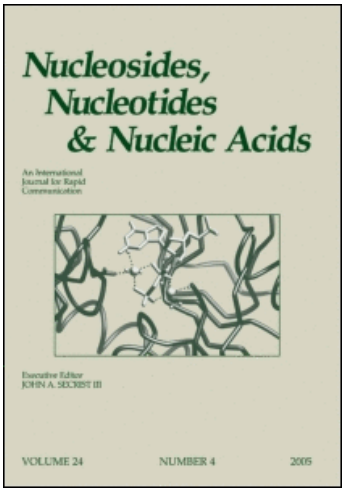

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SYNTHESIS OF THE 6'-FLUORO DERIVATIVES OF CARBOCYCLIC 2',3'-DIDEOXY-3'-OXA-ADENOSINE

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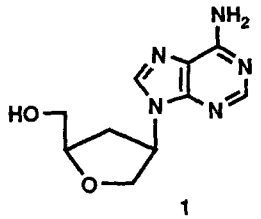
ABSTRACT. Different strategies for the synthesis of the 6'-α and β-fluoro derivatives of carbocyclic 2',3'-dideoxy-3'-oxa-adenosine are described.

Although a diversity of structures have shown *in-vitro* antiretroviral activity against Human Immunodeficiency Virus (HIV),[1] the etiologic agent of Acquired Immunodeficiency Syndrome (AIDS),[2] 2'3'-dideoxynucleosides are the only class of compounds that have demonstrated activity in humans.[3-5] Besides 3'-azido-3'-deoxythymidine (AZT), the first drug approved for the treatment of patients with AIDS and ARC (AIDS-related Complex), both 2',3'-dideoxyinosine (ddI) and 2',3'-dideoxycytidine (ddC) have been granted an expanded access through an "open-label safety protocol" while they are undergoing advanced clinical evaluations. To date, these three drugs represent the best hope for people inflicted with this terrible disease. However, the use of these drugs is often hampered by their dose-limiting side effects. Taken together with the emergence of AZT-resistant mutant viruses,[6] the situation clearly calls for better therapeutic agents for the treatment of AIDS and the less severe stages of HIV infection.

As part of our anti-HIV program, we have prepared a novel series of carbocyclic 2',3'-dideoxy-3'-oxa-nucleosides which can be exemplified by structure **1**.[7] These compounds were designed to be resistant to acid-mediated degradation, thus eliminating one major catabolic pathway of 2',3'-dideoxynucleosides, particularly those with the purine bases such as ddI and ddA. The adenine analog (**1**) was found



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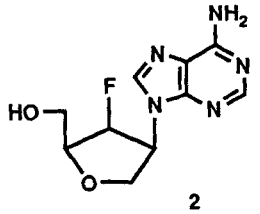

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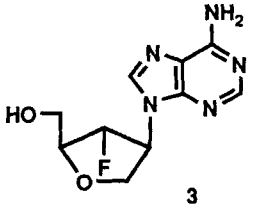

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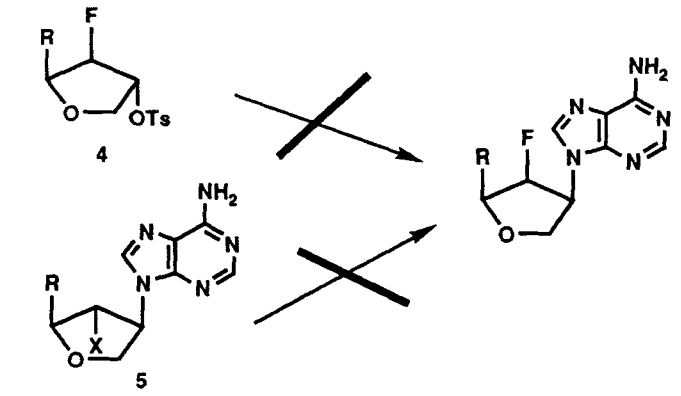
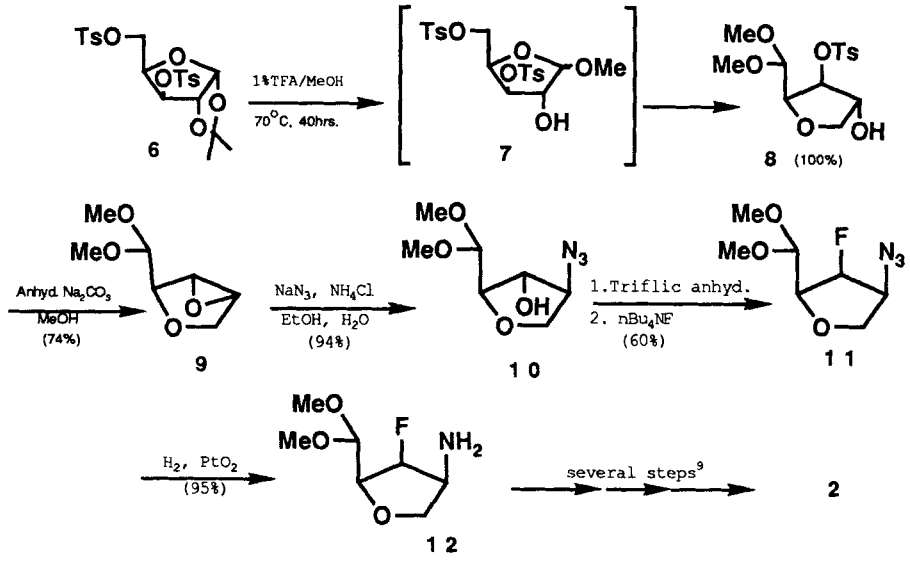
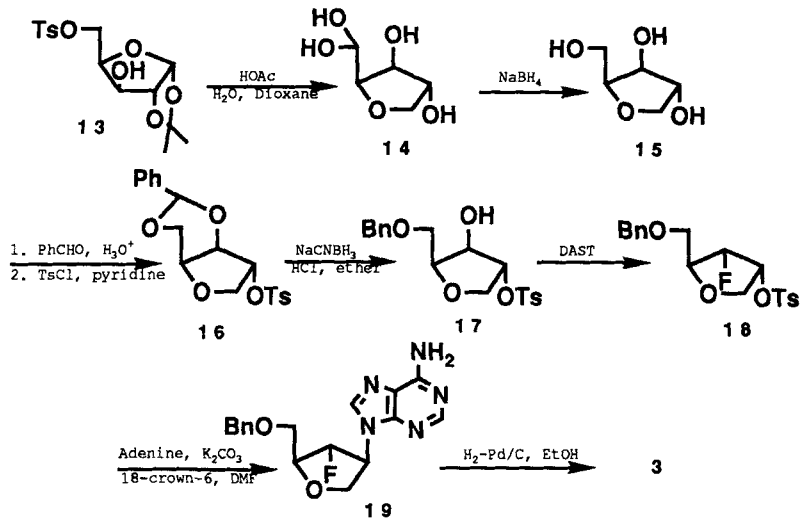


SCHEME 1



SCHEME 2

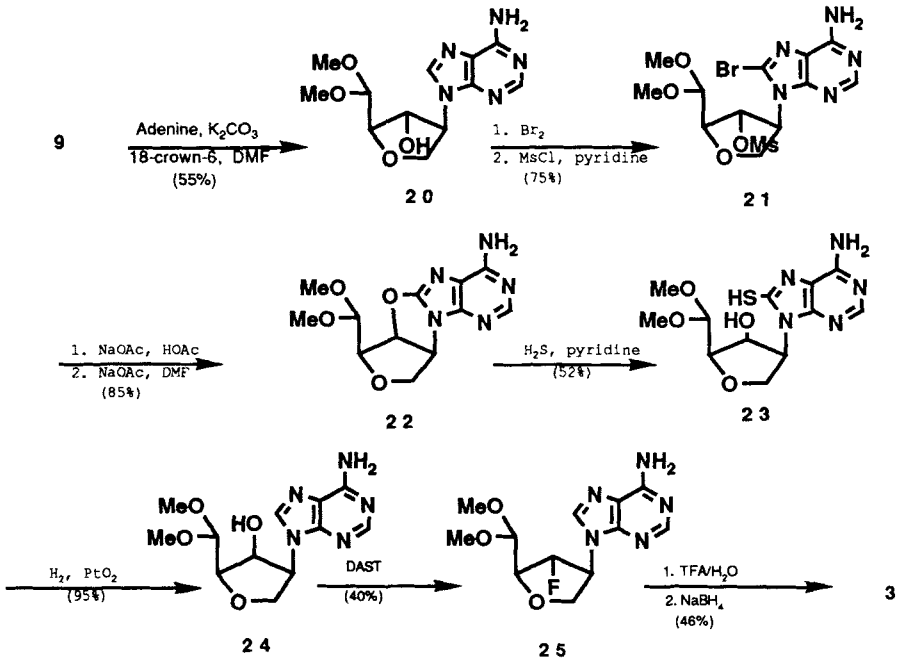


SCHEME 3

to exhibit anti-HIV activity in CD4+ cells as well as in human peripheral blood T4 cells, and to be substantially more resistant to degradation by acid, adenosine deaminase and purine nucleoside phosphorylase than ddA.[8] These encouraging results prompted us to explore the synthesis of the 6'-fluoro derivatives, **2** and **3**.

Two initial approaches to the 6'-β-fluoro compound **2** involved elaboration of key intermediates **4** and **5** (SCHEME 1). However, attempts to perform SN2 type displacements on the leaving groups in **4** and **5** were not successful. The target compound was eventually obtained via the azide intermediate **11**, followed by reduction and elaboration of the adenine ring[9] on the NH_2 group in **12** (SCHEME 2).

Interestingly, contrary to the above findings, synthesis of the 6'-α-fluoro compound **3** can be accomplished either through a direct displacement of the tosyl group in the fluoro compound **18** with adenine (SCHEME 3) or by a reaction of the 6'-β-OH nucleoside **24** with DAST (SCHEME 4). The intermediate **18** was prepared as shown; however, the compound was unexpectedly unstable thus rendering this synthesis unsuitable for scale-up. Synthesis of the β-OH isomer **24** originally involved inversion at the C-6' center of **20**. Unfortunately, the product obtained after an oxidation-reduction sequence was found to have epimerized at C-1'. Consequently, we turned to the alternative sequence shown in SCHEME 4. Ring opening of the 6'-8-anhydro-nucleoside **22** with H_2S/pridine followed by a catalytic reduction of the SH group gave a moderate yield of the 6'-β-OH compound **24** which was then converted to **3**.



SCHEME 4

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