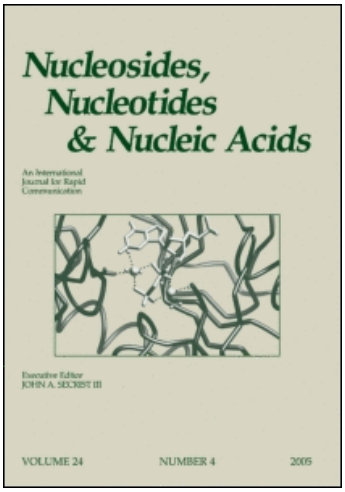

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Synthesis of (*Z*)-(1-Fluoro-2-hydroxymethyl-cyclopropylmethyl)purines

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ABSTRACT

(*Z*)-(1-fluoro-2-hydroxymethylcyclopropylmethyl)purines were designed, synthesized and evaluated their antiviral activity against poliovirus, HSV, and HIV.

Key Words: Antiviral; Fluorine; Cyclopropylmethylpurine.

The loss of furan oxygen in carba-nucleosides is believed to have critical effects on their antiviral activity.[1] It has also been suggested that a fluoromethylene group is a better isostere of oxygen than is methylene.[2] Therefore, carbocyclic and acyclic derivatives substituted by fluorine at the oxygen position in natural nucleoside are also attractive targets.[3] In addition, cyclopropyl group could render the conformational rigidity to the flexible acyclic molecule due to its unique steric and

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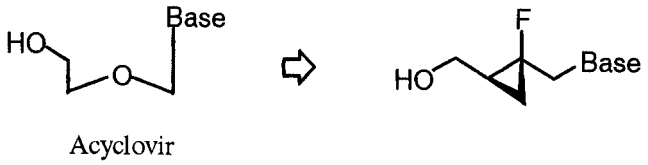
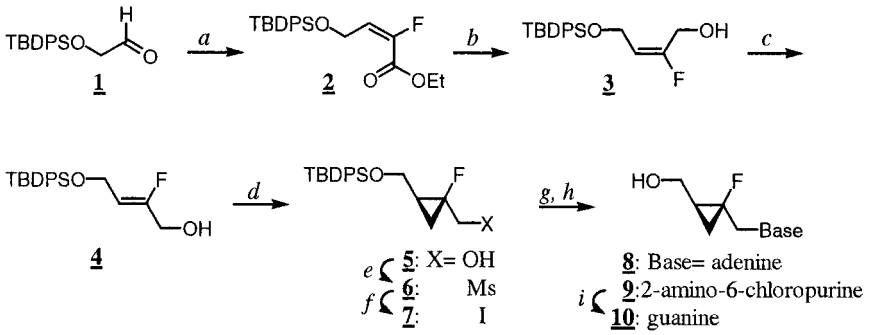


Figure 1.

conformational effect. Herein, we report on the design and syntheses of a series of (*Z*)-(1-fluoro-2-hydroxymethylcyclopropylmethyl)purines in an attempt to mimic acyclovir by installing a fluoro group and a cyclopropyl group (Fig. 1).

As shown in Sch. 1, the synthesis of the target molecules had been started with the reaction of the aldehyde **1** and triethyl 2-fluoro-2-phosphonoacetate. Due to its well-known preference for *E*-selectivity,[4] the direct formation of (*Z*)-fluoroalkenoate from aldehyde **1** was not an easy task to achieve. As an alternative way, we decided to synthesize the (*E*)-isomer selectively, and then isomerize to (*Z*)-isomer. Thus, after the stereoselective formation of (*E*)-isomer using *i*-PrMgCl as a base at 0°C ($E:Z = 16:1$), the resulting ester **2** was selectively reduced with Dibal-H at −78°C to afford the corresponding fluorinated (*E*)-allyl alcohol in 89% yield. Double bond isomerization of (*E*)-allyl alcohol to (*Z*)-isomer was effected by thiophenol and AIBN in refluxing benzene to give the (*Z*)-isomer **4** ($Z:E = 6.3:1$) in 71% yield. The key synthetic intermediate (*Z*)-[2-(*tert*-butyldiphenylsilanyloxymethyl)-1-fluorocyclopropyl] methanol, was synthesized from the corresponding fluorinated (*Z*)-allyl alcohol by the Lewis acid-catalyzed Furukawa modification of Simmon-Smith reaction.[5] The fluorinated cyclopropyl alcohol **4** was, then, converted to the corresponding iodide **7** via the mesylate **6**. The coupling of **7** with adenine and 2-amino-6-chloropurine in the presence of Cs_2CO_3 in DMF, followed by removal of TBS group afforded the desired nucleosides **8** and **9** in 60% and 29% yields, respectively.



Scheme 1. *Reagents and conditions*: *a*) $(EtO)_2$ P(O)$CHFCO_2Et$, *i*-PrMgCl, 0°C, 67%; *b*) Dibal-H, CH_2Cl_2, −78°C, 89% *c*) thiophenol, AIBN, benzene, reflux, 71%; *d*) Et_2Zn, $Zn(CH_2I)_2$, in situ ZnI_2, CH_2Cl_2, 0°C,))), 75%; *e*) MsCl, TEA, 0°C; *f*) NaI, acetone, 84% (2 steps); *g*) Cs_2CO_3, Base, DMF, 60°C *h*) TBAF, THF; *i*) $HSCH_2CH_2OH$, CH_3ONa, CH_3OH, reflux, 43%.

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Treatment of **9** with 2-mercaptoethanol and sodium methoxide in methanol, followed by hydrolysis with acetic acid gave **10** in 43% yield. The synthesized nucleosides (**8**, **9**, **10**) 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.

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