SYNTHESIS AND ANTI-HIV ACTIVITY OF 3'-CYANO-2',3'-DIDEOXYTHYMIDINE AND 3'-CYANO-2',3'-DIDEHYDRO-2',3'-DIDEOXYTHYMIDINE[1]

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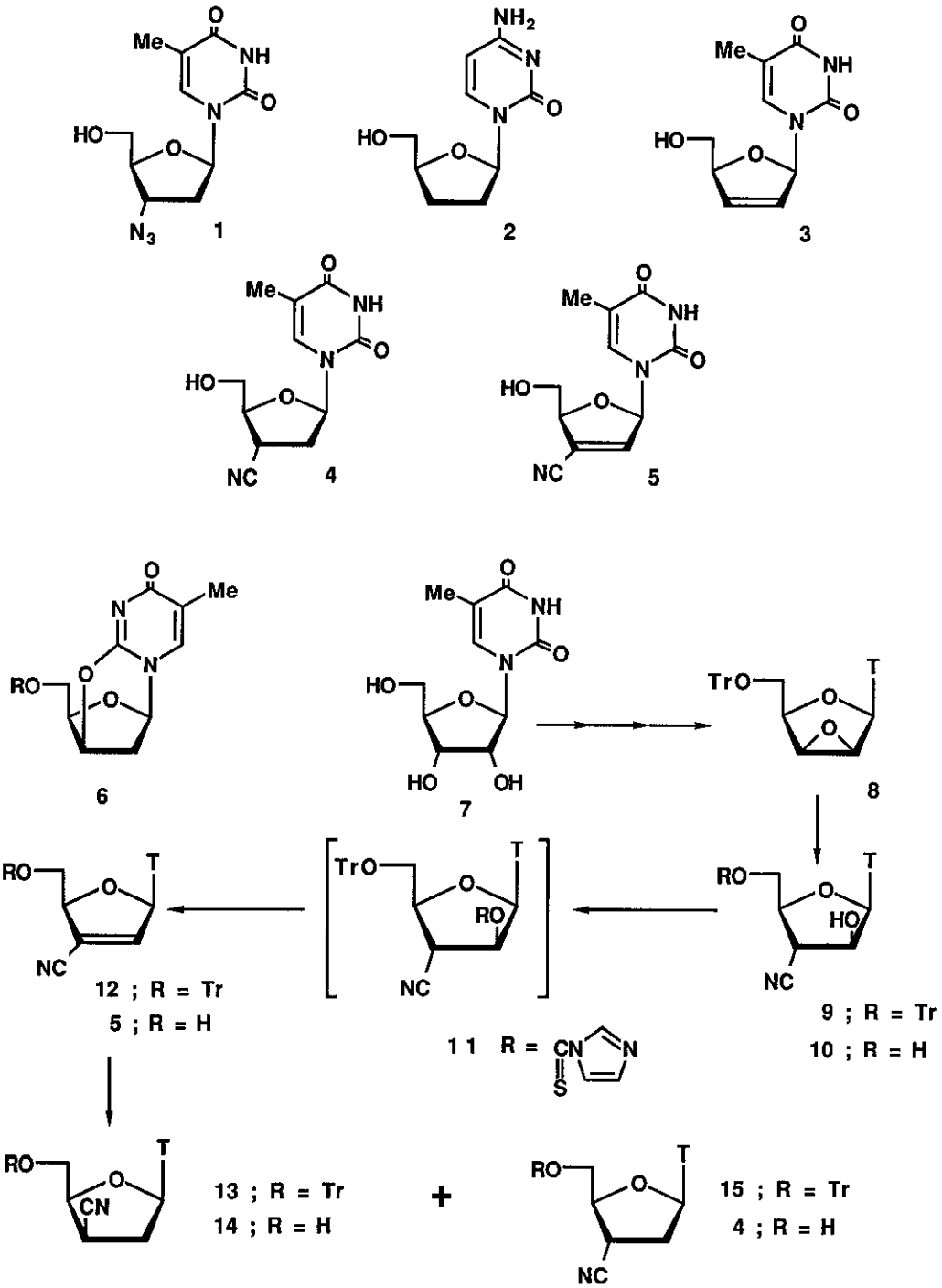
Abstract——————3'-Cyano-2',3'-dideoxy- and 3'-cyano-2',3'-didehydro-2',3'-dideoxy-thymidines (**4**, **5**) have been synthesized from 5-methyluridine (**7**). Anti-HIV activity of these compounds is also described.

Human immunodeficiency virus (HIV) infection is essential for the pathogenesis of the acquired immunodeficiency syndrome (AIDS). One of the most promising chemotherapeutic target enzymes for the retrovirus replication is the HIV reverse transcriptase, and nucleoside analogues have been recognized as candidates for anti-HIV agents. Among the 2',3'-dideoxynucleosides, 3'-azido-2',3'-dideoxythymidine (**1**, AZT) has an inhibitory effect on the replication of human T-cell lymphotropic virus type III and is currently under clinical use.[2] 2',3'-Dideoxycytidine (**2**)[3] and 2',3'-didehydro-2',3'-dideoxythymidine (**3**, DHT)[4] have also been reported to exhibit promising antiretroviral activity. Moreover, 3'-cyano-2',3'-dideoxythymidine (**4**, CNT) was recently reported to be more effective than AZT.[5] The synthetic method for CNT, however, has not been reported yet.[6] We report the synthesis and anti-HIV activity of CNT (**4**) including the DHT analogue, 3'-cyano-2',3'-didehydro-2',3'-dideoxy-thymidine (**5**) in this communication.

Initial attempts to introduce a cyano group into the 3'-position of thymidine by cleavage of the 2,3'-anhydro linkage in **6** were unsuccessful. Then, we turned our attention to cleave the lyxo-epoxy ring in **8** by cyanide ion. The starting material, 1-(5'-*O*-trityl-2',3'-epoxy-β-D-lyxosyl)-5-methyluracil (**8**), was readily prepared in three steps from 5-methyluridine (**7**) in 46% overall yield.[7] Treatment of **8** with lithium cyanide (2.2 equiv) in tetrahydrofuran (THF) under reflux conditions gave the desired 3'-cyano derivative (**9**) in 60% isolated yield. However, the reaction of **8** with lithium cyanide in *N*,*N*-dimethylformamide (DMF), sodium cyanide in DMF, or potassium cyanide with 18-crown-6 in THF or DMF gave an intractable mixture and compound **9** was obtained only in poor yield. This nucleoside **9** was then detritylated by 98% formic acid

(room temperature for 5 min then lyophilized) to afford a crystalline 3'-cyano-3'-deoxy-β-D-arabinofuranosylthymine (**10**, 74%, mp 238-240°C).[8]



Deoxygenation of the 2'-hydroxy group in **9** was next examined. Treatment of **9** with *N,N*-thiocarbonyldiimidazole in DMF for 2 days at room temperature afforded a nucleoside product; the structure was assigned as 3'-cyano-2',3'-didehydro-2',3'-dideoxy derivative (**12**) but not the intermediate, thiocarbonylimidazole ester (**11**). Therefore, the reaction proceeded by syn-elimination from **11** under these conditions. The deprotection of **12** by formic acid furnished one of the target nucleoside **5** (99%, mp 201-202°C).[9]

Reduction of the 2',3'-acrylonitrile system in **12** was next examined with the conventional method such as hydrogenolysis with Pd/C under hydrogen atmosphere or using sodium borohydride. In both cases, however, a major product obtained did not contain the cyano group as confirmed by the ir spectrum measurement. After several attempts to obtain **13** or **15**, we found that the hydrosilylation of **12** with Rh catalyst gave satisfactory results. When **12** was heated with triethylsilane and a catalytic amount of tris(triphenylphosphine)rhodium(I) chloride in acetonitrile at 50°C in a sealed tube, (3'R)- and (3'S)-cyano-3'-deoxy derivatives (**13**, **15**) were obtained after separation by silica gel column chromatography in 63% and 25% yields, respectively. Each nucleosides (**13**, **15**) were deblocked by formic acid to afford **14**[10] as a crystalline solid in 71% yield (mp 206-207°C, ref[6] mp 201-202°C) and one of the target nucleosides **4** as a homogeneous foam[11] in 87% yield, respectively. The configurations at the 3'-position of **4** and **14** were determined by NOE mesurements. When the 6-H's in thymine moiety of **4** and **14** were irradiated, the NOE at the 3'-H was observed in **4** (4.4%) while compound **14** showed no NOE. Compound **13** can be isomerized with sodium methoxide in methanol to reach equilibrium between **13** : **15** in a ratio of about 2 : 3.

Inhibition of the cytopathogenicity of HIV by the compounds (**4**, **5**, and **10**) described in this communication was tested by using HTLV-I-carrying MT-4 cells.[4a] However, none of them showed any inhibitory activity up to 500 μg/ml concentration. These results are in conflict with the previous report[5] that CNT (**4**) is more active than AZT.

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8. Nmr (DMSO-d_6, δ, ppm) : 1.76 (3H, d, $J_{Me,6}$ = 1.0 Hz, 5-Me), 3.54-3.75 (3H, m, H-3',5',5''), 4.80 (1H, m, H-2'), 5.37 (1H, t, J = 5.6 Hz, 5'-OH), 6.09 (1H, d, $J_{1',2'}$ = 6.4 Hz, H-1'), 6.33 (1H, d, J = 5.9 Hz, 2'-OH) 7.54 (1H, d, $J_{Me,6}$ = 1.0 Hz, H-6), 8.46 (1H, brs, NH). Ir (KBr, ν, cm^{-1}): 2350 (CN). Ms m/z: 267 (M^+).

9. Nmr (DMSO-d_6, δ, ppm): 1.89 (3H, d, $J_{Me,6}$ = 1.5 Hz, 5-Me), 2.39 (1H, t, J = 4.8 Hz, 5'-OH), 4.06 (2H, dd, $J_{5',OH}$ = 4.8, $J_{4',5'}$ = 1.8 Hz, H-5',5''), 5.02 (1H, ddd, $J_{1',4'}$ = 4.4, $J_{2',4'}$ = $J_{4',5'}$ = 1.8 Hz, H-4'), 6.66 (1H, dd, $J_{1',2'}$ = 1.8 Hz, H-2'), 7.14 (1H, dd, $J_{1',2'}$ = 1.8, $J_{1',4'}$ = 4.4 Hz, H-1'), 7.52 (1H, d, $J_{Me,6}$ = 1.5 Hz, H-6), 8.48 (1H, brs, NH). Ir (KBr, ν, cm^{-1}): 2230 (CN). Ms m/z : 249 (M^+).

10. Nmr (DMSO-d_6, δ, ppm): 1.79 (3H, d, $J_{Me,6}$ = 1.0 Hz, 5-Me), 2.29 (1H, m, $J_{1',2'a}$ = $J_{2'a,3'}$ = 6.6 , $J_{2'a,2'b}$ = 13.2 Hz, H-2'a), 2.64 (1H, m, $J_{1',2'b}$ = 6.6, $J_{2'b,3'}$ = 7.7 Hz, H-2'b), 3.37 (3H, m, H-3',5',5''), 4.16 (1H, dt, $J_{3',4'}$ = 7.1, $J_{4',5'}$ = 4.4 Hz, H-4'), 5.30 (1H, t, J = 4.9 Hz, 5'-OH), 6.08 (1H, t, $J_{1',2'a}$ = $J_{1',2'b}$ = 6.6 Hz, H-1'), 7.66 (1H, d, $J_{Me,6}$ = 1.0 Hz, H-6), 11.37 (1H, brs, NH). The NOE was observed upon irradiation of H-6: 5-Me (6.7%), H-2'a (2.7%), H-3' (4.4%), H-1' (7.1%). Ir (KBr, ν, cm^{-1}): 2340 (CN). Ms m/z : 251 (M^+).

11. Nmr (D_2O, δ, ppm): 1.87 (3H, d, $J_{Me,6}$ = 1.6 Hz, 5-Me), 2.64 (1H, ddd, $J_{1',2'a}$ = 4.0, $J_{2'a,3'}$ = 9.2, $J_{2'a,2'b}$ = 13.9 Hz, H-2'a), 2.85 (1H, ddd, $J_{1',2'b}$ = 7.7, $J_{2'b,3'}$ = 9.2 Hz, H-2'b), 3.52 (1H, q, $J_{3',4'}$ = 9.2 Hz, H-3'), 3.84 (1H, dd, $J_{4',5'}$ = 4.0, $J_{5',5''}$ = 12.8 Hz, H-5'), 3.96 (1H, dd, $J_{4',5''}$ = 2.9 Hz, H-5''), 4.37 (1H, m, H-4'), 6.20 (1H, dd, $J_{1',2'a}$ = 4.0, $J_{1',2'b}$ = 7.7 Hz, H-1'), 7.59 (1H, d, $J_{Me,6}$ = 1.6 Hz, H-6). The NOE was observed upon irradiation of H-6: H-2'a (8%), 5-Me (8%). Ir (KBr, ν, cm^{-1}): 2210 (CN). Ms m/z : 251 (M^+).

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