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# CHEMICAL MODIFICATION OF THE SUGAR MOIETY OF PYRIMIDINE NUCLEOSIDES *VIA* A 4',5'-EPOXYURIDINE INTERMEDIATE

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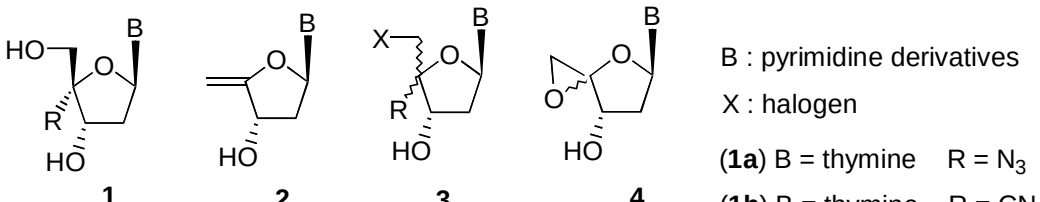
**Abstract** – The reaction of 4',5'-unsaturated nucleoside (**5**) with *m*-CPBA provided different products depending on the solvent. 4',5'-Epoxynucleoside (**6**) was generated as a key intermediate although **6** was not stable enough to isolate and further reaction progressed. When the reaction was performed in $CH_2Cl_2$, 2,4'-cyclonucleoside (**7**) and 4'-ketonucleoside (**8**) were obtained. On the other hand, 4'-alkoxy derivatives (**9** and **11**) together with their epimers (**10** and **12**) were aquired as a mixture by the nucleophilic attack of alcohol.

## INTRODUCTION

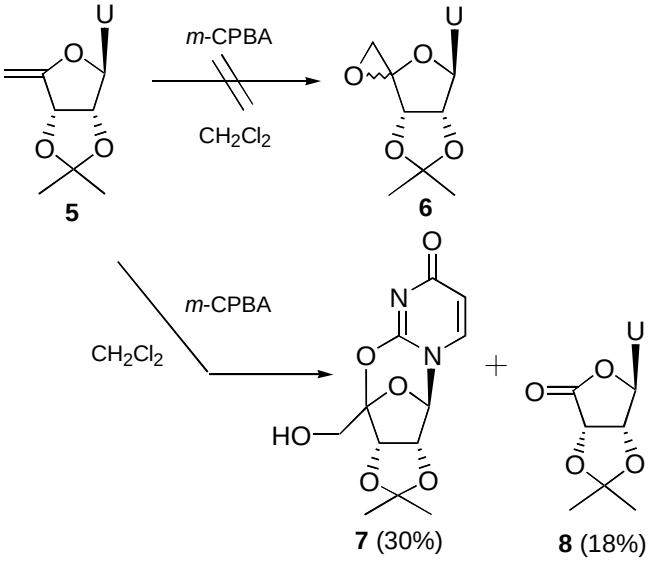
Nucleosides modified in the sugar moiety have been recognized as attractive synthetic targets for the development of potential antiviral and antitumor agents.[1] Recently, 4'-substituted nucleosides (**1**) have received much attention because of the discovery of potent anti-HIV agents such as 4'-azidothymidine (**1a**)[2] and 4'-cyanothymidine (**1b**).[3] The modification of the 4'-position of the sugar moiety using 4',5'-unsaturated derivatives (**2**) was reported previously.[2,4,5] In these cases, 4'-substituted 5'-halogeno derivatives (**3**)[2,4] were key intermediates and it is quite important to transform the 5'-halogen to the OH group, because the 5'-hydroxy group of nucleosides is supposed to be important for their biological activities. We considered that 4',5'-epoxynucleosides (**4**)[2,5] are very useful intermediates for the synthesis



of 4'-substituted nucleosides (**1**). Here, we report the synthesis of 4'-alkoxyuridine derivatives *via* 4',5'-epoxyuridine starting from the 4',5'-unsaturated uridine derivative (**5**).[6]

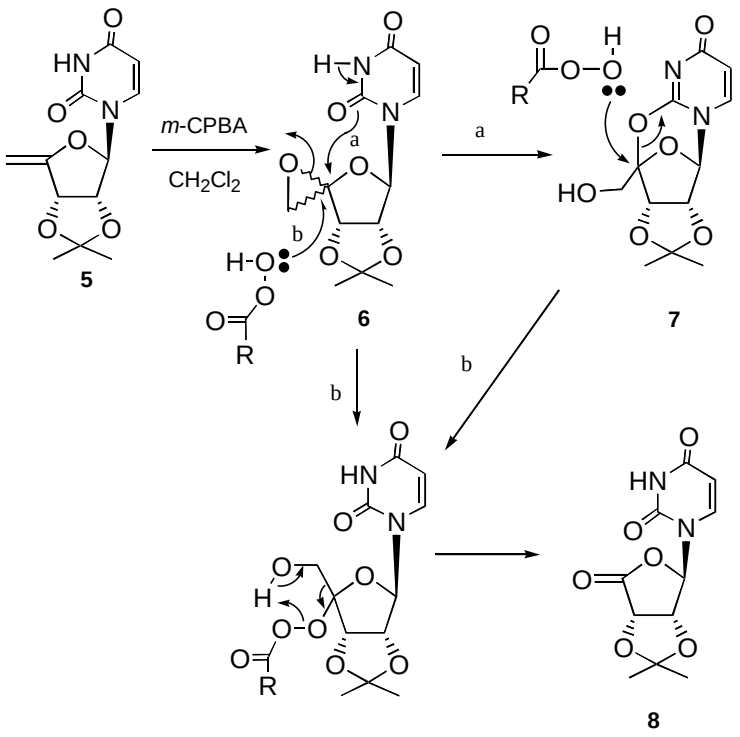
## RESULTS AND DISCUSSION

The oxidation reaction of 4',5'-didehydro-5'-deoxy-2',3'-*O*-isopropylideneuridine (**5**) using *m*-CPBA in $CH_2Cl_2$ at room temperature was completed within 30 min and gave unexpected 2,4'-didehydro-(2,3-*O*-isopropylidene-α-L-lyxosyl)uracil (**7**) and 1-[4-(2,3-*O*-isopropylidene-β-D-erythrolactonyl)]uracil (**8**) in 30 and 18% yields, respectively, together with uracil formed by the glycosyl bond cleavage under acidic conditions (Scheme 1). A plausible reaction mechanism of the conversion of **5** into **7** and **8** *via* 4',5'-epoxy compound (**6**) is shown in Scheme 2. It was assumed that the anticipated 4',5'-epoxy intermediate (**6**) was obtained by the reaction of **5** with *m*-CPBA. The subsequent ring-opening of the epoxide by the nucleophilic attack of the oxygen atom at the 2-position of the uracil ring gave the corresponding 2,4'-cyclo compound (**7**) (path a). On the other hand, 4'-keto compound (**8**) was generated by the nucleophilic attack of another *m*-CPBA to 4',5'-epoxy compound (**6**) or 2,4'-cyclo compound (**7**) (path b). The 4'-keto compound (**8**) was not stable and the formation of uracil by the acid-catalyzed (silica gel) hydrolytic cleavage of the glycosyl bond proceeded during the two-dimensional development of TLC analysis.



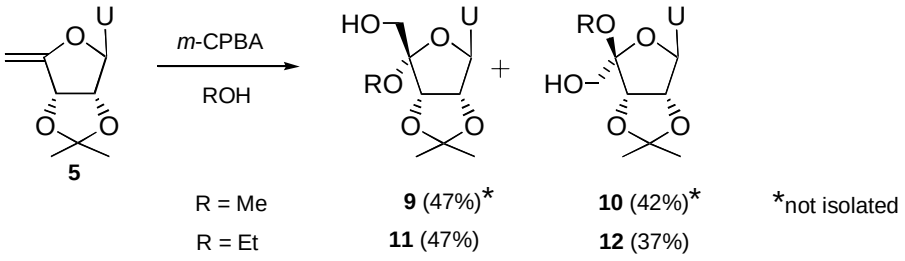

**Scheme 1**

To confirm the formation of intermediary **6**, the reaction of **5** with *m*-CPBA was followed by $^1$H NMR spectrum in $CDCl_3$. Consequently, the complete conversion of the starting material (**5**) was observed within 30 min and the formation of the expected epoxide (**6**) was confirmed by $^1$H NMR spectrum[5a,7] although **6** decomposed gradually in the NMR tube. Therefore, the epoxide (**6**) is quite labile under the acidic reaction conditions[2] and it is extremely difficult to isolate.



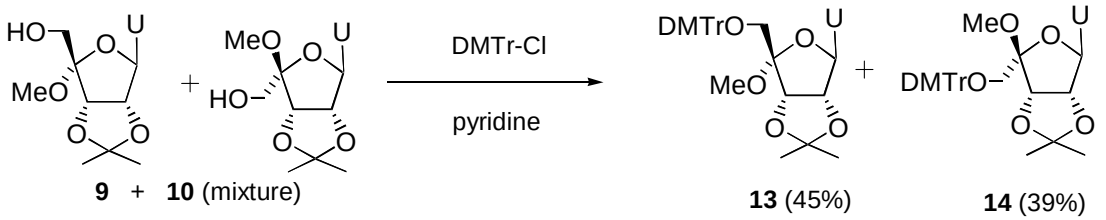

**Scheme 2**

Next, we examined the epoxidation reaction of **5** in MeOH, as a solvent and a nucleophile.[8] As the result, the 4'-methoxy derivative (**9**) and its epimer (**10**) were obtained as a mixture (Scheme 3). The use of EtOH instead of MeOH as a solvent gave the corresponding 4'-ethoxy derivative (**11**) and its epimer (**12**). The ratio of α- to β-isomer was roughly 1:1.




**Scheme 3**

The mixture of **9** and **10** was not separable. To isolate each isomer (**9** and **10**), the purified mixture was at first protected at the 5'-position as the trityl ether and benzoic acid ester while the corresponding 5'-*O*-Bz and 5'-*O*-Tr derivatives were also not separable. On the other hand, when the mixture of **9** and **10** was converted to the 5'-*O*-DMTr(4,4'-dimethoxytrityl) derivatives (**13** and **14**), the separation of **13** and **14** could be achieved easily by silica gel column chromatography in 45 and 39% isolated yields based upon the original starting material (**5**), respectively (Scheme 4). The stereochemistry of these compounds was determined by $^1$H NMR and NOE[5a] spectral analysis in $CDCl_3$. The 5-H resonance of **13** appeared at a significantly higher field (δ 5.34 ppm) compared with that of **14** (δ 5.70 ppm) due to the anisotropic effect of the benzene ring of β-5'-*O*-DMTr group reported by Haraguchi *et al*.[9] (Figure. 1).




**Scheme 4**

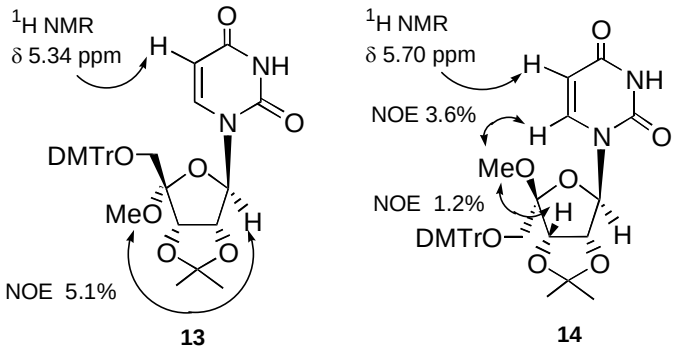



**Figure 1**

Concomitantly, the 5'-*O*-DMTr group of **13** was cleaved by 80% AcOH and a 90% yield of 2',3'-*O*-isopropyliden-4'-methoxyuridine (**9**) was isolated and its $^1$H NMR spectral data was consistent with the data of **9** in the crude mixture together with **10** (Scheme 3).

Next, we investigated deprotection of the 2',3'-*O*-isopropylidene group of **12**. The deprotection reaction was carried out at 50 °C in 80% AcOH although the yield of **15** was not satisfactory (12%) because of the formation of uracil arising from the acid-catalyzed cleavage of the glycosyl bond.

The epoxidation reaction of 4',5'-didehydro-5'-deoxy-2',3'-*O*-isopropylideneuridine (**5**) afforded different products depending on the kind of solvent used. The reaction of **5** with *m*-CPBA in $CH_2Cl_2$ solvent afforded 2,4'-cyclonucleoside derivative (**7**) and 4'-ketonucleoside derivative (**8**). On the other hand, the reaction of **5** with *m*-CPBA in an alcohol solvent afforded 4'-alkoxide derivatives (**9**), (**10**), (**11**) and (**12**).

## EXPERIMENTAL

$^1$H and $^{13}$C NMR spectra were recorded on a JEOL EX 400 spectrometer or a JEOL GX 270 spectrometer ($^1$H: 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 MS 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 uncorrected. IR spectra were recorded on a Perkin Elmer model 1600 FT-IR spectrophotometer. All reagents were commercially available and used without further purification. Compounds known in the literature were characterized by comparison of their $^1$H NMR spectral data with the previously reported data.

**1-(2,3-Isopropylidene-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)uracil (5)[6]**

To a stirred solution of 2',3'-isopropylidene-5'-*O*-tosyluridine[6] (5.7 g, 13 mmol) in dry THF (10 mL) was added *t*-BuOK (4.5 g, 40 mmol) at rt under argon atmosphere. The reaction mixture was stirred for 30 min at rt and the solvent was evaporated *in vacuo*. The residue was subjected to silica gel column chromatography ($CHCl_3$ : MeOH = 200 : 1) to give **5** (3.0 g, 87%) as a white foam.

IR (KBr) $\nu_{max}/cm^{-1}$: 1688, 1459, 1381, 1222 and 1071. MS (EI) *m/z*: 266 ($M^+$, 13%), 155 ($S^+$, 4%), 113 ($B^+$+2, 14%). $^1$H NMR (DMSO-$d_6$) δ: 11.42 (1H, br s, $N^3$-H), 7.71 (1H, d, *J*=7.8 Hz, 6-H), 5.89 (1H, br s, 1'-H), 5.62 (1H, d, *J*=7.8 Hz, 5-H), 5.24 (1H, d, *J*=6.1 Hz, 3'-H), 5.10 (1H, d, *J*=6.1 Hz, 2'-H), 4.36 (1H, br s, 5'-Ha), 4.18 (1H, br s, 5'-Hb), 1.39 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$), 1.30 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$). $^{13}$C NMR (DMSO-$d_6$) δ: 163.37 (4-C and 4'-C) 150.29 (2-C), 143.96 (6-C), 112.43 (2',3'-*O*-isopropylidene), 101.62 (5-C), 95.22 (1'-C), 84.95 (5'-C), 82.06 (2'-C), 79.48 (3'-C), 26.46 (2',3'-*O*-isopropylidene-$CH_3$). HRMS ($FAB^+$) *m/z* Calcd for $C_{12}H_{15}N_2O_5$ ($M^+$+1): 267.0981. Found: 267.0992.

**2,4'-Didehydro-(2,3-*O*-isopropylidene-α-L-lyxosyl)uracil (7) and 1-[4-(2,3-*O*-isopropylidene-β-D-erythrolactonyl)]uracil (8)**

To a stirred solution of **5** (133 mg, 0.5 mmol) in dry $CH_2Cl_2$ (10 mL) was added *m*-CPBA (65%, 172 mg, 0.65 mmol) at rt under argon atmosphere. The reaction mixture was stirred for 30 min at rt. The precipitate was collected to give **7** (42 mg, 30%). The filtrate was evaporated *in vacuo* and the residue was subjected to silica gel column chromatography ($CHCl_3$ : MeOH = 80 : 1) to afford **8** (24 mg, 18%) as a pale yellow oil.

**7:** mp: 171 °C ($CH_2Cl_2$). MS (EI) *m/z*: 267 ($M^+$-$CH_3$, 12%), 113 (100%). $^1$H NMR (DMSO-$d_6$) δ: 7.71 (1H, d, *J*=7.3 Hz, 6-H), 6.21 (1H, s, 1'-H), 5.93 (1H, d, *J*=7.3 Hz, 5-H), 5.57 (1H, t, *J*=6.4 Hz, 5'-OH), 5.08 (1H, d, *J*=5.4 Hz, 2'-H), 4.95 (1H, d, *J*=5.4 Hz, 3'-H), 3.94 (1H, dd, *J*=6.4 and 12.7 Hz, 5'-Ha), 3.87 (1H, dd, *J*=6.4 and 12.7 Hz, 5'-Hb), 1.45 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$), 1.26 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$). Anal. Calcd for $C_{12}H_{14}N_2O_6$: C, 51.07; H, 5.00; N, 9.92. Found: C, 50.80; H, 4.96; N, 9.82.

**8:** IR (KBr) $\nu_{max}/cm^{-1}$: 1807(lactone), 1698, 1459, 1386, 1280 and 1064. MS (EI) *m/z*: 253 ($M^+$-$CH_3$, 30%), 113 ($B^+$+2, 31%). $^1$H NMR ($CDCl_3$) δ: 9.21 (1H, br s, $N^3$-H), 7.24 (1H, d, *J*=8.3 Hz, 6-H), 5.82 (1H, d, *J*=8.3 Hz, 5-H), 5.55 (1H, s, 1'-H), 5.20 (1H, d, *J*=6.1 Hz, 2'-H), 5.06 (1H, d, *J*=6.1 Hz, 3'-H), 1.51 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$), 1.45 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$). $^{13}$C NMR ($CDCl_3$) δ: 171.84 (4'-C), 162.79 (4-C), 150.17 (2-C), 143.40 (6-C), 114.93 (2',3'-*O*-isopropylidene-C($CH_3$)), 103.55 (5-C), 93.53 (1'-C), 80.15 (3'-C), 76.25 (2'-C), 26.29 (2',3'-*O*-isopropylidene-$CH_3$), 25.08 (2',3'-*O*-isopropylidene-$CH_3$). HRMS ($FAB^+$) *m/z* Calcd for $C_{11}H_{13}N_2O_6$ ($M^+$+1): 269.0774. Found: 269.0780.

**5'-Deoxy-4',5'-epoxy-2',3'-*O*-isopropylideneuridine (6)**

The solution of **5** (13 mg, 0.05 mmol) and *m*-CPBA (65%, 17 mg, 0.065 mmol) in $CDCl_3$ (0.7 mL) was allowed to stand at rt under argon atmosphere in the NMR tube. The mixture was monitored periodically by measuring the $^1$H NMR spectrum. After 30 min, the disappearance of the starting material (**5**) and formation of expected (**6**) were detected by the $^1$H NMR spectrum although **6** decomposed gradually under the same conditions.

$^1$H NMR ($CDCl_3$) δ: 9.50 (1H, br s, $N^3$-H), 7.42 (1H, d, *J*=7.9 Hz, 6-H), 5.81 (1H, s, 1'-H), 5.80 (1H, d, *J*=7.9 Hz, 5-H), 5.16 (1H, d, *J*=6.0 Hz, 2'-H), 4.87 (1H, d, *J*=6.0 Hz, 3'-H), 3.29 (1H, d, *J*=3.5 Hz, 5'-Ha), 3.15 (1H, d, *J*=3.5 Hz, 5'-Ha), 1.56 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$), 1.38(3H, s, 2',3'-*O*-isopropylidene -$CH_3$).

**2',3'-*O*-Isopropyliden-4'-methoxyuridine (9) and 1-(2,3-*O*-isopropylidene-4-methoxy-α-L-lyxofuranosyl)uracil (10)**

To a stirred solution of **5** (2.66 g, 10 mmol) in dry MeOH (50 mL) was added *m*-CPBA (65%, 4.31 g, 16.3 mmol) at rt 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 = 200 : 1) to afford **9** (1.55 g, 49%) and **10** (1.33 g, 43%) as a mixture. Yields were estimated by the integration ratios of the $^1$H NMR spectra of the mixture.

**9:** $^1$H NMR ($CDCl_3$) δ: 9.09 (1H, br s, $N^3$-H), 7.43 (1H, d, *J*=8.3 Hz, 6-H), 5.77 (1H, d, *J*=8.3 Hz, 5-H), 5.70 (1H, d, *J*=2.4 Hz, 1'-H), 5.13 (1H, d, *J*=6.8 Hz, 3'-H), 5.03 (1H, dd, *J*=2.4 and 6.8 Hz, 2"-H), 3.78-3.93 (2H, m, 5'-H x 2), 3.46 (3H, s, 4'-$OCH_3$), 1.62 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$), 1.37 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$).

**10:** $^1$H NMR ($CDCl_3$) δ: 8.87 (1H, br s, $N^3$-H), 7.32 (1H, d, *J*=8.3 Hz, 6-H), 6.36 (1H, br s, 1'-H), 5.77 (1H, d, *J*=8.3 Hz, 5-H), 4.98 (1H, d, *J*=5.9 Hz, 2'-H), 4.75 (1H, d, *J*=5.9 Hz, 3'-H), 3.78-3.93 (2H, m, 5'-H x 2), 3.28 (3H, s, 4'-$OCH_3$), 1.58 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$), 1.37 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$).

**2',3'-*O*-Isopropyliden-4'-ethoxyuridine (11) and 1-(2,3-O-isopropylidene-4-ethoxy-α-L-lyxofuranosyl)uracil (12)**

To a stirred solution of **5** (133 mg, 0.5 mmol) in dry EtOH (50 mL) was added *m*-CPBA (65%, 130 mg, 0.49 mmol) at rt under argon atmosphere. The reaction mixture was stirred for 15 h and the mixture was concentrated *in vacuo*. The residue was subjected to silica gel column chromatography ($CHCl_3$ : MeOH = 100 : 1) to give **12** (60 mg, 37%) as the first fraction (white foam) and **11** (77 mg, 47%) as the second fraction (white foam).

**11:** MS (EI) *m/z*: 313 ($M^+$-$CH_3$, 14%), 217 ($S^+$, 4%), 138 (100%). $^1$H NMR ($CDCl_3$) δ: 9.65 (1H, br s, $N^3$-H), 7.38 (1H, d, *J*=7.8 Hz, 6-H), 5.78 (1H, d, *J*=7.8 Hz, 5-H), 5.75 (1H, d, *J*=2.4 Hz, 1'-H), 5.12 (1H, d, *J*=6.8 Hz, 3'-H), 4.98 (1H, dd, *J*=6.8 and 2.4 Hz, 2'-H), 3.45-3.85 (4H, m, 4'-$OCH_2CH_3$ and 5'-H x 2),

2.87 (1H, br s, 5'-OH), 1.63 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$), 1.37 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$), 1.18-1.29 (3H, m, 4'-$OCH_2CH_3$). Anal. Calcd for $C_{14}H_{20}N_2O_7$: C, 51.21; H, 6.14; N, 8.53. Found: C, 51.05; H, 6.25; N, 8.32.

**12:** MS (EI) *m/z*: 313 ($M^+$-$CH_3$, 5%), 217 ($S^+$, 9%), 112 ($B^+$-1, 44%), 59(100%). $^1$H NMR ($CDCl_3$) δ: 9.40 (1H, br s, $N^3$-H), 7.49 (1H, d, *J*=8.1 Hz, 6-H), 6.34 (1H, d, *J*=1.5 Hz, 1'-H), 5.78 (1H, d, *J*=8.1 Hz, 5-H), 4.98 (1H, dd, *J*=6.3 and 1.5 Hz, 2'-H), 4.77 (1H, d, *J*=6.3 Hz, 3'-H), 3.83-3.95 (2H, m, 4'-$OCH_2CH_3$), 3.64-3.75 (1H, m, 5'-Ha), 3.45-3.56 (1H, m, 5'-Hb), 2.27 (1H, br s, 5'-OH), 1.58 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$), 1.36 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$), 1.18 (3H, t, *J*=6.8 Hz, 4'-$OCH_2CH_3$). HRMS ($FAB^+$) *m/z* Calcd for $C_{14}H_{21}N_2O_7$ ($M^+$+1): 329.1348. Found: 329.1353.

**5'-*O*-(4,4'-Dimethoxytrityl)-2',3'-*O*-isopropyliden-4'-methoxyuridine (13) and 1-[5-*O*-(4,4'-dimethoxytrityl)-2,3-*O*-isopropylidene-4-methoxy-α-L-lyxofuranosyl]uracil (14)**

To a stirred solution of a mixture of **9** and **10** (314 mg, 1.0 mmol; **9** : **10** = 9 : 8) in dry pyridine (5 mL) was added DMTr-Cl(4,4'-dimethoxytrityl chloride) (508 mg, 1.5 mmol) at rt under argon atmosphere. The reaction mixture was stirred for 9 h and the mixture was concentrated *in vacuo* and remaining pyridine was removed as a toluene azeotrope. The residue was partitioned between $CHCl_3$ and sat. $NaHCO_3$. The organic layer was washed with water and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was subjected to silica gel column chromatography ($CHCl_3$ : MeOH = 100 : 1) to afford **13** (275 mg, 45%) as the first fraction (white foam) and **14** (243 mg, 39%) as the second fraction (white foam).

**13:** IR (KBr) $\nu_{max}$/$cm^{-1}$: 1693, 1508, 1458, 1380, 1249 and 1087. MS (EI) *m/z*: 616 ($M^+$, 2%), 303 ($DMTr^+$, 100%). $^1$H NMR ($CDCl_3$) δ: 8.72 (1H, br s, $N^3$-H), 7.63 (1H, d, *J*=8.1 Hz, 6-H), 7.23-7.36 (9H, m, DMTr-H), 6.82-6.85 (4H, m, DMTr-H), 6.22 (1H, d, *J*=2.4 Hz, 1'-H), 5.34 (1H, d, *J*=8.1 Hz, 5-H), 5.10 (1H, d, *J*=6.8 Hz, 3'-H), 4.75 (1H, dd, *J*=6.8 and 2.4 Hz, 2'-H), 3.80 (6H, s, DMTr-$OCH_3$), 3.56 (1H, d, *J*=9.8 Hz, 5'-Ha), 3.36 (1H, d, *J*=9.8 Hz, 5'-Hb), 3.31 (3H, s, 4'-$OCH_3$), 1.61 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$), 1.38 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$). $^{13}$C NMR ($CDCl_3$) δ: 162.69 (4-C), 158.78 (DMTr-C), 149.83 (2-C), 144.04 (DMTr-C), 140.42 (6-C), 134.91 (DMTr-C), 130.21 (DMTr-C), 130.17 (DMTr-C), 128.20 (DMTr-C), 128.02 (DMTr-C), 127.25 (DMTr-C), 116.26 (DMTr-C), 113.31 (DMTr-C), 106.33 (2',3'-*O*-isopropylidene), 102.94 (5-C), 88.77 (1'-C), 87.36 (4'-C), 84.67 (2'-C), 80.85 (3'-C), 62.87 (5'-C), 55.27 (DMTr-$OCH_3$), 50.62 (4'-$OCH_3$), 25.99 (2',3'-*O*-isopropylidene-$CH_3$), 25.88 (2',3'-*O*-isopropylidene-$CH_3$). HRMS (EI) *m/z* Calcd for $C_{34}H_{36}N_2O_9$ ($M^+$): 616.2421. Found: 616.2414.

**14:** IR (KBr) $\nu_{max}$/$cm^{-1}$: 1690, 1508, 1458, 1380, 1250 and 1099. MS (EI) *m/z*: 616 ($M^+$, 2%), 303 ($DMTr^+$, 100%). $^1$H NMR ($CDCl_3$) δ: 8.68 (1H, br s, $N^3$-H), 7.56 (1H, d, *J*=7.8 Hz, 6-H), 7.20-7.45 (9H, m, DMTr-H), 6.80-6.83 (4H, m, DMTr-H), 6.24 (1H, d, *J*=1.5 Hz, 1'-H), 5.70 (1H, d, *J*=7.8 Hz, 5-H), 4.98 (1H, dd, *J*=5.4 and 1.5 Hz, 2'-H), 4.88 (1H, d, *J*=5.4 Hz, 3'-H), 3.79 (6H, s, DMTr-$OCH_3$), 3.56 (1H,

d, *J*=10.3 Hz, 5'-Ha), 3.17 (1H, d, *J*=10.3 Hz, 5'-Hb), 2.86 (3H, s, 4'-$OCH_3$), 1.50 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$), 1.42 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$). $^{13}$C NMR ($CDCl_3$) δ: 162.53 (4-C), 158.58 (DMTr-C), 158.54 (DMTr-C), 150.60 (2-C), 144.35 (DMTr-C), 140.76 (6-C), 135.66 (DMTr-C), 135.19 (DMTr-C), 130.38 (DMTr-C), 130.21 (DMTr-C), 128.29 (DMTr-C), 128.71 (DMTr-C), 126.86 (DMTr-C), 113.92 (DMTr-C), 112.97 (DMTr-C), 112.07 (2',3'-*O*-isopropylidene), 102.65 (5-C), 91.28 (1'-C), 86.14 (4'-C), 84.77 (2'-C), 83.72 (3'-C), 57.55 (5'-C), 55.21 (DMTr-$OCH_3$), 48.56 (4'-$OCH_3$), 26.06 (2',3'-*O*-isopropylidene-$CH_3$), 25.42 (2',3'-*O*-isopropylidene-$CH_3$). HRMS (EI) *m/z* Calcd for $C_{34}H_{36}N_2O_9$ ($M^+$): 616.2421. Found: 616.2410.

**2',3'-*O*-Isopropyliden-4'-methoxyuridine (9)**

**13** (50 mg, 0.05 mmol) was dissolved in 80% AcOH (10 mL) and the mixture was stirred for 9 h at rt under argon atmosphere. The reaction mixture was concentrated *in vacuo* and remaining AcOH was removed as a toluene azeotrope. The residue was subjected to silica gel column chromatography ($CHCl_3$ : MeOH = 50 : 1) to afford **9** (23 mg, 90%) as a pale yellow oil.

MS (EI) *m/z*: 299 ($M^+$-$CH_3$, 18%), 203 ($S^+$, 6%), 138 (100%), 113 ($B^+$+2, 29%). $^1$H NMR ($CDCl_3$) δ: 9.56 (1H, br s, $N^3$-H), 7.35 (1H, d, *J*=7.8 Hz, 6-H), 5.78 (1H, d, *J*=7.8 Hz, 5-H), 5.73 (1H, d, *J*=2.4 Hz, 1'-H), 5.12 (1H, d, *J*=6.8 Hz, 3'-H), 5.02 (1H, dd, *J*=6.8 and 2.4 Hz, 2'-H), 3.76-3.85 (2H, m, 5'-H x 2), 3.46 (3H, s, 4'-$OCH_3$), 1.62 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$), 1.37 (3H, s, 2',3'-*O*-isopropylidene-$CH_3$). $^{13}$C NMR ($CDCl_3$) δ: 163.27 (4-C), 150.21 (2-C), 142.71 (6-C), 115.95 (2',3'-*O*-isopropylidene), 107.14 (4'-C), 102.93 (5-C), 93.64 (1'-C), 83.55 (2'-C), 81.24 (3'-C), 62.37 (5'-C), 50.48 (4'-$OCH_3$), 26.05 (2',3'-*O*-isopropylidene-$CH_3$), 25.55 (2',3'-*O*-isopropylidene-$CH_3$). HRMS ($FAB^+$) *m/z* Calcd for $C_{13}H_{19}N_2O_7$ ($M^+$+1): 315.1192. Found: 315.1185.

**1-(4-Ethoxy-α-L-lyxofuranosyl)uracil (15)**

**12** (210 mg, 0.61 mmol) was dissolved in 80% AcOH (10 mL) and the mixture was stirred at 50 °C for 30 h under argon atmosphere. The reaction mixture was concentrated *in vacuo* and remaining AcOH was removed as a toluene azeotrope. The residue was subjected to silica gel column chromatography ($CHCl_3$ : MeOH = 15 : 1) to afford **15** (23 mg, 12%) as a white foam.

$^1$H NMR (DMSO-$d_6$) δ: 11.37 (1H, br s, $N^3$-H), 7.35 (1H, d, *J*=8.2 Hz, 6-H), 6.00 (1H, d, *J*=7.3 Hz, 1'-H), 5.80 (1H, d, *J*=8.2 Hz, 5-H), 5.41-5.43 (2H, m, 2'-OH and 3'-OH), 4.67 (1H, t, *J*=5.6 Hz, 5'-OH), 4.37-4.43 (1H, m, 2'-H), 3.82 (1H, d, *J*=4.5 Hz, 3'-H), 3.39-3.71 (4H, m, 4'-$OCH_2CH_3$ and 5'-H x 2), 1.15 (3H, t, *J*=7.0 Hz, 4'-$OCH_2CH_3$). HRMS ($FAB^+$) *m/z* Calcd for $C_{11}H_{17}N_2O_7$ ($M^+$+1): 289.1036. Found: 289.1046.

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7. The corresponding epoxide protons of **6** was observed at 3.29 (1H, d, *J*=3.5 Hz, 5'-Ha) and 3.15 (1H, d, *J*=3.5 Hz, 5'-Ha) ppm by $^{1}$H NMR spectrum(See EXPERIMENTAL).
8. Prisbe *et al*. reported similar conditions using 3'-*O*-*t*-butyldimethylsilyl-4',5'-dehydro-2',5'-deoxyadenosine and 4',5'-dehydro-2'-deoxythymidine.[2]
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