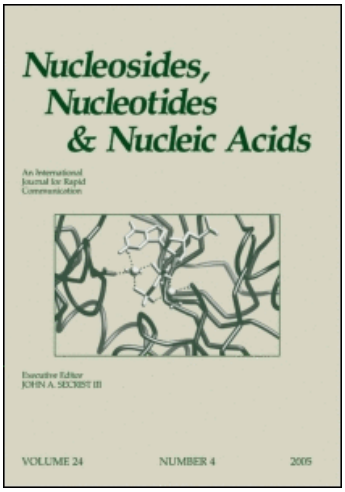

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A Facile Synthetic Method for 3'-α-Fluoro- 2',3'-dideoxyadenosine

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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′-α-Fluoro-2′,3′-dideoxy purine nucleosides have attracted much attention because of their potential antiviral activity.[1] These nucleosides are usually synthesized by replacing a 3′-β hydroxyl group with fluorine to obtain the corresponding 3′-α fluorides by S_N2-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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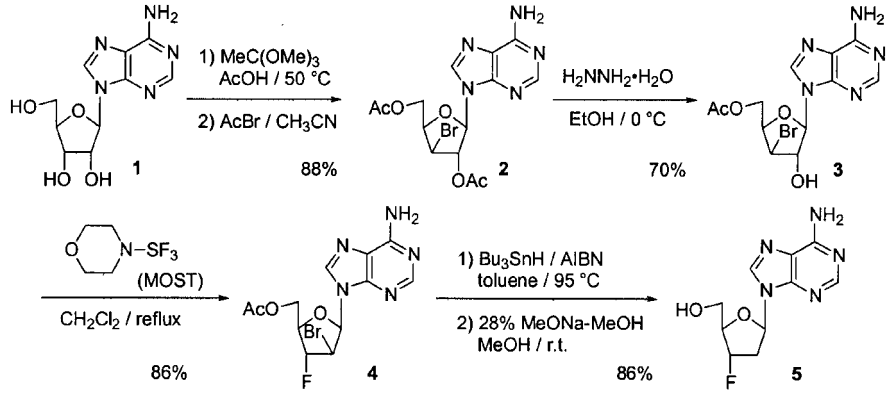
synthesizing C3′-α fluorinated nucleosides, the synthesis of fluorinated sugar derivatives requires many steps and condensation is subject to α-anomer formation. Consequently, a better method for the synthesis of 3′-α-fluoro nucleosides is desired.

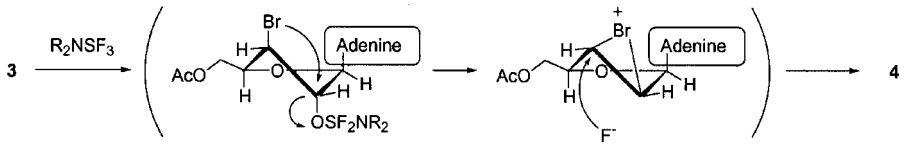
RESULTS AND DISCUSSION

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[3] 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.[1]

In conclusion, 3′-α-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′-α-fluoro-2′,3′-dideoxyadenosine.



Scheme 2. The rearrangement of bromine.

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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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