SYNTHESIS OF 2',3'-DIDEOXY-3'-METHYLIDENETHYMIDINE AND 2',3'-DIDEHYDRO-2',3'-DIDEOXY-3'-METHYLTHYMIDINE : DEOXYGENATION OF THE ALLYLIC ALCOHOL SYSTEM IN 3'-DEOXY-3'-METHYLIDENE-5-METHYLURIDINE[1]

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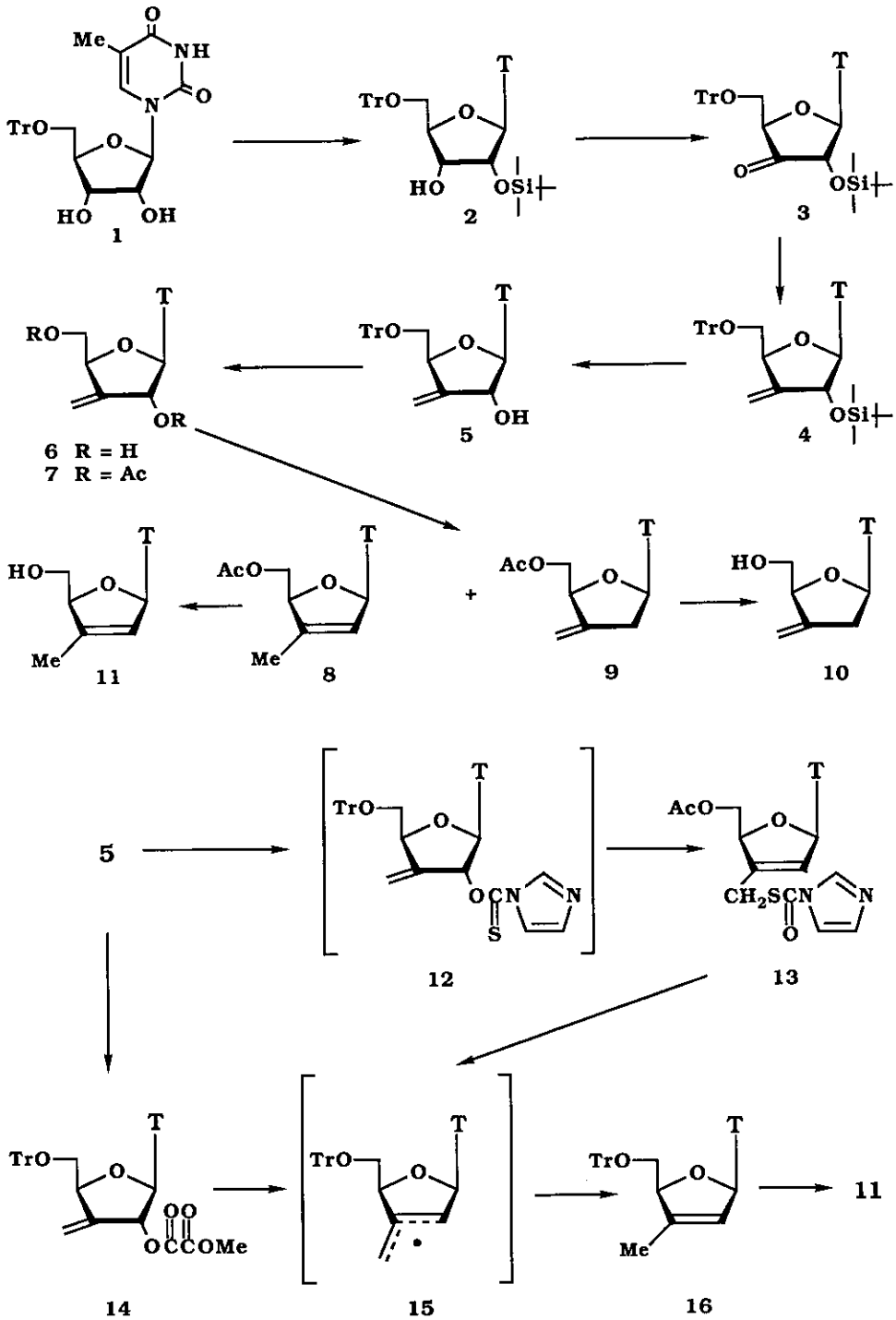
Abstract———Synthesis of 2',3'-dideoxy-3'-methylidenethymidine (**10**) was accomplished by palladium calalyzed deoxygenation of 3'-deoxy-3'-methylidene-5-methyluridine derivative (**7**). 2',3'-Didehydro-2',3'-dideoxy-3'-methylthymidine (**11**) was synthesized by radical deoxygenation of 3'-deoxy-3'-methylidene-5-methyluridine derivatives.

Nucleoside antibiotics such as angustmycin A[2] and neplanocin A[3], which bear an unsaturated sugar in their structures, exhibit interesting biological properties including antileukemic, antiparasitic and antibacterial activities. Recently, we have reported that 2'-deoxy-2'-methylidenecytidine (DMDC) showed potent antineoplastic activity against not only several human leukemic cell lines but also adenocarcinoma and carcinoma cell lines.[4] Furthermore, 2',3'-didehydro-2',3'-dideoxythymidine (DHT) has been reported by us[5a] and others[5b,c] to be a potent inhibitor of the growth of human immunodeficiency virus (HIV) *in vitro*. A common structural feature of these nucleosides can be found in a double bond functionality in the sugar moiety, which may play an important role for exhibiting such biological activities. Now we design new types of unsaturated-deoxysugar nucleosides such as compounds **10** and **11** for potential anti-HIV agents.

Our strategy for the synthesis of the target nucleosides is to utilize the allylic alcohol system in 3'-deoxy-3'-methylidene-5-methyluridine derivatives. Deoxygenation of their 2'-hydroxy groups would lead to the target nucleoside **10** or **11**. Allylic acetates are known to be converted into olefins by using organopalladium chemistry. Regioselectivity in the attack of hydride on (π-allyl)palladium intermediate is also elucidated to some extent.[6] Application of this methodology to the nucleoside chemistry is of great interest.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Compound **1** was silylated to give **2**.[7] Oxidation of **2** by CrO_3-pyridine-acetic anhydride system[8] in CH_2Cl_2 gave the 3'-ketone **3** in 93% yield, which was then subjected to the Wittig methylenation ($Ph_3P^+CH_3\ Br^-$ and BuLi, room temperature for 3 h) to afford the methylidene-nucleoside **4** in 99% yield. The desilylation of **4** by tetrabutylammonium fluoride (TBAF) in THF to give **5** (room temperature for 30 min, 99% yield) and detritylation with formic acid (97%, room temperature for 5 min) followed by acetylation furnished 2',3'-di-*O*-acetyl-3'-deoxy-3'-methylidene-5-methyluridine (**7**, Ac_2O and 4-dimethylaminopyridine in acetonitrile, room temperature for 1 h, 89% yield from **5**). Reduction of **7** with $LiBH_4$ as a hydride donor in the presence of Ph_3P and a catalytic amount of $(PhCN)_2PdCl_2$ in THF at room temperature gave **8** and **9** in 50% yield in a ratio of 3:1. However, the use of triethylammonium formate as a hydride source in acetonitrile at reflux temperature afforded **8** and **9** (12 : 88) in 44% yield. A regioselective reduction was observed when **7** was treated with a combination of triethylammonium formate (2 mol eq.), Bu_3P (0.2 mol eq.), and $Pd(OAc)_2$[6b] in acetonitrile for 15 min at 80°C to afford **8** and **9** in a ratio of 1 : 9 (76% yield). Compounds **9** and **8** were separated from each other by silica gel column chromatography (8% EtOH in $CHCl_3$) and deblocked to furnish the target nucleosides 2',3'-dideoxy-3'-methylidenethymidine (**10**, 95% yield)[9] and 2',3'-didehydro-2',3'-dideoxy-3'-methylthymidine (**11**, 98% yield)[10], respectively.

For the specific synthesis of **11**, we carried out a radical deoxygenation of **5**. Treatment of **5** with 1,1'-thiocarbonyldiimidazole (1.5 mol eq.) in DMF for 24 h at room temperature resulted in the formation of the 2',3'-didehydro-2',3'-dideoxy-3'-imidazolylcarbonylthiomethyl derivative (**13**, 84% yield) as a result of the allylic rearrangement of the intermediate **12**. The desulfurization of **13** with Bu_3SnH and 2,2'-azobis(isobutyronitrile) (AIBN) in hot toluene gave 3'-methyl derivative of DHT (**16**, 83%) exclusively. Detritylation of **16** with HCO_2H (97%) for 2 min at room temperature gave **11** (54% yield). Deoxygenation of 2'-*O*-methyloxalyl ester (**14**) with Bu_3SnH and AIBN in hot toluene[11] also gave **16** (91% yield) exclusively. Thus, it is clear that the allyl radical intermediate (**15**) gives preferentially the endo-olefin compound **16**.

Inhibition of the cytopathogenicity of HIV by **10** and **11** was tested by using HTLV-1-carrying MT-4 cells.[5a, 12] None of them showed any inhibitory activity up to 500 μg/ml concentrations.

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7. Compound **1** was prepared by the method of J. F. Codington, R. Fecher, and J. J. Fox (*J. Org. Chem.*, 1962, **27**, 163). Compound **1** was treated with *tert*-butyldimethylsilyl chloride (1.1 mol eq.) and imidazole (1.1 mol eq.) in *N,N*-dimethylformamide (DMF) for 19 h at room temperature. The products were separated by silica gel column chromatography to give **2** in 45% yield as a foam and the 3'-silylated compound in 33% yield.
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9. Compound **10** was obtained as a homogeneous foam. Nmr (D_2O, δ, ppm, 270 MHz): 1.87 (3H, d, $J_{5\text{-Me},6}$ = 1.1 Hz, 5-Me), 2.84 (1H, m, H-2'), 3.21 (1H, br dd, $J_{2'',1'}$ = 7.1, $J_{2',2''}$ = 17.0 Hz, H-2''), 3.79 (1H, dd, $J_{5',4'}$ = 4.0, $J_{5',5''}$ = 12.5 Hz, H-5'), 3.90 (1H, dd, $J_{5'',4'}$ = 2.9, $J_{5',5''}$ = 12.5 Hz, H-5''), 4.65 (1H, br s, H-4'), 5.14 (1H, d, J = 2.2 Hz, H-3''a), 5.30 (1H, d, J = 2.2 Hz, H-3''b), 6.25 (1H, dd, $J_{1',2'}$ = 5.3, $J_{1',2''}$ = 7.1 Hz, H-1'), 7.64 (1H, d, $J_{6,5\text{-Me}}$ = 1.1 Hz, H-6). Ms *m/z*: 238 (M^+).
10. Mp 208-210°C (EtOAc). Nmr ($CDCl_3$, δ, ppm, 270 MHz): 1.86 (3H, d, $J_{5\text{-Me},6}$ = 1.1 Hz, 5-Me), 1.94 (3H, d, $J_{3'\text{-Me},2'}$ = 1.1 Hz, 3'-Me), 2.50 (1H, br s, 5'-OH), 3.82 (1H, br d, $J_{5',5''}$ = 12.5 Hz, H-5'), 3.96 (1H, br d, $J_{5',5''}$ = 12.5 Hz, H-5''), 4.67 (1H, br s, H-4'), 5.45 (1H, d, $J_{1',2'}$ = $J_{2',3'\text{-Me}}$ = 1.1 Hz, H-2'), 6.95 (1H, d, $J_{1',2'}$ = $J_{1',4'}$ = 1.1 Hz, H-1'), 7.52 (1H, d, $J_{6,5\text{-Me}}$ = 1.1 Hz, H-6), 8.28 (1H, br s, NH). Ms *m/z*: 238 (M^+).
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12. The antiviral test was performed by Drs. N. Yamamoto and H. Nakashima of Yamaguchi University, to whom our thanks are due.

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