

## NOTE

## Synthesis of Novel 2',3'-Didehydro-2',3'-dideoxynucleoside

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The unsaturated nucleoside, viz., 2',3'-didehydro-2',3'-dideoxy-5-iodo-6-methyluridine **4** has been prepared *via* cyclic thionocarbonate **2** followed by deoxygenation.

**Key Words:** Synthesis, Nucleoside.

Many unsaturated and dideoxy nucleosides have been reported chemotherapeutic agents<sup>1-5</sup>. 2',3'-Didehydro-3'-deoxythymidine (d<sub>4</sub>T)<sup>6,7</sup> has undergone pre-clinical toxicology for investigation of new drug application. Several methods are now available for the preparation of 2',3'-unsaturated nucleosides in literature, Horwitz<sup>1</sup> and his co-workers used the base-promoted elimination of 3'-O-sulfonyl esters of 2'-deoxynucleosides. In the recent past, such nucleosides have been obtained directly from ribonucleosides *via* reaction with acetoxisobutyryl halides<sup>2,3</sup>. 2',3'-Dideoxynucleosides have been obtained through the Barton deoxygenation of dithiocarbonates or thionocarbonates<sup>8</sup>. Compounds **1-4** have been characterized by the required physicochemical data given in the experimental section.

Melting points were recorded in open capillaries and are uncorrected. <sup>1</sup>H NMR and UV spectra were recorded on Bruker DR X 300 spectrometer and Shimadzu UV-1601 spectrophotometer respectively. Microanalysis was done on a Carlo-Erba 1008 instrument. Chemicals used were of AR grade (Sigma, BDH & E. Merck).

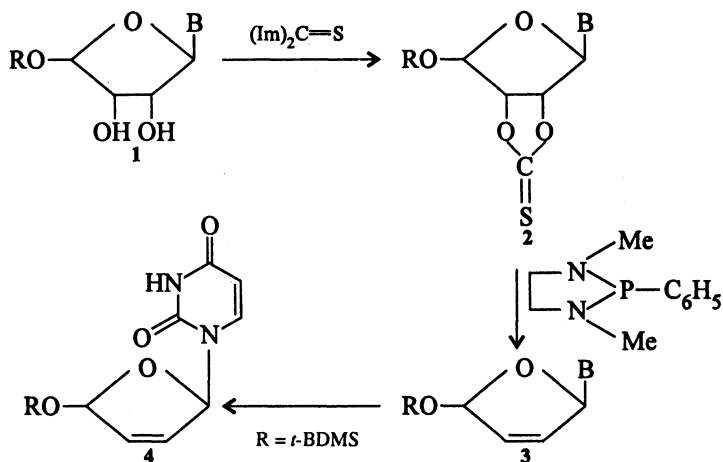
**5'-O-(*t*-Butyldimethylsilyl)-5-iodo-6-methyluridine (1):** 5-iodo-6-methyluridine (1.436 g, 3.74 mmol), imidazole (9 mmol) and DMF (30 mL) were treated with *t*-butyl dimethylsilyl chloride (5 mmol) to yield the product (1.39 g) on a silica-gel column using CHCl<sub>3</sub>-MeOH (35 : 1) in 73% yield as a colourless solid, m.p. 214–15°C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.02 (6H, s, Me<sub>2</sub>Si), 0.81 (9H, s, Me<sub>3</sub>C-Si), 1.68 (3H, s, 6-CH<sub>3</sub>), 3.62–3.93 (5H, m, 2', 3', 4' and 5'-H), 4.97 (1H, d, J = 4.39 Hz, 3'-OH), 5.25 (1H, d, J = 5.57 Hz, 2'-OH), 5.71 (1H, d, J = 5.57 Hz, 1'-H), 11.25 (1H, s, NH); Calcd. for C<sub>16</sub>H<sub>27</sub>N<sub>2</sub>O<sub>6</sub>ISi: C, 38.55; H, 5.47; N, 5.62; Found: C, 38.59; H, 5.48; N, 5.58.

**5'-O-(*t*-Butyldimethylsilyl)-5-iodo-6-methyl-2',3'-O-thionocarbonyluridine (2):** 5'-O-(*t*-Butyldimethylsilyl)-5-iodo-6-methyluridine (0.372 g, 1.0 mmol) was stirred with 1,1'-thiocarbonyldiimidazole in THF. The solvent was removed under vacuum and the residue was purified by flash chromatography using  $\text{CHCl}_3$  : MeOH (50 : 1) as the eluent to obtain 0.28 g (68%) yield of the product as a glassy material.  $^1\text{H NMR}$  ( $\text{DMSO-d}_6$ ) 0.08 (6H, s,  $\text{Me}_2\text{Si}$ ), 0.88 (9H, s,  $\text{Me}_3\text{CSi}$ ), 1.92 (3H, s, 6- $\text{CH}_3$ ), 3.84 (2H, d,  $J = 5.57$  Hz, 5'-H), 4.42 (1H, m, 4'-H), 5.52 (1H, m, 2'-H), 5.73 (2H, m, 1'- and 3'-H), 9.20 (1H, s, NH exchangeable); Calcd. for  $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_6\text{ISSi}$ : C, 37.78; H, 4.66; N, 5.18; S, 5.93; Found: C, 37.75; H, 4.68; N, 5.20; S, 5.90.

**5'-O-(*t*-Butyldimethylsilyl)-5-iodo-6-methyl-2',3'-didehydro-2',3'-dideoxyuridine (3):** A solution of compound 2 (0.08 g, 0.15 mmol) and 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (0.4 mL) in THF (2 mL) was stirred for 24 h. The solvent was removed under reduced pressure and the residue was purified by chromatography by using  $\text{CHCl}_3$ -MeOH (50 : 1) as the eluent to obtain 0.038 g (55%) yield as a colourless powder, m.p. 175–77°C; UV (MeOH)  $\lambda_{\text{max}}$  267 nm;  $^1\text{H NMR}$  ( $\text{DMSO-d}_6$ ) 0.08 (6H, s,  $\text{Me}_2\text{Si}$ ), 0.92 (9H, s,  $\text{Me}_3\text{CSi}$ ), 1.91 (3H, d,  $J = 1.17$  Hz, 6- $\text{CH}_3$ ), 3.83 (2H, d,  $J = 3.8$  Hz, 5'-H), 4.82 (1H, m, 4'-H), 5.82 (1H, br s,  $J = 6.2$  Hz, 2'-H), 6.24 (1H, br s,  $J = 6.2$  Hz, 3'-H), 6.96 (1H, m, 1'-H), 8.52 (1H, brs, NH, exchangeable); Calcd. for:  $\text{C}_{16}\text{H}_{25}\text{N}_2\text{O}_4\text{ISi}$ : C, 41.38; H, 5.42; N, 6.03; Found: C, 41.40; H, 5.39; N, 6.02.

**2',3'-Didehydro-2',3'-dideoxy-5-iodo-6-methyluridine (4):** Compound 3 (0.232 g, 0.5 mmol) was deprotected with 1 M solution of tetra-*n*-butylammonium fluoride (1 mL, 1 mmol). The solvent was evaporated and purified by chromatography using  $\text{CHCl}_3$ -MeOH (30 : 1) as the eluent to obtain 0.14 g (80%) yield as colourless solid, m.p. 169°C;  $^1\text{H NMR}$  ( $\text{DMSO-d}_6$ ) 1.92 (3H, d,  $J = 1.17$  Hz, 6- $\text{CH}_3$ ), 4.75 (1H, m, 4'-H), 4.96 (1H, t,  $J = 4.98$  Hz, 5'-OH exchangeable), 5.83 (1H, br s,  $J = 6.2$  Hz, 2'-H), 6.42 (1H, br s,  $J = 6.2$  Hz, 3'-H), 6.80 (1H, m, 1'-H), 11.28 (1H, s, NH exchangeable); Calcd. for:  $\text{C}_{10}\text{H}_{11}\text{N}_2\text{O}_4\text{IC}$ , 34.09; H, 3.13; N, 7.95; Found: C, 34.12; H, 3.14; N, 7.98.

Deoxygenation of ribonucleosides *via* cyclic thionocarbonates was explored and was applied to uridine<sup>4</sup>, but the yield was low.  $\text{N}^3$ -methylation was also observed in some cases. A similar deoxygenation of 2',3'-thionocarbonate of adenosine employing Raney nickel failed to afford 2',3'-didehydro-2',3'-dideoxyadenosine<sup>9</sup>. 2',3'-thionocarbonate of 5'-O-*t*-butyldimethylsilyl-5-iodo-6-methyluridine was prepared with thiocarbonyldiimidazole in 65% yield. Thionocarbonate (2) was deoxygenated to the product under mild conditions using 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine. Desilylation of compound (3) afforded 2',3'-didehydro-2',3'-dideoxy-5-iodo-6-methyluridine (4) in 80% yield. The unsaturated nucleoside (4) was characterized by elemental analysis and spectral data.



Scheme-1

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