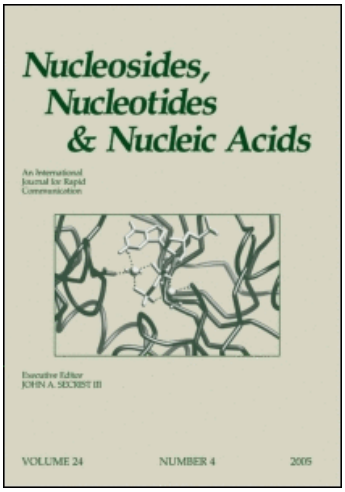


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

DESIGN AND SYNTHESIS OF NOVEL FLUOROCYCLOPROPANOID NUCLEOSIDES

Young Rang Lee[a]; Ju-Hyun Park[a]; Raok Jeon[a]; Lak Shin Jeong[b]; Moon Woo Chun[c]; Hee-Doo Kim[c]
[a] College of Pharmacy, Sookmyung Women's University, Seoul, Korea [b] College of Pharmacy, Ewha Womans University, Seoul, Korea [c] College of Pharmacy, Seoul National University, Seoul, Korea

Online publication date: 31 March 2001

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 20(4–7), 677–679 (2001)

DESIGN AND SYNTHESIS OF NOVEL FLUOROCYCLOPROPANOID NUCLEOSIDES

Young Rang Lee,[1] Ju-Hyun Park,[1] Raok Jeon,[1] Lak Shin Jeong,[2] Moon Woo Chun,[3] and Hee-Doo Kim[3]

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

ABSTRACT

Novel fluorocyclopropanoid nucleosides were designed, synthesized and evaluated their antiviral activities against poliovirus, HSV, HIV, and HBV.

Despite the intensive synthetic efforts, cyclopropanoid nucleosides have not been of interest until A-5021 was discovered recently (1). A-5021, (1′S,2′R)-9-[[1′,2′-bis(hydroxymethyl)cycloprop-1′-yl]methyl]guanine, was reported more active than acyclovir or penciclovir against HSV, HCMV and VZV (2). In an effort to search for the chemically and enzymatically stable carbonucleoside, we designed (*E*)-(1′-fluoro-2′-hydroxymethylcyclopropylmethyl)purines and pyrimidines. The underlying concept for our design is to seek relatively conformationally-locked compound with minimal structural disturbance from acyclic carbonucleoside such as acyclovir or penciclovir.

To meet such a requirement, we need to introduce cyclopropane and fluorine moiety. Due to its hybrid character of cyclic and acyclic molecules, cyclopropyl group could render the conformational rigidity to the target molecule. It is also envisioned that fluorine could play a role to control the conformation by *gauche* effect between fluorine and nitrogen in nucleoside base moiety (3). As shown in Scheme 1, N-alkylation of purine or pyrimidine bases with the mesylate **7** or the iodide **8** under basic condition (NaH, DMF, 80°C) was chosen as a simple and convenient approach to the synthesis of the fluorocyclopropanoid nucleoside **9**. The key

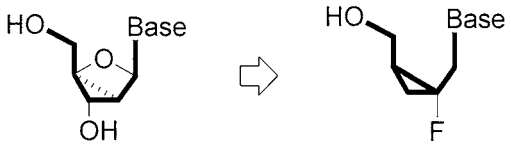
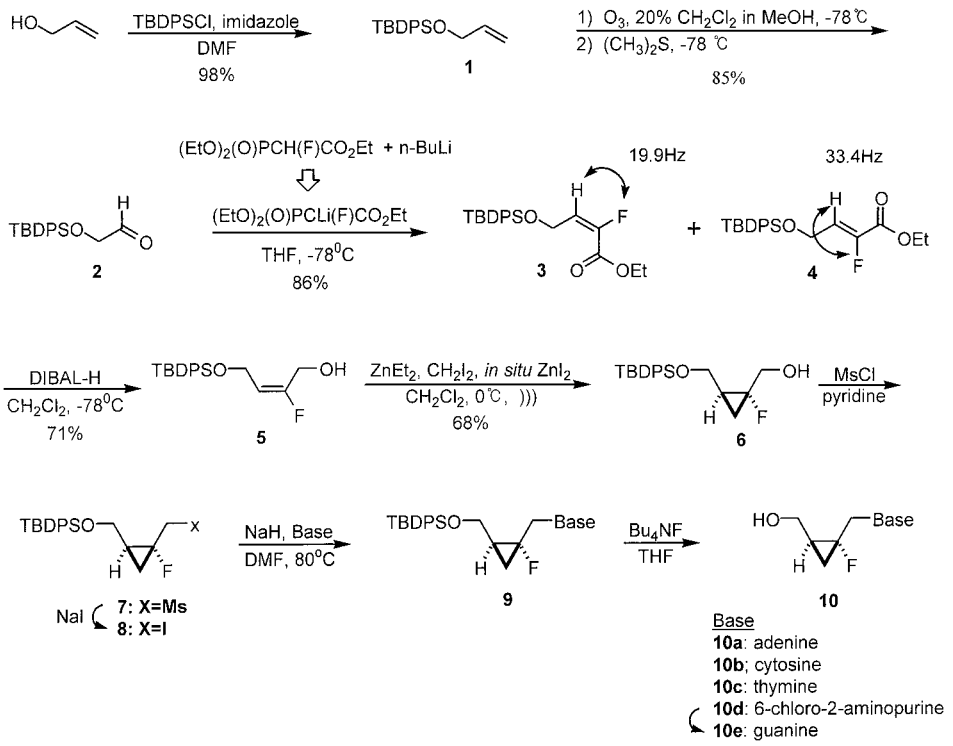


Figure 1.

synthetic intermediate **7** or **8** were synthesized starting from allyl alcohol. Protection of allyl alcohol with TBDPSCl, followed by ozonolysis afforded the aldehyde **2** in good yield. Introduction of fluorine and double bond for the installation of cyclopropyl group was achieved by Horner-Wadsworth-Emmons reaction of the aldehyde **3** with triethyl 2-fluoro-2-phosphonoacetate using n-BuLi in THF. The α-fluoro-α, β-unsaturated ester **3** with (E)-stereochemistry was formed preferentially over **4** in a ratio of 95 to 5. Unusual preference of (E)-isomer is well-known phenomenon in Horner-Wadsworth-Emmons reaction of aldehydes with triethyl 2-fluoro-2-phosphonoacetate (4). The similar stereoselectivity was also observed when using Pr′MgBr in THF at 0°C. The relatively unstable ester **3** was directly subjected to DIBAL-H reduction in CH_2Cl_2 at −78°C to room temperature to furnish the allylic alcohol **5** in 71% yield. Conventional cyclopropanation of the allylic



Scheme 1.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

alcohol **5** using Simmons-Smith or Furukawa modification method proceeded too slowly, and provided the desired product **6** in low yield. However, encouraged with the previous reports on Lewis acid-catalyzed cyclopropanation (5), we had tried several kinds of Lewis-acid, then, finally selected ZnI_2. The tendency of alkylzinc alkoxides (ROZnEt) to aggregate in solution (6) could be circumvented by sonification. By the dual action of sonification and ZnI_2, chemical yield and the reaction rate were greatly improved.

Unseparable mixture of **5** and **6** by conventional chromatography could be isolated using radial chromatography. The fluorinated cyclopropyl alcohol **6** was, then, converted to the corresponding mesylate **7** or iodide **8**. The coupling **7** or **8** with purine or pyrimidine bases under basic conditions, followed by removal of TBDPS group to afford the desired nucleosides **10a**(81% from **8**), **10b**(46% from **7**), **10c**(40% from **8**), and **10d**(40% from **8**), respectively. Treatment of **10d** with 2-mercaptoethanol and sodium methoxide in methanol, followed by hydrolysis with glacial acetic acid gave **10e** in 14% yield. The synthesized nucleosides (**10a**∼**e**) were evaluated for their antiviral activity against poliovirus, HSV-1, HSV-2, HBV and HIV. However, all compounds were found to be inactive in the assay.

ACKNOWLEDGMENT

This research was supported by the grant from the Good Health R & D project (HMP-98-D-4-0057), Ministry of Health and Welfare, Korea.

REFERENCES

1. Rife, J.; Ortuno, R. M. *Org. Lett*., **1999**, 1, 1221–1223.
2. Sekiyama, T.; Hatsuya, S.; Tanaka, Y.; Uchiyama, M.; Ono, N.; Iwayama, S.; Oikawa, M.; Suzuki, K.; Okunishi, M.; Tsuji, T. *J. Med. Chem*., **1998**, 41, 1284–1298.
3. Pankiewicz, K. W. *Carbohydr. Res*., **2000**, 327, 87–105.
4. Sano, S.; Ando, T.; Yokoyama, K.; Nagao, Y. *Synlett*, **1998**, 777–779.
5. Charette, A. B.; Brochu, C. *J. Am. Chem. Soc*., **1995**, 117, 11367–11368.
6. Denmark, S.E.; O'Connor S. P. *J. Org. Chem*., **1997**, 62, 584–594.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Request Permission or Order Reprints Instantly!