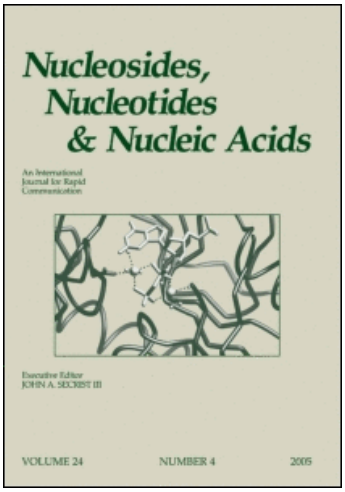

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Synthesis of [1′-Fluoro-2′,2′-*bis*-(hydroxymethyl)-cyclopropylmethyl]purines as Antiviral Agents

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ABSTRACT

[1′-fluoro-2′,2′-*bis*-(hydroxymethyl)cyclopropylmethyl]purines were designed, synthesized and their antiviral activity against poliovirus, HSV and HIV was evaluated.

Key Words: Antiviral; Cyclopropylmethyl purines; Carbonucleoside.

As an effort to search for the chemically and enzymatically stable carbonucleoside,[1] we designed [1′-fluoro-2′,2′-*bis*-(hydroxymethyl)cyclopropylmethyl]purines as novel antiviral agents.[2] The basic strategy for our design is to seek a conformationally locked acyclic carbonucleoside with minimal structural disturbance from a natural nucleoside (Fig. 1). Due to its unique steric and conformational effect, a cyclopropyl group could render the conformational rigidity to the flexible acyclic

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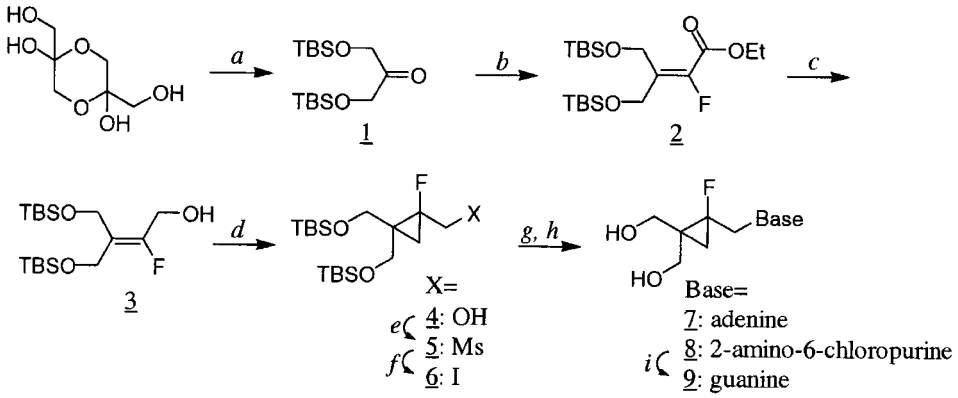

Scheme 1. Reagents and conditions. *a*) TBSCl, imidazole, DMF, 98%; *b*) $(EtO)_2P(O)CHFCO_2Et$, n-BuLi, THF, 94%; *c*) Dibal-H, CH_2Cl_2, −78°C, 89%; *d*) Et_2Zn, $Zn(CH_2I)_2$, *in situ* ZnI_2, CH_2Cl_2, 0°C, 63%; *e*) MsCl, TEA, 0°C; *f*) NaI, acetone, 78%(2 steps); *g*) Cs_2CO_3, Base, DMF, 60°C; *h*) TBAF, THF; *i*) $HSCH_2CH_2OH$, CH_3ONa, CH_3OH, reflux, 71%.

molecule. It is also envisioned that a fluoromethylene group could act as a bioisoster of oxygen.[3]

As shown in Sch. 1, the synthesis of the target molecules was started by treating dihydroxyacetone with TBSCl in DMF. Introduction of a fluorine group was effected by treating **2** with triethyl 2-fluoro-2-phosphonoacetate and n-BuLi using Horner-Wadsworth-Emmons reaction. The resulting α-fluoro-α,β-unsaturated ester was selectively reduced with Dibal-H at −78°C to afford the corresponding fluorinated allyl alcohol in 89% yield. The key synthetic intermediate, [2,2-*bis*-(*tert*-butyl-dimethylsilanyloxymethyl)-1-fluorocyclopropyl]methanol was synthesized from the corresponding fluorinated allyl alcohol **3** by the Lewis acid-catalyzed Furukawa modification of Simmon-Smith reaction.[4] The fluorinated cyclopropyl alcohol **4** was, then, converted to the corresponding iodide **6** via the mesylate **5**. The coupling of **6** with adenine and 2-amino-6-chloropurine in the presence of Cs_2CO_3 in DMF, followed by removal of the TBS group afforded the desired nucleosides **7** and **8** in 52% and 38% yields, respectively. Treatment of **8** with 2-mercaptoethanol and sodium methoxide in methanol, followed by hydrolysis with acetic acid gave **9** in 71% yield. The synthesized nucleosides (**7, 8, 9**) were evaluated for their antiviral activity against poliovirus, HSV-1, HSV-2, and HIV. However, all compounds were found to be inactive in the assay.

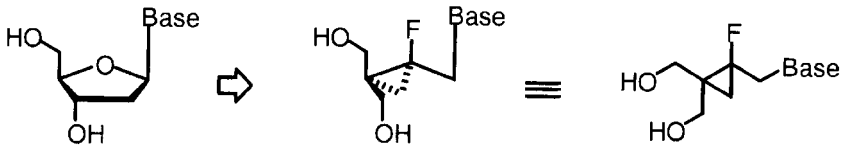

Figure 1.

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REFERENCES

1. Marquez, V.E. Carbocyclic nucleosides. In *Advances in Antiviral Drug Design*; JAI Press, 1996; Vol. 2, 89–146.
2. Lee, Y.R.; Park, J.-H.; Jeon, R.; Jeong, L.S.; Chun, M.W.; Kim, H.-D. Design and synthesis of novel fluorocyclopropanoid nucleosides. Nucleosides Nucleotides & Nucleic Acids **2001**, *20*, 677–679.
3. Blackburn, G.M.; Kent, D.E. Synthesis of α- and α, γ-fluoroalkylphosphonates. J. Chem. Soc. (Perkins I) **1986**, *6*, 913–917.
4. Charette, A.B.; Brochu, C. A new strategy for the Lewis acid-catalyzed cyclopropanation of allylic alcohols. J. Am. Chem. Soc. **1995**, *117*, 11,367–11,368.

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