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Synthesis of β-L-2',3'-Dideoxy-2'-fluoro-3'-hydroxy-methylarabinofuranosyl Pyrimidine Nucleosides

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Abstract: β-2',3'-Dideoxy-2'-fluoro-3'-hydroxymethylarabinofuranosylthymine **10** and cytosine **12** were synthesized from *L*-xylose and were found to be inactive against HIV-1 in acutely infected lymphocytes.

Keywords: L-Nucleoside, anti-HIV, L-xylose, synthesis.

L-Nucleosides have attracted considerable attention since many analogs have exhibited a higher antiviral potency and selectivity than their corresponding D-isomers[1]. In particular, (-)-(2*R*, 5*S*)-1-[(2-hydroxymethyl)-oxathiolan-5-yl]cytosine (3TC, Lamivudine)[2],its 5-fluoro analog [(-)-FTC, Coviracil][3] and (-)-β-*L*-2',3'-dideoxy-5-fluorocytidine (*L*-FddC)[4] are in various stages of preclinical or clinical trials as anti-HIV and anti-HBV agents. Furthermore, the introduction of a 2'-β-fluoro atom in L-nucleosides has also resulted in excellent anti-HBV activity[5]. Cognizant of similar potent antiviral activities of β-D-2', 3'-dideoxy-3'-hydroxymethylribofuranosyl cytosine and adenine[6], we are interested in constructing other structurally related *L*-nucleosides containing both the 3'-hydroxymethyl and 2'-fluoro groups[7]. Herein, we report the synthesis of β-*L*-2', 3'-dideoxy-2'-fluoro-3'-hydroxymethylarabino- furanosyl thymine and cytosine, **10** and **12**, respectively.

The synthesis of **10** and **12** was started from ketone **2**, which was prepared from *L*-xylose according to the reported procedure (**Scheme 1**)[6a, b]. Ketone **2**, upon hydroboration with BH_3 and H_2O_2/NaOH at room temperature, was stereoselectively converted to **3**. Due to the presence of the bulky 1, 2-isopropylidene group, the hydride addition is facilitated from the least hindered side to form the 3', 4' *trans*-dihydroxymethyl groups. Owing to strong basic conditions of the reaction,

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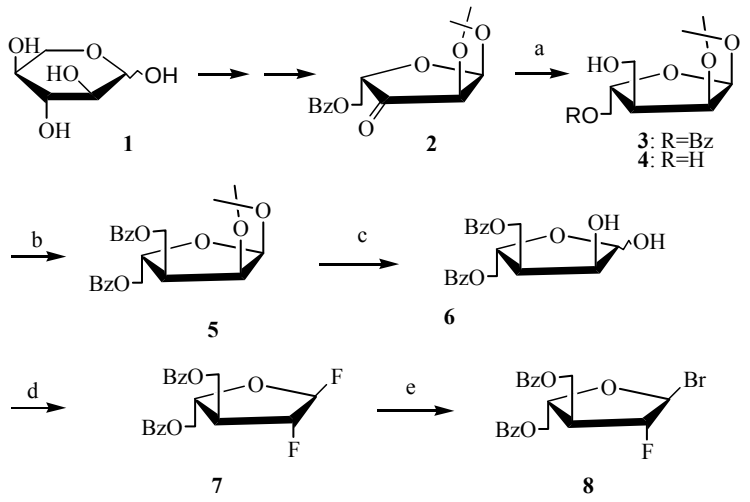
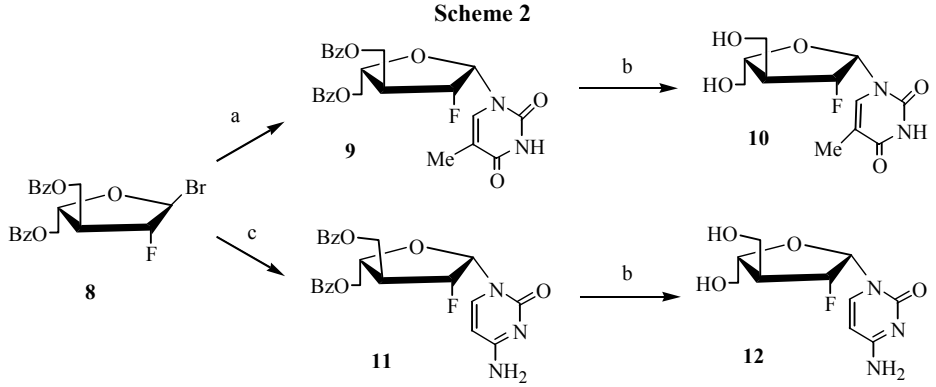
Scheme 1



(a) BH_3/THF, rt, 1 h; then NaOH, H_2O_2, rt, 3 h; (b) BzCl, Py, CH_2Cl_2, rt, overnight; (c) H_2SO_4 (cat.), 75% aqueous 1,4-dioxane, 90 °C, 3h; (d) DAST, CH_2Cl_2, rt, overnight; (e) 45% HBr, HOAc, rt, 1 h.

Scheme 2



(a) silylated thymine, MeCN, reflux, overnight; (b) NH_3, MeOH, rt, overnight; (c) silylated cytosine, MeCN, reflux, overnight.

the major compound **3** was partially debenzoylated to **4**. Treatment of the mixture of **3** and **4** with benzoyl chloride in pyridine led to **5** in 59% overall yield from **2**. The configuration of **5** was deciphered from the coupling constant ($J_{2,3}$= 4.8 Hz) in ^{1}H NMR spectroscopy, confirming the *cis* geometry of H-2 and H-3[6a, b].

The 1, 2-isopropylidene group in **5** was hydrolyzed by a catalytic amount of H_2SO_4 in 75% aqueous 1,4-dioxane at 90^{o}C for 3 h to give the 1, 2-dihydroxy derivative **6** in 78% yield as an anomeric mixture. Compound **6** was fluorinated with diethylaminosulfur trifluoride (DAST) at room temperature affording only the α-difluoro product **7** in 52% yield. The stereochemistry of **7** was assigned on the basis of its similar chemical shift and coupling constants for H_1 (6.00 ppm, $J_{1,2}$ = 5.9 and $J_{1,F}$ = 59

Hz) to the related compound,5-*O*-benzoyl-1,2,3-deoxy-1,2-difluoro-α-D-arabinofuranose (5.95 ppm, $J_{1,2}$ = 5.0 and $J_{1,F}$ = 60 Hz) in ^{1}H NMR spectroscopy [8]. Since the direct condensation of a 1, 2-difluoro sugar with a base usually gave poor yield[8], **7** was first converted to the corresponding bromo derivative **8** by treatment with 45% HBr/HOAc at room temperature (**Scheme 2**). Subsequent condensation of **8** with the silylated thymine in acetonitrile, under refluxing conditions, yielded the β-isomer **9** (47%), which was deprotected with 2 mol/L methanolic ammonia to the desired nucleoside **10** (70%). The corresponding cytosine analog **12** was prepared in 80% yield in a similar manner *via* **9** (67%). Again, the anomeric configuration of **12** was determined by studying its NMR NOESY data and by comparing its ^{1}H NMR spectrum (5.96 ppm, $J_{1',2'}$ = 2.4 and $J_{1',F}$ = 18 Hz) with that of the related compound, β-D-2',3'-dideoxy-2'-fluoro-β-D-ribofuranosylcytosine (5.96 ppm, $J_{1',2'}$ = 3.0 and $J_{1',F}$ = 19 Hz)[9].

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