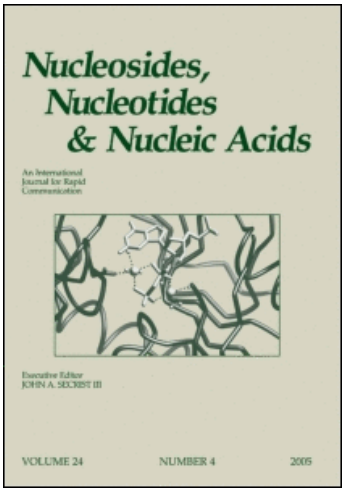

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Moon Woo Chun[ab]; Myong Jung Kim[a]; Hea Ok Kim[c]; Hyung Ryong Moon[d]; Hee-Doo Kim[e]; Joong Hyup Kim[f]; Lak Shin Jeong[d]
[a] College of Pharmacy, Seoul National University, Seoul, Korea [b] Seoul National University, Seoul, Korea [c] Division of Chemistry and Molecular Engineering, Seoul National University, Seoul, Korea [d] College of Pharmacy, Ewha Womans University, Seoul, Korea [e] College of Pharmacy, Sookmyung Women's University, Seoul, Korea [f] Korea Institute of Science and Technology, Seoul, Korea

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Synthesis and Biological Evaluation of Pyrimidine Nucleosides Fused with 3′,4′-Tetrahydrofuran Ring

Moon Woo Chun,[1,*] Myong Jung Kim,[1] Hea Ok Kim,[2] Hyung Ryong Moon,[5] Hee-Doo Kim,[3] Joong Hyup Kim,[4] and Lak Shin Jeong[5]

[1]College of Pharmacy and
[2]Division of Chemistry and Molecular Engineering,
Seoul National University, Seoul, Korea
[3]College of Pharmacy, Sookmyung Women's University, Seoul, Korea
[4]Korea Institute of Science and Technology, Seoul, Korea
[5]College of Pharmacy, Ewha Womans University, Seoul, Korea

ABSTRACT

Pyrimidine nucleosides fused with 3′,4′-tetrahydrofuran ring were synthesized, starting from 1,2;5,6-di-*O*-isopropylidene-D-glucose and assayed for antiviral activities. Thymine analogue **1** and its corresponding 2′-deoxy analogue **3** exhibited high cytotoxicity instead of giving antiviral activities.

A number of 2′,3′-dideoxy nucleosides have been discovered to possess significant antiviral activity against HIV-1 and other viruses. Since it has been suggested that proper conformation of the dideoxynucleosides is required for them to exhibit antiviral activity,[1] bicyclic nucleoside analogues like the fused oxetanyl or cyclopropanyl derivatives of thymidine[2,3] have been synthesized and reported

*Correspondence: Moon Woo Chun, Seoul National University, 56-1 Shinrim-dong San, Kwanak-gu, 151-742 Seoul, Korea; Fax: +82 2 888 0649; E-mail: mwchun@snu.ac.kr.

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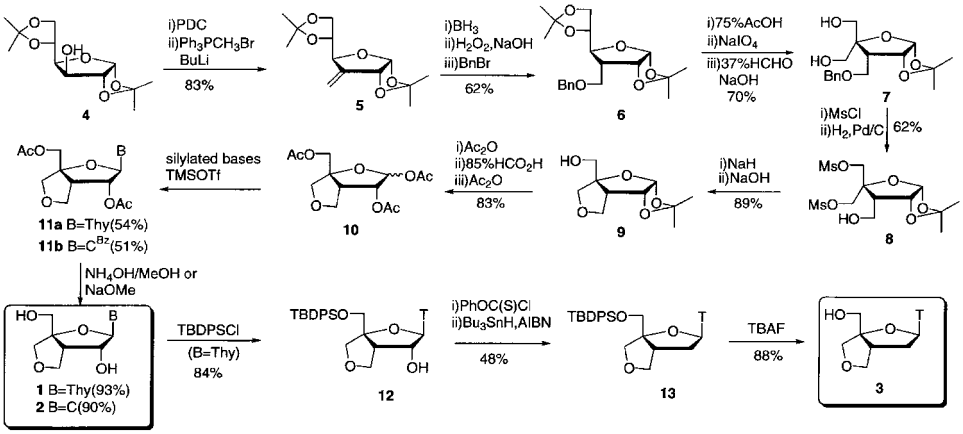

Scheme 1.

to inhibit HIV replication. However, 3′,4′-cyclopentane fused pyrimidine nucleosides did not show antiviral activity.[4] Based on these findings, we report the synthesis of pyrimidine nucleosides fused with 3′,4′-tetrahydrofuran ring starting from 1,2;5,6-di-*O*-isopropylidene-D-glucose as potential antiviral agents to obtain further information regarding the correlation between sugar ring conformation and antiviral activity.

1,2;5,6-Di-*O*-isopropylidene-D-glucose (**4**) was oxidized with PDC and Wittig reaction of the resulting ketone gave the olefin **5**. Hydroboration-oxidation of **5** followed by benzylation of the resulting hydroxyl group yielded the benzyl ether **6**. Selective removal of 5,6-*O*-isopropylidene of **6** using 75% acetic acid followed by oxidative cleavage of the diol with $NaIO_4$ afforded the aldehyde. Aldol reaction of the aldehyde using 37% aqueous formaldehyde and NaOH and then in situ Cannizzarro reaction produced diol **7** in good yield.

Mesylation of **7** followed by catalytic hydrogenolysis afforded **8**, which underwent intramolecular cyclization in the presence of NaH and hydrolysis of the sulfonate using aqueous NaOH to give **9**. Treatment of **9** with acetic anhydride gave the acetate which was hydrolyzed with 85% aqueous formic acid and then successively acetylated to give glycosyl donor **10**. Condensation of **10** with silylated thymine and N^4-benzoylcytosine gave the protected nucleosides **11a** and **11b**, respectively. Deacylation of **11a** and **11b** gave the desired nucleosides **1** and **2**, respectively. Regioselective protection of primary hydroxyl group of **1** as a TBDPS ether followed by treatment with phenyl chlorothionoformate and then tributyltin hydride in the presence of AIBN furnished 2′-deoxy derivative **13**. Deblocking of 5′-silyl group of **13** afforded the final 2′-deoxy analogue **3**.

The final nucleosides **1**, **2** and **3** were assayed for antiviral activities against HIV-1, VSV and HCMV, among which thymine analogue **1** and its corresponding 2′-deoxy analogue **3** exhibited high cytotoxicity without antiviral activities.

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