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A Facile Synthetic Method for 3'-α-Fluoro- 2',3'-dideoxyadenosine

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A Facile Synthetic Method for 3'-α-Fluoro-2',3'-dideoxyadenosine

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ABSTRACT

A facile method for the synthesis of 3'- α -fluoro-2', 3'-dideoxyadenosine (5) has been developed using a novel rearrangement of 3'- β -bromine to the 2'- β position during 3'- α fluorination.

Key Words: Anti-HIV; Nucleosides; Fluorination; Rearrangement.

INTRODUCTION

 $3'\text{-}\alpha\text{-Fluoro-}2',3'\text{-dideoxy}$ purine nucleosides have attracted much attention because of their potential antiviral activity. These nucleosides are usually synthesized by replacing a 3'- β hydroxyl group with fluorine to obtain the corresponding 3'- α fluorides by $S_N2\text{-type}$ nucleophilic substitution, however, the synthesis of nucleoside derivatives bearing a 3'- β hydroxyl group from a natural ribonucleoside requires a multi-step synthesis and gives a poor yield. While the condensation of fluorinated sugar derivatives with a nucleoside base is a conventional approach to

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synthesizing C3'- α fluorinated nucleosides, the synthesis of fluorinated sugar derivatives requires many steps and condensation is subject to α -anomer formation. Consequently, a better method for the synthesis of 3'- α -fluoro nucleosides is desired.

RESULTS AND DISCUSSION

5'-O-Acetyl-3'- β -bromo-3'-deoxyadenosine (3) was conveniently synthesized from adenosine (1) according to the procedure described in Sch. 1. The 2'- β -bromo-3'- α -fluoro-2',3'-dideoxyadenosine (4) was prepared in a single step by treating 3'- β -bromo nucleoside $3^{[2]}$ with morpholinosulfur trifluoride (MOST). Direct fluorination by S_N2 -type nucleophilic substitution at the 2'- β position was not observed. The reaction also proceeded by treatment with diethylaminosulfur trifluoride (DAST), however this gave a poor yield (49% yield). We assume the reaction might proceed via a unique intramolecular rearrangement of bromine from the 3'- β to 2'- β position, simultaneous with 3'- α fluorination (Sch. 2). After radical debromination of 4, the 5'-O-acetyl group was deprotected to obtain the desired nucleoside 5. The spectroscopic properties of 5 were identical in all respects to the published data. 4

In conclusion, $3'-\alpha$ -fluoro-2', 3'-dideoxyadenosine (5) was synthesized from 5'-O-acetyl-3'- β -bromo-3'-deoxyadenosine (3), which is easily obtained from adenosine (1). The bromine group on 3 was rearranged from the 3'- β to 2'- β position during the reaction with dialkylaminosulfur trifluoride. The present method is useful for

Scheme 1. Synthesis of $3'-\alpha$ -fluoro-2',3'-dideoxyadenosine.

Scheme 2. The rearrangement of bromine.

the synthesis of various 3'- α -fluoro purine nucleosides. The details of the rearrangement are now under investigation in our laboratories.

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