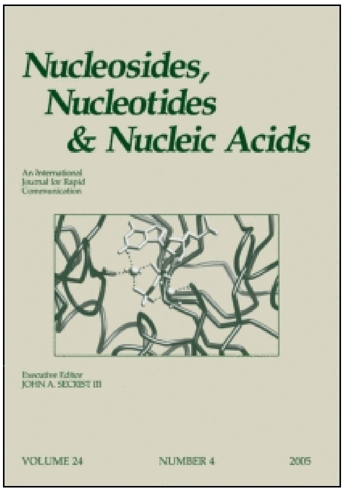

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NEW CLASSES OF FLUORINATED L-NUCLEOSIDES; SYNTHESIS AND ANTIVIRAL ACTIVITY

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ABSTRACT: The synthesis of 3'-fluorinated apionucleosides **7** and 2'-fluoro-2',3'-unsaturated L-nucleosides **8** *via* common synthon, 2-fluoro-butenolide **2**, has been described. Among the newly synthesized nucleosides, L-2'-F-d4C, L-2'-F-d4FC and L-2'-F-d4A exhibit significant anti-HIV and anti-HBV activities.

A wide variety of fluorinated nucleosides, including L-FMAU,[1] FLT,[2] 2'-F-ddC,[3] and 2'-F-ddA,[4] have been known to possess significant antiviral activity against human immunodeficiency virus (HIV), herpes simplex virus (HSV) and/or hepatitis B virus (HBV). Due to the significant biological effect of fluorine atom in nucleoside analogs, several groups have prepared vinylic fluoride containing D-nucleosides, among which cytosine derivative was found to exert anti-HIV activity.[5] It is also known that 4'-fluoro nucleosides and 3'-fluoro carbocyclic oxetanocin type of nucleosides exhibit interesting biological activities.[6] Recently, Ahn and coworkers reported the synthesis of racemic fluorinated apionucleosides as novel 4'-substituted nucleosides.[7] Additionally, L-nucleosides, such as 3TC,[8] L-Fd4C,[9] and L-FMAU,[1] have been reported as promising antiviral agents with their favorable toxicity profiles. In view of these findings, it was of interest to synthesize the titled nucleosides as shown in SCHEME 1.

In order to achieve the synthesis of our target compounds **7** & **8**, (*R*)-2-fluoro-4-[(*tert*-butyldimethylsiloxy)methyl]-2-buten-4-olide (**2**), which was prepared from 2,3-*O*-isopropylidene-L-glyceraldehyde **1** in 3 steps,[10] was utilized as a chiral template for the synthesis of the key intermediates **5** and **6** as illustrated in SCHEME 1. The L-

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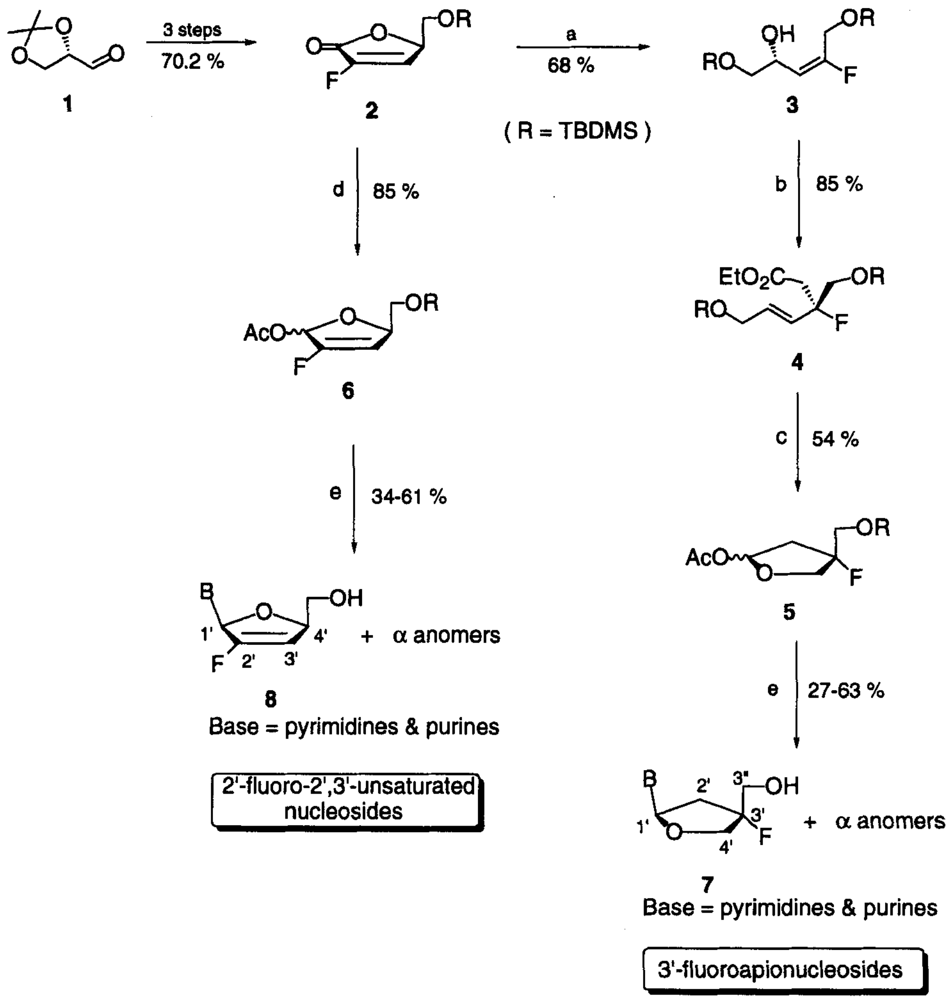

Reagents: a. (i) DIBAL-H, CH_2Cl_2; (ii) $CeCl_3 \cdot 7H_2O$, $NaBH_4$; (iii) TBDMSCl, imidazole; b. $(EtO)_3CCH_3$, propionic acid, 135 °C; c. (i) O_3/ DMS; (ii) DIBAL-H, toluene; (iii) Ac_2O, pyr.; d. (i) DIBAL-H, CH_2Cl_2; (ii) Ac_2O, pyr.; e. (i) silylated bases, TMSOTf, DCE, or CH_3CN; (ii) deprotection and base modifications

SCHEME 1

glyceraldehyde derivative **1** was subjected to the Horner-Emmons conditions in the presence of triethyl α-fluoro-phosphonoacetate and NaHMDS, followed by cyclization and silyl protection of hydroxyl group to give the desired lactone intermediate **2**. Reduction of compound **2** followed by selective protection of primary alchohol produced suitably protected allylic alcohol **3**, which was then subjected to Claisen rearrangement conditions in the presence of triethylorthoacetate and catalytic amounts of acid to furnish γ, δ-unsaturated fluoro ester **4**.[11] The intermediate **4** was ozonized followed by reduction and acetylation to yield 3-fluorinated apiosyl acetals **5**. Condensation of **5** with silylated pyrimidine or purine bases on Vorbrüggen conditions followed by deprotection (and further base modifications in case of purine derivatives) afforded a series of 3'-fluororinated apionucleosides **7**. For the preparation of adenine and hypoxanthine derivatives, 6-chloropurine was coupled with **5** and the resulting nucleoside intermediate was further converted into adenosine and inosine analogs in established methods, respectively.[12] Guanine derivative was also prepared by condensation of 2-amino-6-chloropurine with acetates **5**, followed by deprotection and hydrolysis.[12] The configurations of β- and α-isomers have been determined by NOESY study and were confirmed by X-ray crystallography.

Compound **6**, the carbohydrate portion of 2'-fluoro-2',3'-unsaturated L-nucleosides **1**, was also prepared from the common synthon **2** as depicted in SCHEME 1. Fluorobutenolide **2** was treated with DIBAL-H in CH_2Cl_2 at -78 °C, following by acetylation afforded the corresponding acetates **6**, which were directly condensed with silylated pyrimidines followed by deprotection to provide final pyrimidine nucleoside analogs. Adenine and hypoxanthine derivatives were obtained by condensation of the key intermediates **6** with silylated 6-chloropurine followed by deprotection and base modifications.[12] Guanine and 2-fluoroadenine derivatives were also prepared by coupling of 6-chloro-2-fluoropurine with acetates **6** followed by further modifications.[12] The stereochemical assignment of the synthesized nucleosides **8** was based on the NOESY study of β- and α-adenine derivatives.

In summary, we have developed efficient synthethic methodology for 3'-fluorinated apionucleosides **7** and 2'-fluorinated unsaturated L-nucleosides **8** *via* the versatile common synthon **2**. The newly synthesized nucleosides were evaluated against HIV-1 and HBV. The preliminary results indicated that several vinyl fluoride containing nucleosides **8**, such as cytosine, 5-fluorocytosine, and adenine derivatives, showed significant anti-HIV-1 and anti-HBV activities. Biological evaluations on the other series of compounds **7** are also in progress.

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