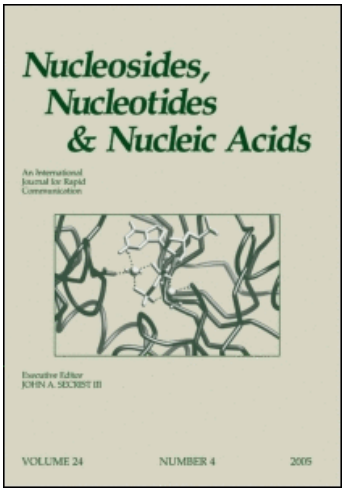


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis and Antiviral Activity of L-2'-Deoxy-2'-up-fluoro-4'-thionucleosides

Lak Shin Jeong[a]; Hyung Ryong Moon[a]; Su Jeong Yoo[a]; Sun Nan Lee[a]; Hee-Doo Kim[b]; Moon Woo Chun[c]
[a] College of Pharmacy, Ewha Womans University, Seoul, Korea [b] College of Pharmacy, Sookmyung Women's University, Seoul, Korea [c] College of Pharmacy, Seoul National University, Seoul, Korea

To cite this Article Jeong, Lak Shin , Moon, Hyung Ryong , Yoo, Su Jeong , Lee, Sun Nan , Kim, Hee-Doo and Chun, Moon Woo(1999) 'Synthesis and Antiviral Activity of L-2'-Deoxy-2'-up-fluoro-4'-thionucleosides', Nucleosides, Nucleotides and Nucleic Acids, 18: 4, 571 — 572
To link to this Article: DOI: 10.1080/15257779908041497
URL: http://dx.doi.org/10.1080/15257779908041497

NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 571–572 (1999)

SYNTHESIS AND ANTIVIRAL ACTIVITY OF L-2'-DEOXY-2'-UP-FLUORO-4'-THIONUCLEOSIDES

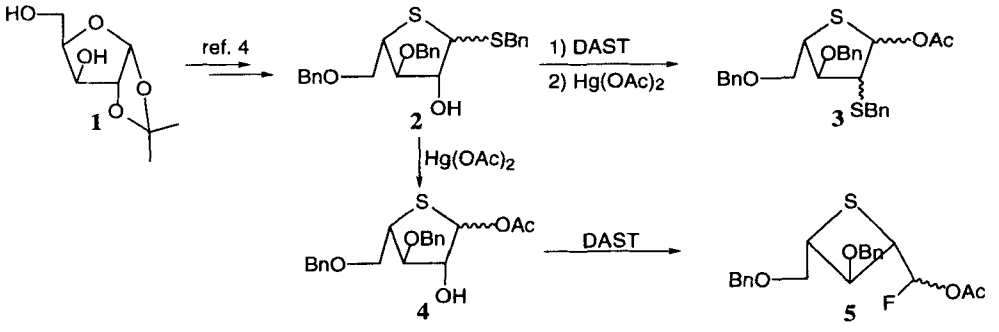
Lak Shin Jeong,[1]* Hyung Ryong Moon,[1] Su Jeong Yoo,[1] Sun Nan Lee,[1] Hee-Doo Kim[2] and Moon Woo Chun[3]

[1]College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea, [2]College of Pharmacy, Sookmyung Women's University, Seoul 140-742, Korea and [3]College of Pharmacy, Seoul National University, Seoul 151-742, Korea

Abstract: L-2'-Deoxy-2'-up-fluoro-4'-thionucleosides were efficiently synthesized from D-xylose via L-4-thioarabitol derivative as a key intermediate and evaluated for antiviral activities against HIV-1, HSV-1,2 and HBV.

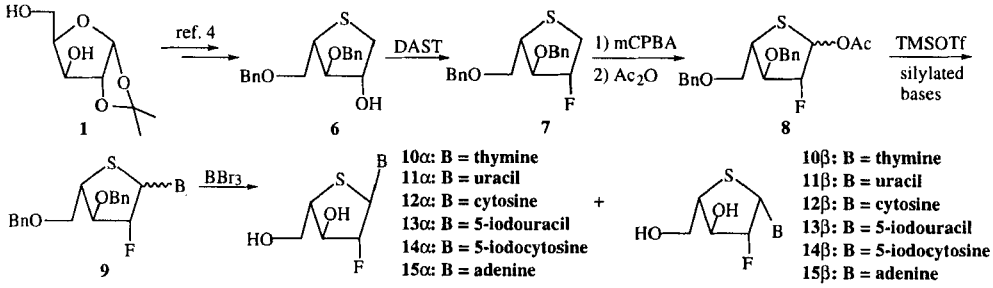
Since the discovery of (-)-L-β-1,3-oxathiolanyl cytosine (3TC, Lamivudine)[1] as potent antiviral agent, a number of L-nucleosides have been synthesized and evaluated for antiviral activity. Among these compounds, 2'-deoxy-2'-fluoro-5-methyl-β-L-arabino-furanosyluracil (L-FMAU) has been reported to exhibit potent anti-hepatitis B virus (HBV) and anti-Epstein-Barr virus (EBV) activities with a favorable toxicity profile.[2] In an effort to discover analogues to L-FMAU based on a "bioisosteric replacement rationale", we synthesized the 4'-thio congener (L-SFMAU) of L-FMAU and compared its antiviral activity with the parent L-FMAU.[3] We also carried out structure-activity relationship study of L-2'-deoxy-2'-up-fluoro-4'-thionucleosides in order to search for new antiviral agents.

Scheme 1



The key intermediate **2** was synthesized from 1,2-isopropylidene-D-xylose (**1**) by the efficient procedure developed by our laboratory.[4] Reaction of **2** with DAST followed by treatment with $Hg(OAc)_2$ did not give the 2-fluoro-4-thiosugar, but yielded a rearranged product **3** by the participation of the anomeric thiobenzyl group. In order to prevent participation from the anomeric center, the thiobenzyl group was converted to an acetate to give **4**. However, treatment of **4** with DAST did not give the rearranged product, but gave the ring-contracted product **5** (Scheme 1).

Scheme 2



To prevent the rearrangement or ring contraction, the substituent at the anomeric center was removed as shown in Scheme 2. Treatment of **6** with DAST gave the 2-fluoro-4-thiosugar **7** with retention of configuration. Compound **7** was converted to the acetate **8** by treating with mCPBA followed by refluxing with acetic anhydride. Condensation of **8** with silylated pyrimidine and purine bases gave the protected nucleosides **9** which were treated with boron tribromide to yield the final nucleosides **10**α–15α and **10**β–15β, respectively. The final nucleosides were assayed against HIV-1, HSV-1, HSV-2, and HBV. The thymine analogue **10**β only exhibited moderate activity against both HSV-1 and HSV-2 and all synthesized compounds were found to be inactive against HIV-1.

Acknowledgment

This research was supported by the grant from the STEPI (97-N6-01-01-A-18).

References

1. Beach, J. W.; Jeong, L. S.; Alves, A. J.; Pohl, D.; Kim, H. O.; Chang, C.-N.; Doong, S.-L.; Schinazi, R. F.; Cheng, Y.-C.; Chu, C. K. *J. Org. Chem.* **1992**, *57*, 2217 and references cited therein.
2. Ma, T.; Pai, S. B.; Zhu, Y. L.; Lin, J. S.; Shanmuganathan, K.; Du, J. F.; Wang, C. W.; Kim, H.; Newton, M. G.; Cheng, Y.-C.; Chu, C. K. *J. Med. Chem.* **1996**, *39*, 2835.
3. Jeong, L. S.; Moon, H. R.; Yoo, S. J.; Lee, S. N.; Chun, M. W.; Lim, Y.-H. *Tetrahedron Lett.* **1998**, *39*, 5201.
4. Jeong, L. S.; Moon, H. R.; Choi, Y. J.; Chun, M. W.; Kim, H. O. *J. Org. Chem.* **1998**, *63*, 4821.