

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

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ABSTRACT

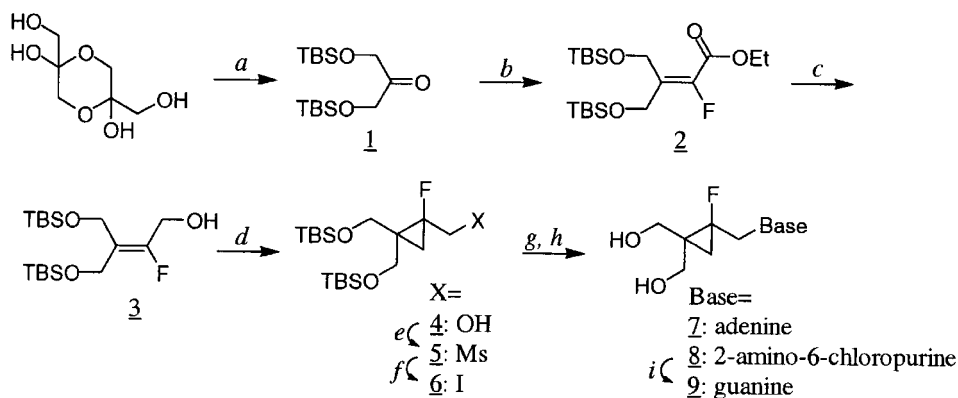
[1'-fluoro-2',2'-bis-(hydroxymethyl)cyclopropylmethyl]purines were designed, synthesized and their antiviral activity against poliovirus, HSV and HIV was evaluated.

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) $(\text{EtO})_2\text{P(O)CHF-CO}_2\text{Et}$, n-BuLi, THF, 94%; c) Dibal-H, CH_2Cl_2 , -78°C , 89%; d) Et_2Zn , $\text{Zn}(\text{CH}_2\text{I})_2$, *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) $\text{HSCH}_2\text{CH}_2\text{OH}$, 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.

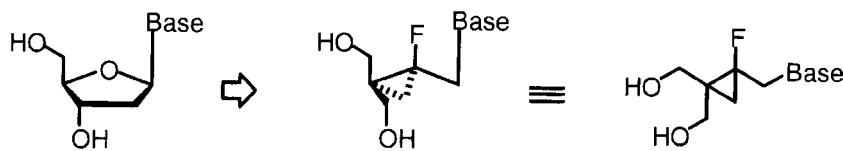


Figure 1.

ACKNOWLEDGMENT

This research was supported by the grant from the Good Health R&D project, Ministry of Health and Welfare, Korea.

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