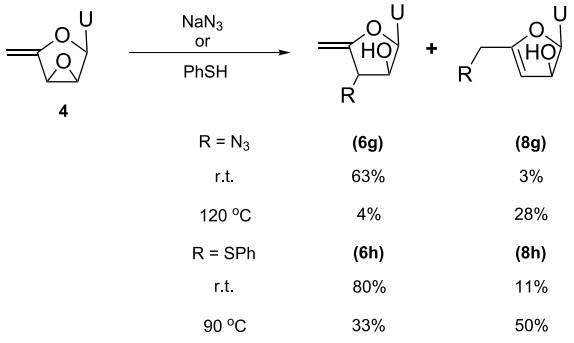
Scheme 1. Synthesis of 1-(2,3-anhydro-5-deoxy-4,5-didehydro-α-L-*erythro*-pent-4-enofuranosyl)uracil **4** from **5**. Reactant and condition: (a) *t*-BuOK, DMF, rt (64%) or (b) LiHMDS, DMF, 0 °C, Ar (92%).

5 equiv of $AlMe_3$ in CH_2Cl_2 under reflux conditions. The regioselective nucleophilic addition of a methyl group to epoxide proceeded on the 3′-position and the 3′-adduct (**6a**) was obtained as the sole product in 81% isolated yield and the isomeric 2′-adduct (**7a**) and other by-products were not detected in the reaction mixture (Scheme 2). To ascertain the generality of this regioselective reaction, treatment of **4** with various nucleophiles was investigated. The results are summarized in Table 1. When MeONa was used as a nucleophile, reflux conditions were required for completion of the reaction. On the other hand, all other additions were achieved at room temperature (entries 3–8). Reactions using $BnNH_2$, $AlMe_3$, MeONa and NaN_3 proceeded without an additional base (entries 1–3, and 7). In the case of BzOH, BzSH and PhSH, Et_3N was employed as a base (entries 5, 6, and 9). When NaH was employed as a base instead of Et_3N for the reaction of BzOH, a lowering of the yield of **6e** and a remaining of the starting material **4** were observed. The reaction of BzOH was very slow (168 h) and the corresponding arabinofuranosyl derivative (**6e′**) was formed as a by-product based upon the hydrolysis of (**6e**), although the 3′-addition of BzSH was completed within 48 h because of the high nucleophilicity.



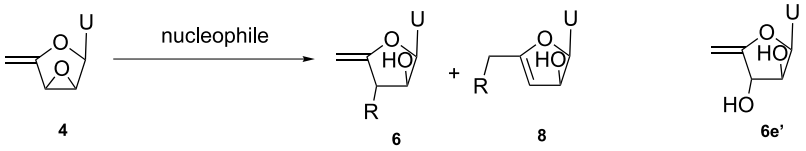
Scheme 2. Reaction of **4** with $AlMe_3$.

Next, we investigated the reaction of **4** with NaN_3 in DMF at room temperature. Similar to the other reactions (entries 1–6), 3′-adduct (**6g**) was afforded as a major product together with 5′-adduct (**8g**),[8] formed by the nucleophilic addition onto the 5′-position of **4** as a side product (3%) (Scheme 3 and Table 1, entry 7). When this reaction was carried out at 120 °C, the 5′-adduct (**8g**) was afforded as a major product (28%) along with 3′-adduct (**6g**) as a minor product (4%) (Scheme 3). In addition, a similar tendency was observed in the reaction of **4** with PhSH (Scheme 3 and Table 1, entry 8). In these reactions, formation of a 2′-adduct (**7**) was never observed as well as in other reactions of **4** with nucleophiles (entries 1–6). Usually, the 3′-cation is more stable than the 2′-cation owing to the electron-withdrawing effect of the 1′-uracil moiety of 2′,3′-epoxyuridine derivatives (**1**) and the formation of 3′-adduct (**2**) was superior to the formation of 2′-adduct (**3**), although the effect is not enough to perform the regioselective 3′-nucleophilic addition. On the other hand, the 3′-position of **4** is the allylic position and it is obvious that the 3′-cation is strongly stabilized by the conjugation with the 4′,5′-double bond as an allylic cation (Fig. 1). Therefore, regioselective nucleophilic addition onto the 3′-position occurred readily and the 3′-adduct (**6**) was obtained regioselectively. In the reaction with a comparatively soft nucleophile such as NaN_3 or PhSH, 5′-adduct (**8**) was also formed as a by-product.[9,10]



Scheme 3. Reaction of **4** with NaN_3 or PhSH.

Table 1. Nucleophilic addition to **4**



Entry	Nucleophile	Additional base	Solvent	Temperature	*T* (h)	R	Yield (%)[a]		
							Product	**6**	**8**
1	$AlMe_3$	—	CH_2Cl_2	reflux	12	Me	**a**	81	nd[b]
2	MeONa	—	MeOH	reflux	6	OMe	**b**	80	nd[b]
3	$BnNH_2$	—	CH_2Cl_2	rt	24	NHBn	**c**	81	nd[b]
4	$CH_2(CO_2Me)_2$	MeONa	MeOH	rt	12	$CH(CO_2Me)_2$	**d**	69	nd[b]
5	BzOH	Et_3N	CH_2Cl_2	rt	168	OBz	**e**	61	nd[b]
6	BzSH	Et_3N	CH_2Cl_2	rt	48	SBz	**f**	52	nd[b]
7	NaN_3	—	DMF	rt	3	N_3	**g**	63	3
8	PhSH	Et_3N	—	rt	1	SPh	**h**	80	11

[a] Isolated yield after chromatographic separation.
[b] Not detectable.

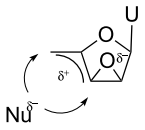
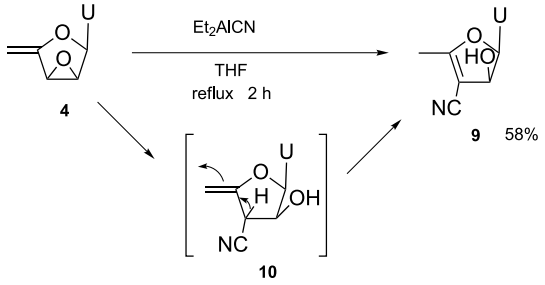


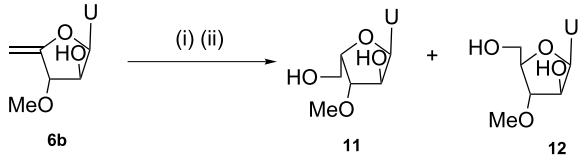
Figure 1.

It was noteworthy that the use of Et_2AlCN as a nucleophile provided 3′,4′-unsaturated-3′-adduct (**9**) as the sole product via isomerization of the 3′-adduct (**10**) because of the efficient activation of 3′-hydrogen of **10** by the strong electron-withdrawing cyano group after regular nucleophilic attack of the cyano anion onto the 3′-position of **4** (Scheme 4).



Scheme 4. Reaction of **4** with Et_2AlCN.

Usually, the 5′-hydroxy group of nucleosides is supposed to be important for biological activity, while 3′-adducts (**6**) do not possess the 5′-hydroxy group. So we investigated the conversion method of the olefin of **6** to a hydroxymethyl group. The hydroboration reaction of **6b** should be applicable to the introduction of the 5′-hydroxy group. The reaction of **6b** with BH_3–THF at room temperature, followed by H_2O_2–NaOH treatment, gave only undesirable α-isomer (**11**). When the reaction was heated at reflux temperature, the desired β-isomer (**12**) was afforded as a minor product (17%) together with corresponding α-isomer (**11**) (53%) (Scheme 5). As the reason for this isomer ratio, it was indicated that the steric hindrance effect of the 3′-methoxy group was more effective than that of the uracil ring. At present, we are unable to determine the underlying cause of this stereoselectivity.



Scheme 5. 5′-Hydroxylation reaction of **6b**: (i) BF_3–THF, THF, reflux (ii) H_2O_2, NaOH.

3. Conclusion

We have shown a simple synthetic method of 1-(2,3-anhydro-5-deoxy-4,5-didehydro-β-D-*erythro*-pent-4-enofuranosyl)uracil (**4**) and mild and efficient regioselective method for the conversion of **4** to 3′-substituted pyrimidine nucleosides (**6**), (**9**), (**11**) and (**12**) without the formation of the corresponding 2′-substituted derivatives. The reaction is general for a variety of nucleophiles and the simplicity of this method makes it an attractive new tool for synthesis of various sugar modified pyrimidine nucleosides.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on a JEOL EX 400 spectrometer or a JEOL GX 270 spectrometer (^1H: 400 or 270 MHz, ^{13}C: 100 MHz). Chemical shifts (δ) are given in ppm relative to residual solvent or tetramethylsilane as an internal standard. Low and high-resolution mass spectra were taken on a JEOL JMS-SX 102 or JMS-D300 machine. Melting points were determined on a Yanagimoto micro-melting-point apparatus and were corrected. IR spectra were recorded on a Perkin Elmer model 1600 FT-IR spectrophotometer. UV spectra were obtained from EtOH solution on a Shimazu UV-260 spectrophotometer. All reagents were commercially available and used without further purification. Compounds known in the literature were characterized by comparison of their ^1H NMR data with the previously reported data.

4.1.1. 1-(2,3-Anhydro-5-deoxy-4,5-didehydro-α-L-*erythro*-pent-4-enofuranosyl)uracil (4). To a stirred solution of **5**[3c] (336 mg, 1.0 mmol) in dry DMF (20 ml) was added 1.0 M THF solution of $LiN[(CH_3)_3Si]_2$ (2.2 ml, 2.2 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 4 h at 0 °C and the mixture was evaporated in vacuo at room temperature. The residue was diluted with water and neutralized with saturated NH_4Cl and extracted with AcOEt. The organic solution was evaporated in vacuo and the residue was subjected to silica gel column chromatography (benzene/AcOEt 3:1) to afford **4** (192 mg, 92%) as a white foam.

MASS *m/z* (relative intensity): 208 (M^+, 43%), 112 ($B^+ + 1$, 18%), 97 (S^+, 100%). ^1H NMR ($CDCl_3$) δ: 8.71 (1H, br s, N^3–H), 7.50 (1H, d, $J=8.3$ Hz, 6-H), 6.39 (1H, s, 1′-H), 5.76 (1H, d, $J=8.3$ Hz, 5-H), 4.74 (1H, d, $J=2.4$ Hz, 5′-Ha), 4.59 (1H, d, $J=2.4$ Hz, 5′-Hb), 4.23 (1H, d, $J=2.9$ Hz, 2′-H), 4.05 (1H, d, $J=2.9$ Hz, 3′-H). ^{13}C NMR ($CDCl_3$) δ: 162.84 (4-C), 154.34 (4′-C), 150.30 (2-C), 140.75 (6-C), 102.80 (5-C), 95.95 (5′-C), 81.79 (1′-C), 56.52 (2′-C), 54.56 (3′-C). HRMS *m/z* calcd for $C_9H_8N_2O_4$: 208.0484. Found: 208.0473.

4.1.2. 1-(3,5-Dideoxy-3-methyl-β-D-*threo*-pent-4-enofuranosyl)uracil (6a). To a stirred solution of **4** (48 mg, 0.23 mmol) in dry CH_2Cl_2 (10 ml) was added 1.0 M hexane solution of $AlMe_3$ (1.20 ml, 1.20 mmol) at room temperature under argon atmosphere. The reaction mixture was refluxed for 12 h and the mixture was partitioned between $CHCl_3$ (30 ml) and water (30 ml). The aqueous layer was filtered using a Celite cake and the filtrate was concentrated in vacuo. The residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 10:1) to afford **6a** (42 mg, 81%) as a white foam.

MASS *m/z* (relative intensity): 224 (M^+, 2%), 113 (S^+ and $B^+ + 2$, 14%), 112 ($B^+ + 1$, 14%), 95 (100%). ^1H NMR (DMSO-d_6) δ: 11.35 (1H, br s, N^3–H), 7.31 (1H, d, $J=8$.

3 Hz, 6-H), 6.26 (1H, d, J=4.9 Hz, 1′-H), 5.77 (1H, d, J=4.9 Hz, 2′-OH), 5.58 (1H, d, J=8.3 Hz, 5-H), 4.32 (1H, d, J=1.5 Hz, 5′-Ha), 4.03 (1H, t, J=4.9 Hz, 2′-H), 4.01 (1H, d, J=1.5 Hz, 5′-Hb), 2.68 (1H, q, J=6.8 Hz, 3′-H), 1.15 (3H, d, J=6.8 Hz, 3′-CH_3). ^{13}C NMR (DMSO-d_6) δ: 163.93 (4-C), 163.15 (4′-C), 150.47 (2-C), 141.47 (6-C), 100.86 (5-C), 85.17 (5′-C), 82.40 (1′-C), 74.36 (2′-C), 41.99 (3′-C), 16.60 (3′-CH_3). Anal. Calcd for $C_{10}H_{12}N_2O_4$ (M_w=224.21): C, 53.57; H, 5.39; N, 12.49. Found: C, 53.30; H, 5.42; N, 12.23.

4.1.3. 1-(5-Deoxy-3-*O*-methyl-β-D-*threo*-pent-4-enofuranosyl)uracil (6b). To a stirred solution of **4** (13 mg, 0.06 mmol) in dry MeOH (5 ml) was added 28% MeOH solution of sodium methoxide (0.06 ml, 0.30 mmol) at room temperature under argon atmosphere. The reaction mixture was refluxed for 6 h and the mixture was neutralized with AcOH. The solvent was evaporated in vacuo. The residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 20:1) to afford **6b** (12 mg, 80%). Residue was recrystallized from MeOH (colorless solid).

Mp: 166–167 °C. MASS m/z (relative intensity): 240 (M^+, 1%), 111 (B^+, 100%). ^{1}H NMR (DMSO-d_6) δ: 11.47 (1H, br s, N^3–H), 7.41 (1H, d, J=8.0 Hz, 6-H), 6.29 (1H, d, J=3.4 Hz, 1′-H), 6.07 (1H, d, J=2.9 Hz, 2′-OH), 5.74 (1H, d, J=8.0 Hz, 5-H), 4.67 (1H, s, 5′-Ha), 4.43 (1H, s, 5′-Hb), 4.21 (1H, br s, 2′-H), 4.13 (1H, br s, 3′-H), 3.42 (3H, s, 3′-OCH_3). ^{13}C NMR (DMSO-d_6) δ: 163.16 (4-C), 157.49 (4′-C), 150.31 (2-C), 141.60 (6-C), 100.62 (5-C), 88.07 (5′-C), 86.70 (1′-C), 83.96 (3′-C), 72.15 (2′-C), 55.76 (3′-OCH_3). Anal. Calcd for $C_{10}H_{12}N_2O_5$ (M_w=240.21): C, 50.00; H, 5.04; N, 11.66. Found: C, 50.07; H, 5.04; N, 11.52.

4.1.4. 1-(3-Benzylamino-3,5-dideoxy-β-D-*threo*-pent-4-enofuranosyl)uracil (6c). To a stirred solution of **4** (137 mg, 0.66 mmol) in dry CH_2Cl_2 (5 ml) was added benzylamine (3.60 ml, 32.9 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 24 h and the mixture was concentrated in vacuo. The residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 30:1) to afford **6c** (169 mg, 81%). Residue was recrystallized from AcOEt (colorless solid).

Mp: 153–155 °C. MASS m/z (relative intensity): 315 (M^+, 5%), 297 (M^+-H_2O, 4%), 224 (M^+-CH_2Ph, 6%), 203 (S^++1, 12%), 186 (S^+-H_2O, 58%), 91 ($PhCH_2^+$, 100%). IR (KBr) cm^{-1}: 3395.9, 1685.7. ^{1}H NMR (DMSO-d_6) δ: 11.41 (1H, br s, N^3–H), 7.27–7.42 (6H, m, Ph-H and 6-H), 6.48 (1H, d, J=3.4 Hz, 1′-H), 5.80 (1H, d, J=4.3 Hz, 2′-OH), 5.65 (1H, d, J=7.8 Hz, 5-H), 4.52 (1H, s, 5′-Ha), 4.21 (1H, br s, 2′-H), 4.19 (1H, s, 5′-Hb), 3.88 (1H, d, J=10 Hz, 3′-$NHCH_2$), 3.78 (1H, d, J=10 Hz, 3′-$NHCH_2$), 3.54 (1H, br s, 3′-H), 2.80 (1H, br s, 3′-NH). Anal. Calcd for $C_{16}H_{17}N_3O_4$ (M_w=315.33): C, 60.94; H, 5.43; N, 13.33. Found: C, 60.94; H, 5.46; N, 13.17.

4.1.5. 1-(3,5-Dideoxy-3-di(methoxycarbonyl)methyl-β-D-*threo*-pent-4-enofuranosyl)uracil (6d). To a stirred solution of dimethyl malonate (1.28 ml, 11.19 mmol) in dry MeOH (5 ml) was added 28% MeOH solution of sodium methoxide (1.08 ml, 5.60 mmol) at room temperature under argon atmosphere. The mixture was added to a stirred solution of **4** (291 mg, 1.40 mmol) in dry MeOH (5 ml) at room temperature under argon atmosphere. The reaction mixture was stirred for 12 h and the mixture was neutralized with AcOH. The solvent was evaporated in vacuo and the residue was diluted with water and extracted with AcOEt. The organic solution was dried over $MgSO_4$ and the solvent was evaporated in vacuo and residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 30:1) to afford **6d** (331 mg, 69%) as a white foam.

MASS m/z (relative intensity): 340 (M^+, 5%), 322 (M^+-H_2O, 100%), 228 (S^+-1, 38%), 211 ($M^+-CH(CO_2Me)_2+2$, 80%). ^{1}H NMR ($CDCl_3$) δ: 9.01 (1H, br s, N^3–H), 7.33 (1H, d, J=8.3 Hz, 6-H), 6.39 (1H, d, J=4.8 Hz, 1′-H), 5.69 (1H, d, J=8.3 Hz, 5-H), 4.86 (1H, d, J=4.8 Hz, 2′-H), 4.60 (1H, d, J=2.4 Hz, 5′-Ha), 4.10 (1H, d, J=2.4 Hz, 5′-Hb), 3.79 (6H, s, $CH_3\times2$), 3.74 (1H, br s, 3′-H), 3.71 (1H, br s, 2′-OH), 3.35–3.43 (1H, m, 3′-$CH(CO_2Me)_2$). HRMS m/z calcd for $C_{14}H_{16}N_2O_8$: 340.0897. Found: 340.0907.

4.1.6. 1-(3-*O*-Benzoyl-5-deoxy-β-D-*threo*-pent-4-enofuranosyl)uracil (6e). To a stirred solution of **4** (107 mg, 0.51 mmol) in dry CH_2Cl_2 (5 ml) was added benzoic acid (188 mg, 1.54 mmol) and Et_3N (0.21 ml, 1.54 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 168 h at room temperature and the solvent was evaporated in vacuo. The residue was diluted with water and extracted with AcOEt and the organic solution was dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 50:1) to afford **6e** (103 mg, 61%) (white foam) and **6e′** (12 mg, 10%) (white foam), respectively.

Compound **6e**. MASS m/z (relative intensity): 330 (M^+, 0.7%), 312 (M^+-H_2O, 13%), 218 (S^+-1, 18%), 208 ($M^+-OCOPh+1$, 19%), 201 (S^+-H_2O, 7%), 105 (PhCO, 100%). IR (KBr) cm^{-1}: 3424.3, 1686.7. ^{1}H NMR ($CDCl_3$) δ: 10.46 (1H, br s, N^3–H), 7.98 (2H, d, J=7.3 Hz, Ph-*o*), 7.32–7.51 (4H, m, Ph-*m* and *p* and 6-H), 6.51 (1H, d, J=3.4 Hz, 1′-H), 5.75 (1H, br s, 3′-H), 5.62 (1H, d, J=8.3 Hz, 5-H), 5.17 (1H, br s, 2′-OH), 4.80 (2H, br s, 2′-H and 5′-Ha), 4.66 (1H, d, J=2.4 Hz, 5′-Hb). HRMS m/z calcd for $C_{16}H_{14}N_2O_6$: 330.0852. Found: 330.0843.

Compound **6e′**. MASS m/z (relative intensity): 226 (M^+, 51%), 208 (M^+-H_2O, 13%), 115 (S^+, 100%). IR (KBr) cm^{-1}: 3383.9, 1686.8. ^{1}H NMR ($CDCl_3$) δ: 10.83 (1H, br s, N^3–H), 7.98 (1H, d, J=8.1 Hz, 6-H), 6.62 (1H, d, J=2.9 Hz, 1′-H), 5.58 (1H, d, J=8.1 Hz, 5-H), 4.81 (1H, br s, 2′-H), 4.72 (1H, d, J=2.7 Hz, 5′-Ha), 4.63 (1H, br s, 3′-H), 4.55 (1H, d, J=2.7 Hz, 5′-Hb). FABHRMS m/z calcd for $C_9H_{11}N_2O_5$: 227.0668. Found: 227.0664.

4.1.7. 1-(3-Benzoylthio-3,5-dideoxy-β-D-*threo*-pent-4-enofuranosyl)uracil (6f). To a stirred solution of **4** (169 mg, 0.81 mmol) in dry CH_2Cl_2 (5 ml) was added thiobenzoic acid (0.29 ml, 2.44 mmol) and Et_3N (0.34 ml, 2.44 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 2 days at room temperature and the solvent was evaporated in vacuo. The residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 45:1) to afford **6f** (145 mg, 52%) as a white foam.

MASS *m/z* (relative intensity): 346 (M^+, 4%), 328 ($M^+ - H_2O$, 3%), 209 ($M^+ - SCH_2Ph$, 5%), 105 (PhCO, 100%), 77 (Ph, 48%). IR (KBr) cm^{-1}: 3425.2, 1683.6. ^1H NMR ($CDCl_3$) δ: 9.64 (1H, br s, N^3–H), 7.93 (2H, d, $J=7.3$ Hz, Ph-*o*), 7.58–7.64 (1H, m, Ph-*p*), 7.44–7.49 (3H, m, Ph-*m* and 6-H), 6.40 (1H, d, $J=3.4$ Hz, 1′-H), 5.65 (1H, d, $J=7.8$ Hz, 5-H), 4.71 (1H, d, $J=1.9$ Hz, 5′-Ha), 4.60–4.67 (3H, m, 3′-H, 2′-H and 2′-OH), 4.44 (1H, d, $J=2.4$ Hz, 5′-Hb). HRMS *m/z* calcd for $C_{16}H_{14}N_2O_5S_1$: 346.0623. Found: 346.0610.

4.1.8. 1-(3-Azido-3,5-dideoxy-β-D-*threo*-pent-4-enofuranosyl)uracil (6g) and 1-(5-azido-3,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)uracil (8g). To a stirred solution of **4** (122 mg, 0.59 mmol) in dry DMF (10 ml) was added sodium azido (57 mg, 0.88 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 3 h at room temperature and the mixture was concentrated in vacuo. The residue was subjected to silica gel column chromatography (benzene/AcOEt 2:1) to give **6g** (93 mg, 63%) as the first fraction (white foam) and **8g** (5 mg, 3%) as the second fraction (white foam).

Compound **6g**. IR (KBr) cm^{-1}: 2104 (N_3). MASS *m/z* (relative intensity): 251 (M^+, 2%), 209 ($M^+ - N_3$, 14%), 167 (100%), 112 ($B^+ + 1$, 39%). ^1H NMR (DMSO-d_6) δ: 11.44 (1H, br s, N^3–H), 7.36 (1H, d, $J=8.3$ Hz, 6-H), 6.29 (1H, d, $J=4.4$ Hz, 2′-OH), 6.24 (1H, d, $J=4.4$ Hz, 1′-H), 5.61 (1H, d, $J=8.3$ Hz, 5-H), 4.69 (1H, d, $J=2.4$ Hz, 5′-Ha), 4.63 (1H, br s, 3′-H) 4.41 (1H, d, $J=2.4$ Hz, 5′-Hb), 4.09 (1H, br s, 2′-H). Anal. Calcd for $C_9H_9N_5O_4$ ($M_w=251.20$): C, 43.03; H, 3.61; N, 27.88. Found: C, 43.13; H, 3.67; N, 27.64.

Compound **8g**. IR (KBr) cm^{-1}: 2105 (N_3). MASS *m/z* (relative intensity): 251 (M^+, 12%), 209 ($M^+ - N_3$, 4%), 167 (100%), 113 ($B^+ + 2$, 44%). ^1H NMR (DMSO-d_6) δ: 11.42 (1H, br s, N^3–H), 7.32 (1H, d, $J=8.0$ Hz, 6-H), 6.42 (1H, d, $J=6.8$ Hz, 1′-H), 5.62 (1H, d, $J=8.0$ Hz, 5-H), 5.57 (1H, d, $J=4.9$ Hz, 2′-OH), 5.29 (1H, d, $J=1.5$ Hz, 3′-H), 4.88–4.91 (1H, m, 2′-H), 4.09 (2H, s, 5′-H×2). ^{13}C NMR (DMSO-d_6) δ: 163.32 (4-C), 154.29 (4′-C), 150.53 (2-C), 142.37 (6-C), 103.89 (5′-C), 100.82 (5-C), 86.02 (1′-C), 70.68 (3′-C), 46.45 (2′-C). HRMS *m/z* calcd for $C_9H_9N_5O_4$: 251.0662. Found: 251.0655.

4.1.9. 1-(3,5-Dideoxy-3-phenylthio-β-D-*threo*-pent-4-enofuranosyl)uracil (6h) and 1-(3,5-dideoxy-5-phenylthio-β-D-*glycero*-pent-4-enofuranosyl)uracil (8h). To a stirred solution of **4** (110 mg, 0.53 mmol) in Et_3N (10 ml) was added thiophenol (82 μl, 0.80 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 1 h at room temperature and the solvent was evaporated in vacuo and a small amount of the remaining Et_3N was removed as the toluene azetrope. The residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 150:1) to give **6h** (134 mg, 80%) as the first fraction (white foam) and **8h** (19 mg, 11%) as the second fraction (white foam).

Compound **6h**. MASS *m/z* (relative intensity): 318 (M^+, 58%), 206 ($S^+ - 1$, 100%), 112 ($B^+ + 1$, 16%). ^1H NMR ($CDCl_3$) δ: 11.04 (1H, br s, N^3–H), 7.23–7.50 (6H, m, 6-H and 3′-SPh), 6.37 (1H, d, $J=2.9$ Hz, 1′-H), 5.46 (1H, d, $J=8.3$ Hz, 5-H), 5.38 (1H, d, $J=4.4$ Hz, 2′-OH), 4.80–4.82 (1H, m, 2′-H), 4.61 (1H, d, $J=2.0$ Hz, 5′-Ha), 4.23 (1H, br s, 3′-H), 4.21 (1H, d, $J=2.0$ Hz, 5′-Hb). ^{13}C NMR ($CDCl_3$) δ: 165.99 (4-C), 157.96 (4′-C), 149.91 (2-C), 142.95 (6-C), 132.63 (SPh-C), 129.25 (SPh-C), 128.17 (SPh-C), 100.41 (5-C), 88.06 (1′-C), 87.41 (5′-C), 74.24 (2′-C), 53.50 (3′-C). Anal. Calcd for $C_{15}H_{14}N_2O_4S_1$ ($M_w=318.35$): C, 56.59; H, 4.43; N, 8.80. Found: C, 56.34; H, 4.49; N, 8.78.

Compound **8h**. MASS *m/z* (relative intensity): 318 (M^+, 33%), 209 ($M^+ - SPh$, 50%), 206 ($S^+ - 1$, 7%), 123 ($PhSCH_2^+$, 100%), 112 ($B^+ + 1$, 9%). ^1H NMR ($CDCl_3$) δ: 10.75 (1H, br s, N^3–H), 7.23–7.47 (6H, m, 6-H and 3′-SPh), 6.46 (1H, d, $J=6.4$ Hz, 1′-H), 5.51 (1H, d, $J=8.3$ Hz, 5-H), 5.16 (2H, br s, 2′-H and 3′-H), 4.58 (1H, d, $J=3.9$ Hz, 2′-OH), 3.66 (2H, s, 5′-H×2). ^{13}C NMR ($CDCl_3$) δ: 165.22 (4-C), 156.88 (4′-C), 150.48 (2-C), 143.00 (6-C), 134.83 (SPh-C), 130.53 (SPh-C), 129.07 (SPh-C), 127.15 (SPh-C), 102.27 (3′-C), 100.74 (5-C), 86.91 (1′-C), 71.88 (2′-C), 31.46 (5′-C). Anal. Calcd for $C_{15}H_{14}N_2O_4S_1$ ($M_w=318.35$): C, 56.59; H, 4.43; N, 8.80. Found: C, 56.30; H, 4.40; N, 8.72.

4.1.10. 1-(3-Cyano-3,5-dideoxy-β-D-*glycero*-pent-3-enofuranosyl)uracil (9). To a stirred solution of **4** (296 mg, 1.42 mmol) in dry THF (10 ml) was added 1.0 M toluene solution of Et_2AlCN (14 ml, 14 mmol) under argon atmosphere. The reaction mixture was refluxed for 2 h. EtOH was added and the mixture was stirred for 30 min and the solvent was evaporated in vacuo. The residue was diluted with water and extracted with AcOEt and the organic solution was dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 30:1) to afford **9** (193 mg, 58%). Residue was recrystallized from acetone and AcOEt (colorless solid).

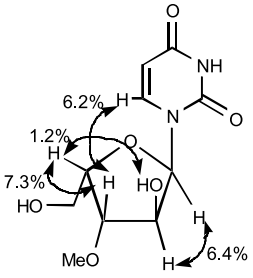
Mp: 219–222 °C. MASS *m/z* (relative intensity): 235 (M^+, 29%), 217 ($M^+ - H_2O$, 9%), 192 ($M^+ - H_2O$–CN+1, 6%), 123 ($S^+ - 1$, 38%), 113 ($B^+ + 2$, 100%). IR (KBr) cm^{-1}: 3426.6, 3196.6, 2218.0 (CN), 1697.9, 1671.7, 1653.5. ^1H NMR (DMSO-d_6) δ: 11.53 (1H, br s, N^3–H), 7.44 (1H, d, $J=7.8$ Hz, 6-H), 6.66 (1H, d, $J=7.3$ Hz, 1′-H), 6.23 (1H, d, $J=5.9$ Hz, 2′-OH), 5.65 (1H, d, $J=7.8$ Hz, 5-H), 5.07–5.11 (1H, m, 2′-H), 2.15 (3H, s, 5′-CH_3). Anal. Calcd for $C_{10}H_9N_3O_4$ ($M_w=235.20$): C, 51.07; H, 3.86; N, 17.87. Found: C, 51.27; H, 3.93; N, 17.68.

4.1.11. 1-(3-*O*-Methyl-α-L-*xylo*-furanosyl)uracil (11) and 1-(3-*O*-methyl-β-D-*arabino*-furanosyl)uracil (12). To a stirred solution of **6b** (30 mg, 0.125 mmol) in dry THF (10 ml) was added 1 M THF solution of BH_3–THF (0.625 ml, 0.625 mmol) at 0 °C under argon atmosphere and the reaction mixture was stirred for 1 h at 0 °C. One molar THF solution of BH_3–THF (1.625 ml, 1.625 mmol) was added to the reaction mixture and the reaction mixture was refluxed for 17 h. After cooling to room temperature, H_2O and 3 N NaOH (0.125 ml, 0.375 mmol) and 30% H_2O_2 (0.12 ml, 1.25 mmol) was added to the reaction mixture. The reaction mixture was stirred for 6 h at room temperature. After acidification with AcOH, the reaction mixture was washed with saturated NaCl and the aqueous layer was extracted with THF. The organic solution was

combined and dried over Na_2SO_4. The solvent was removed in vacuo and the mixture was analyzed by the ^1H NMR (17% of the **12** was detected). The crude mixture was purified by silica gel column chromatography ($CHCl_3$/MeOH 15:1) to give **11** (53%).

Compound **11**. FABMASS *m/z* (relative intensity): 259 ($M^+ + 1$, 7%), 154 (100%). ^1H NMR (DMSO-d_6) δ: 11.25 (1H, br s, N^3–H), 7.41 (d, $J=8.2$ Hz, 6-H), 5.92 (1H, d, $J=3.6$ Hz, 1′-H), 5.76 (1H, d, $J=4.5$ Hz, 2′-OH), 5.55 (1H, d, $J=8.2$ Hz, 5-H), 4.72 (1H, t, $J=5.5$ Hz, 5′-OH), 4.28–4.34 (1H, m, 3′-H), 4.21–4.25 (1H, m, 2′-H), 3.74–3.76 (1H, m, 4′-H), 3.48–3.63 (2H, m, 5′-H×2), 3.36 (3H, s, 3′-OCH_3). NOE experiment, 4′-H/3′-H (7.3%), 4′-H/2′-OH (1.2%), 3′-H/6-H (6.2%) and 1′-H/2′-H (6.4%). FABHRMS *m/z* calcd for $C_{10}H_{15}N_2O_6$: 259.0930. Found: 259.0938.

Compound **12**. ^1H NMR (DMSO-d_6) δ: 11.28 (1H, br s, N^3–H), 7.60 (d, $J=8.2$ Hz, 6-H), 5.90 (1H, d, $J=4.5$ Hz, 1′-H), 5.76 (1H, d, $J=5.1$ Hz, 2′-OH), 5.57 (1H, d, $J=8.2$ Hz, 5-H), 5.08 (1H, t, $J=5.7$ Hz, 5′-OH), 4.12–4.16 (1H, m, 2′-H), 3.79–3.84 (1H, m, 3′-H), 3.66–3.68 (1H, m, 4′-H), 3.58–3.61 (2H, m, 5′-H×2), 3.34 (3H, s, 3′-OCH_3). FABHRMS *m/z* calcd for $C_{10}H_{15}N_2O_6$: 259.0930. Found: 259.0943.



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10. Detailed results for the reaction mechanism will be reported in due course.