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Synthesis and Antiviral Activity of Fluoro-substituted Apio Dideoxynucleosides

Joon Hee Hong[1], Hea Ok Kim[2], Hyung Ryong Moon[1], and Lak Shin Jeong[1]

[1]*Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea and* [2]*College of Medicine, Yonsei University, Seoul 120-752, Korea*

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Novel fluoro-substituted apio dideoxynucleosides ((±)-**3a** and (±)-**3b**) were efficiently synthesized starting from 1,3-dihydroxyacetone via Horner-Emmons olefination as a key step. Cyclization of fluoro ester (±)-**6** under acidic conditions to the fluorolactone was smoothly proceeded in favor of *trans*-fluorolactone due to the favorable transition state with equatorial hydroxymethyl substituent. Unfortunately, the final nucleosides (±)-**3a** and (±)-**3b** were found to be inactive against several viruses such as HIV-1, HSV-1, HSV-2 and HCMV.

Key words: Apio nucleosides, Antiviral, Horner-Emmons olefination

INTRODUCTION

Nonclassical nucleosides continue to be a promising challenge for the development of new antiviral agents since the discovery of L-β-1,3-oxathiolanyl cytosine (3TC, Lamivudine) (Jeong *et al.*, 1992, 1993; Schinazi *et al.*, 1992) as anti-human immunodeficiency virus (HIV) and anti-hepatitis B virus (HBV) agent. The apio dideoxynucleoside (Bamford *et al.*, 1991; Terao *et al.*, 1991; Jeong *et al.*, 2001) also belongs to the class of nonclassical nucleoside in that 4-hydroxymethyl of the 2,3-dideoxyribose moves to the C3 position. This class of nucleosides like **1** showed not only the antiviral activity, but also metabolic advantages such as resistances to adenosine deaminase and glycosyl bond hydrolysis, when compared to the classical 2,3-dideoxynucleosides.

Based on these findings, we have recently reported the synthesis of the apio dideoxynucleosides ((±)-**2a** and (±)-**2b**) with azido or amino substituent at the C3 position (Jeong *et al.*, 1998). These nucleosides were found to be inactive against HIV-1, herpes simplex virus (HSV)-1, HSV-2, and human cytomegalovirus (HCMV), but amino-substituted adenine derivative (±)-**2b** exhibited potent anti-HBV activity in 2.2.15 cells (Jeong, unpublished results). Therefore, in addition to C3 position, it was interesting to put the fluorine at the C2 position of the apio dideoxynucleosides because fluorine atom serves as a bioisostere of hydrogen or hydroxyl and to compare their antiviral activities (Fig. 1). Here we report the synthesis of the fluoro-substituted apio dideoxynucleosides ((±)-**3**), starting from 1,3-dihydroxyacetone via Horner-Emmons olefination as a key step and their antiviral activity.

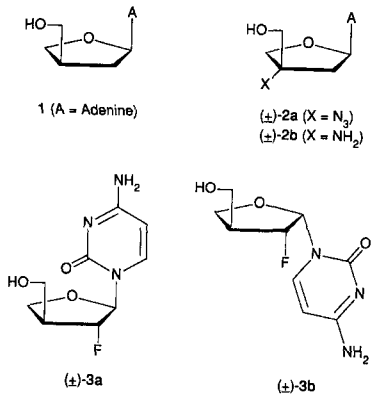


Fig. 1. Rationale to the design of the target nucleosides

MATERIALS AND METHODS

Ultra violet (UV) spectra were recorded on a Beckman DU-68 spectrophotometer and ^{1}H and ^{13}C NMR spectra

Correspondence to: Lak Shin Jeong, Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea
E-mail: lakjeong@mm.ewha.ac.kr

were recorded on Varian-400 spectrometer, using $CDCl_3$ or DMSO-d_6 and chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane as internal standard. Elemental analyses were performed in the general instrument laboratory of Ewha Womans University, Korea. TLC was performed on Merck precoated $60F_{254}$ plates. Column chromatography was performed using silica gel 60 (230-400 mesh, Merck). All the anhydrous solvents were distilled over CaH_2 or P_2O_5 or Na/benzophenone prior to use.

Bis(*tert*-butyldimethylsilyloxy)acetone (4)

To a solution of 1,3-dihydroxyacetone dimer (4 g, 22 mmol) and imidazole (12.0 g, 56 mmol) in DMF (10 mL) was added a solution of *t*-butyldimethylsilyl chloride (16.56 g, 110 mmol) and the mixture was stirred at rt for 48 h. To this mixture was added water and the mixture was extracted with hexanes. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was purified by silica gel column chromatography (Hexanes:ethyl acetate=15:1) to give **4** (6.2 g, 90%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 12H, 4 × $(CH_3)_2Si$), 0.92 (s, 18H, *t*-BuSi), 4.41 (s, 4H, 1-H and 3-H).

3-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldimethylsilyloxymethyl)-2-fluoro-2-bute-noic acid ethyl ester (5)

A solution of triethyl-2-fluorophosphonoacetate (0.61 g, 2.53 mmol) in THF (30 mL) was cooled to -78°C and *n*-Butyllithium (1.6 M solution in hexane, 529 mmol) was added dropwise. The mixture was kept at -78°C for 20 min, then a solution of **4** (1.0 g, 3.14 mmol) in THF (25 mL) was added. After being stirred at -78°C for 1 h, the reaction mixture was quenched by adding aqueous NH_4Cl and extracted with hexanes. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to dryness, which was purified by silica gel column chromatography (hexanes:EtOAc=50:1) to give fluoroester derivative **5** (1.17 g, 91.8%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H, $(CH_3)_2Si$), 0.08 (s, 6H, $(CH_3)_2Si$), 0.89 (s, 9H, -*t*-BuSi), 0.90 (s, 9H, -*t*-BuSi), 1.35 (t, *J*=6.8 Hz, 3H, $-CH_3$-), 4.23 (d, *J*=2.0 Hz, 2H, $-CH_2OSi$-), 4.30 (q, *J*=6.8 Hz, 2H, $-CH_2$-), 4.44 (d, *J*=3.6 Hz, 2H, $-CH_2$ OSi-).

3-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldimethylsilyloxymethyl)-2-fluoro-bu-tyric acid ethyl ester (6)

To a solution of compound **5** (340 mg, 0.83 mmol) in anhydrous EtOAc (500 mL) was added a catalytic amount of 5% Pd/C (34 mg). To this reaction mixture was connected double balloon of H_2 gas, and stirred at 0°C for 7 h. The reaction mixture was filtered through a Celite pad, solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes:EtOAc=50:1) to give **6** as an oil (336 mg, 98.5%): ^{1}H NMR ($CDCl_3$) δ 0.03 (d, *J*=2.0 Hz, 6H, $(CH_3)_2Si$-), 0.06 (s, 6H, $(CH_3)_2Si$-), 0.88 (s, 9H, *t*-BuSi), 0.90 (s, 9H, *t*-BuSi), 1.31 (t, *J*=7.2 Hz, 3H, $-CH_3$), 3.60-3.76 (m, 6H, $2xCH_2SiO$-,$-CH_2$-), 4.22-4.27 (m, 1H, CH), 5.09 (dd, *J*=3.6, 48.0 Hz, 1H, -CHF-).

(±)-3-Fluoro-4-hydroxymethyl-dihydro-furan-2-one (7)

A compound **6** (200 mg, 0.49 mmol) was dissolved in cosolvent of H_2O/THF/H_2SO_4 (20 mL/60 mL/1 mL). The reaction mixture was stirred at rt for 6 h, and quenched by adding saturated $NaHCO_3$ solution until pH 7. The neutralized mixture was evaporated under reduced pressure carefully to avoid bumping. The residue was coevaporated with toluene two times, and the residue was suspended over EtOAc and methanol cosolvent (1:1), and filtered through a Celite pad. The filterate was evaporated under reduced pressure, and purified by silica gel column chromatography (CH_2Cl_2:MeOH=10:1) to give crude lactone derivative **7** as diastereomeric mixtures. Without further purification, the crude compound **7** was subjected to the next reaction.

(±)-3,4-*trans*-4-(*tert*-Butyldimethylsilyloxymethyl)-3-fluoro-dihydro-furan-2-one (8a) and its *cis* isomer (8b)

The crude compound **7** was dissolved in anhydrous methylene chloride (20 mL) and DMF (10 ml). To this reaction mixture were added imidazole (152 mg) and TBDMSCl (168 mg, 1.11 mmol). The mixture were stirred for 5 h at rt. The solvent was evaporated under reduced pressure and the residue was extracted with diethyl ether and water. The organic layer was washed with brine and dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes:EtOAc=10:1) to give compound **8a** (58.3 mg, 48% in two step yield) and **8b** (14 mg, 11.5% in two step yield) as a colorless oil: Compound **8a**: ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 3H, $(CH_3)_2Si$-), 0.09 (s, 3H, $(CH_3)_2Si$-), 0.90 (s, 9H, t-BuSi-), 2.84-2.91 (m, 1H, H-4), 3.77 (dd, *J*=3.2, 10.7 Hz, 1H, $SiO-CH_a$), 3.90 (dd, *J*=4.0, 10.7 Hz, 1H, $SiO-CH_b$), 4.18, (t, *J*=9.1 Hz, 1H, H_a-5), 4.44 (t, *J*=9.1 Hz, 1H, H_b-5), 5.18 (dd, *J*=8.3, 51.4 Hz, 1H, H-3).

Compound **8b**: ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 6H, $(CH_3)_2$ Si-), 0.88 (s, 9H, t-BuSi-), 2.86-2.89 (m, 1H, H-4), 3.78-3.86 (m, 2H, $SiO-CH_2$), 4.35-4.40, (m, 2H, H-5), 5.23 (dd, *J*=7.6, 50.1 Hz, 1H, H-3).

(±)-3,4-*trans*-4-(*tert*-Butyldimethylsilyloxymethyl)-3-fluoro-tetrahydro-furan-2-ol (9)

The starting material **8a** (238 mg, 0.96 mmol) was dissolved in anhydrous toluene (10 mL), and to which was added Dibal-H (1.16 mL, 1 M in toluene) at -78°C. The reaction mixture was stirred at -78°C for 15 min, and quenched by adding MeOH (1 mL). The mixture was stirred for 2 h at rt, and the insoluble salts were removed

by filtration. After evaporation of solvents, the residue was purified by silica gel column chromatography (hexanes:EtOAc=5:1) to give lactol derivative **9** as a colorless oil (216 mg, 90%): ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 1H, $(CH_3)_2Si$), 0.13 (s, 5H, $(CH_3)_2Si$), 0.89 (s, 1.8H, t-BuSi-), 0.92 (s, 7.2H, t-BuSi-), 2.57-2.67 (m, 1H, H-4), 3.61-3.78 (m, 1H, SiO-CH_a), 3.87 (dd, *J*=5.2, 8.8 Hz, 1H, SiO-CH_b), 3.93 (dd, *J*=3.6, 10.4 Hz, 1H, H_a-5), 4.20 (t, *J*=8.8 Hz, 0.2 H, H_b-5), 4.29 (t, *J*=8.8 Hz, 0.8 H, H-4b), 4.88 (d, *J*=52.0 Hz, 1H, H-3), 5.36 (t, *J*=10.0 Hz, 1H, H-2).

(±)-Acetic acid 3,4-*trans*4-(*tert*-butyldimethylsilyloxymethyl)-3-fluoro-tetrahydro-furan-2-yl ester (10)

The lactol **9** (200 mg, 0.79 mmol) was dissolved in pyridine (10 mL) at 0°C, and to which was added Ac_2O (0.15 mL, 1.59 mmol). The reaction mixture was stirred overnight at rt. After removal of the solvent, the residue was extracted with ethyl acetate and water. The organic layer was washed with brine and dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes:EtOAc=5:1) to give **10** as a colorless oil (200 mg, 86%): ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 6H, $(CH_3)_2Si$-), 0.07 (s, 6H, $(CH_3)_2Si$-), 0.89 (s, 9H, t-BuSi), 0.90 (s, 9H, t-BuSi), 2.07 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.62-2.73 (m, 1H, H-4), 3.72 (d, *J*=7.2 Hz, 2H, SiO-CH_2), 3.84 (dd, *J*=6.4, 9.2 Hz, 1H, H_a-5), 4.28 (t, *J*=8.8 Hz, 1H, H_b-5), 5.01 (dd, *J*=2.0, 51.6 Hz, 1H, H-3), 6.29 (d, *J*=11.6 Hz, 1H, H-2).

(±)-(β)-1-(3,4-trans-3-Fluoro-4-hydroxymethyl-tetrahydro-furan-2-yl)-*N*^{4}-benzoylcytosine (12a) and (±)-(α)-1-(3,4-Trans-3-fluoro-4-hydroxymethyl-tetrahydro-furan-2-yl)-*N*^{4}-benzoylcytosine (12b)

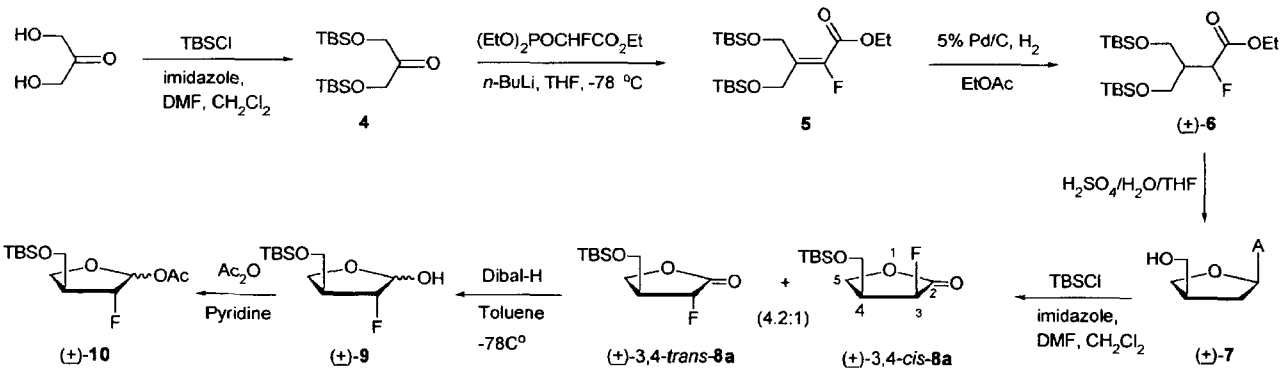
A mixture of *N*^{4}-benzoylcytosine (307 mg, 1.42 mmol), anhydrous HMDS (10 mL) and ammonium sulfate (catalytic amount) was refluxed under nitrogen atmosphere until a clear solution was obtained (10 h) and all reaction solvent was removed under high vacuum with exclusion of moisture to give a colorless oil, which was dissolved in dry dichloroethane (10 mL). To a solution of the silylated *N*^{4}-benzoylcytosine were added the acetate **10** (208 mg, 0.71 mmol) in dry dichloroethane and TMSOTf (0.26 mL, 1.42 mmol) at 0°C and the resulting reaction mixture was stirred at rt for 5 h. Saturated $NaHCO_3$ solution (3 mL) was added to the reaction mixture, which then was extracted with methylene chloride (20 mL × 2). Combined organic layer was washed with brine and dried over an-hydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was separated by silica gel column chromatography (hexanes:EtOAc=1:1) to give compound **11** (205 mg, 64.5%) as an anomeric mixture. Since it was impossible to separate the anomers in this stage, the anomeric mixture was dissolved in anhydrous THF (15 mL), which was treated with TBAF (1 M solution in THF, 1.0 mL) and then stirred at rt for 3 h. After concentration, the residues were purified by silica gel column chromatography ($CHCl_3$:MeOH=10:1) to give an anomeric mixture of **12a** and **12b**. In order to separate this mixture, preparative TLC was used (hexanes/ethyl acetate/acetone=3/2/3) to give compound **12a** (63.5 mg, 41.6% in two steps) and **12b** (60.7 mg, 39.7% in two steps), respectively: Compound **12a**: UV (MeOH) λ_{max} 305 nm; ^{1}H NMR ($CDCl_3$) δ 2.74-2.84 (m, 1H, H-4), 3.58 (dd, *J*=5.3, 11.4 Hz, 1H, $HOCH_a$), 3.86 (dd, *J*=4.5, 11.4 Hz, 1H, $HOCH_b$), 4.28 (dd, *J*=5.3, 9.2 Hz, 1H, H_a-4), 4.53 (t, *J*=8.7 Hz, 1H, H_b-4), 5.61 (d, *J*=50.7 Hz, 1H, H-3), 5.89 (d, *J*=16.6 Hz, 1H, H-2), 7.45-7.91 (m, 7H, Ph, H-5, and H-6), 9.05 (br s, 1H, NH); Compound **12b**: UV (MeOH) λ_{max} 305 nm; ^{1}H NMR ($CDCl_3$) δ 2.81-2.89 (m, 1H, H-4), 3.74-3.87 (m, 2H, $HOCH_2$), 4.05 (dd, *J*=3.3, 9.0 Hz, 1H, H_a-4), 4.46 (dd, *J*=7.1, 9.0 Hz, 1H, H_b-4), 5.46 (dd, *J*=2.8, 52.0 Hz, 1H, H-3), 6.18 (dd, *J*=2.8, 19.8 Hz, 1H, H-2), 7.51-7.95 (m, 7H, Ph, H-5, and H-6), 8.68 (br s, 1H, NH).

(±)-(β)-1-(3,4-*trans*-3-Fluoro-4-hydroxymethyl-tetrahydro-furan-2-yl)cytosine (3a)

Compound **12a** (90 mg, 0.27 mmol) was dissolved in saturated methanolic ammonia (20 mL) and the resulting solution was stirred at rt overnight. The reaction solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (CH_2Cl_2:MeOH=5:1) to give **3a** as a white solid (43.6 mg, 72 %): mp 169°C; UV (H_2O) λ_{max} 270 nm; ^{1}H NMR (DMSO-d_6) δ 2.52-2.63 (m, 1H, H-4), 3.33-3.43 (m, 2H, $HOCH_2$), 3.9 (dd, *J*=8.9, 5.7 Hz, 1H, H_a-5), 4.21 (t, *J*=8.5 Hz, 1H, H_b-5), 4.92 (t, *J*=5.3 Hz, 1H, OH), 5.18 (dt, *J*=2.4, 53.0 Hz, 1H, H-3), 5.70 (d, *J*=7.7 Hz, 1H, H-5), 5.73 (dd, *J*=14.0, 1.6 Hz, 1H, H-2), 7.19 (br d, 2H, NH_2), 7.52 (d, *J*=7.3 Hz, 1H, H-6); ^{13}C NMR (DMSO-d_6) δ?59.4, 71.06, 92.10, 93.83, 96.88, 98.66, 141.28, 155.09, 165.85. Anal. Calcd for $C_9H_{12}FN_3O_3$: C, 47.16; H, 5.28; N, 18.33. Found: C, 47.19; H, 5.15; N, 18.33.

(±)-(α)-1-(3,4-*trans*-3-Fluoro-4-hydroxymethyl-tetrahydro-furan-2-yl)cytosine (3b).

Compound **12b** (102 mg, 0.31 mmol) was dissolved in saturated methanolic ammonia (20 mL) and the resulting solution was stirred at rt overnight. The reaction solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (CH_2Cl_2:MeOH=5:1) to give **3a** as a white solid (53.6 mg, 76%): mp 214 °C; UV (H_2O) λ_{max} 270 nm; ^{1}H NMR (DMSO-d_6) δ 2.56-2.65 (m, 1H, H-4), 3.43 (dd, *J*=6.9, 10.9 Hz, 1H, $HOCH_a$), 3.51 (dd, *J*=5.7, 10.9 Hz, 1H, $HOCH_b$), 3.72 (dd, *J*=4.1, 8.5 Hz, 1H, H_a-5), 4.25 (dd, *J*=7.7, 8.5 Hz, 1H, H_b-5), 5.01 (t, *J*=5.2 Hz, 1H, OH), 5.11 (dd, *J*=2.0, 53.4 Hz, 1H, H-3), 5.70 (d, *J*=7.3 Hz,



Scheme 1. Synthesis of the glycosyl donor containing fluoro substituent

1H, H-5), 5.95 (dd, 3.6, 19.3 Hz, 1H, H-2), 7.09 (br d, 2H, NH_2), 7.49 (d, J=7.3 Hz, 1H, H-6); ^{13}C NMR (DMSO-d_6) δ 47.11, 59.27, 68.25, 85.85, 92.25, 94.10, 141.60, 154.70, 165.57. Anal. Calcd for $C_9H_{12}FN_3O_3$: C, 47.16; H, 5.28; N, 18.33. Found: C, 47.56; H, 5.25; N, 18.54.

RESULTS AND DISCUSSION

Our synthetic strategy to the target nucleosides is first to synthesize the glycosyl donor and then to condense with nucleosidic base. Synthesis of the glycosyl donor **10** is shown in Scheme 1.

1,3-Dihydroxyacetone was protected as *t*-butyldimethylsilyl ether **4** (90%) under the standard conditions. Horner-Emmons olefination of **4** with fluorophosphonate at -78°C gave the fluoro olefin **5** in excellent yield. Catalytic hydrogenation of **5** with palladium on carbon in ethyl acetate afforded the fluoro ester (±)-**6** (99%) which was cyclized under the acidic conditions to the fluorolactone (±)-**7** as an inseparable diastereomeric mixture in favor of (±)-3,4-*trans* isomer over (±)-3,4-*cis*-isomer. The possible chair-like transition state for the major formation of (±)-3,4-*trans* isomer is well shown in Fig. 2, whose hydroxymethyl side chain prefers the equatorial position to the axial position.

The inseparable mixture (±)-**7** was treated with *t*-butyldimethylsilyl chloride and imidazole to give the silyl lactones (±)-**8a** (48%) and (±)-**8b** (12%) in 4:1 ratio, which could be easily separated by silicagel column chromatography. The stereochemistry of fluorine was easily confirmed by ^1H NOE experiment. NOE effect between H-3 and TBSO-CH_2 of (±)-**8a** was larger than that of (±)-**8b**. Reduction of lactone (±)-**8a** with DIBAL-H at -78°C gave the lactol (±)-**9** (90%) which was acetylated with acetic anhydride to yield the glycosyl donor (±)-**10** (86%).

The synthetic route to the final nucleosides ((±)-**3a** and (±)-**3b**) from the glycosyl donor (±)-**10** is described in Scheme 2. Condensation of the acetate (±)-**10** with silylated N^4-benzoylcytosine in the presence of trimethylsilyl

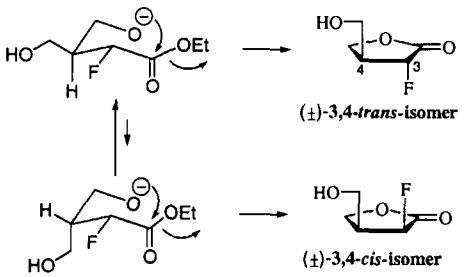
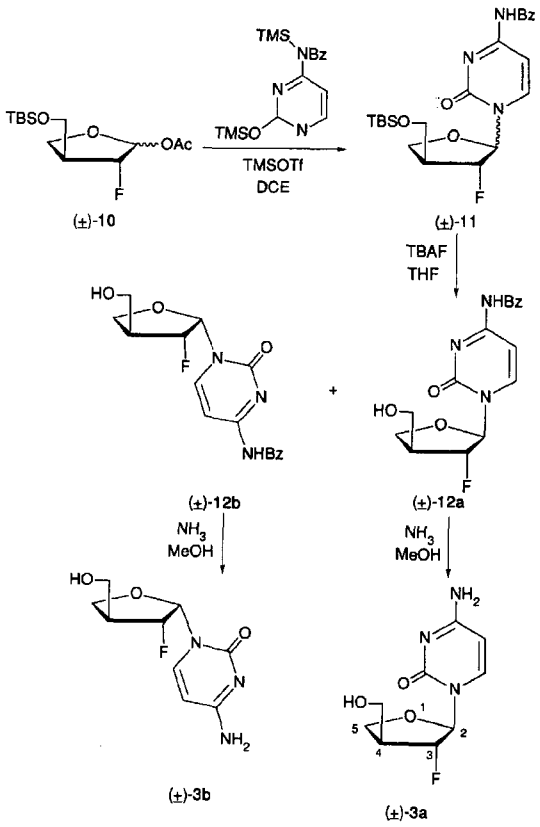


Fig. 2. Possible transition states to the cyclization



Scheme 2. Conversion of the glycosyl donor to the final fluoro substituted apio nucleosides

trifluoromethanesulfonate (TMSOTf) in 1,2-dichloroethane afforded the inseparable anomeric mixture, which was treated with *n*-tetrabutylammonium fluoride in tetrahydrofuran to give the β-isomer (±)-**12a** (42%) and the α-isomer (±)-**12b** (40%), respectively after silica gel column chromatography. ^{1}H NOE experiment was also employed to confirm the anomeric configuration. NOE effect between H-2 and CH_2-OH of (±)-**12a** was smaller than that of (±)-**12b**. Deprotection of each anomers (±)-**12a** and (±)-**12b** with methanolic ammonia afforded the final β-isomer (±)-**3a** (72%) and the α-isomer (±)-**3b** (76%), respectively.

The final nucleosides (±)-**3a** and (±)-**3b** were assayed against several viruses such as HIV-1, HSV-1, HSV-2, and HCMV. These compounds were found to be inactive against all viruses tested without cytotoxicity up to 100 μg/mL.

In summary, we have accomplished the synthesis of the fluoro-substituted apio dideoxynucleosides, starting from 1,3-dihydroxyacetone via Horner-Emmons olefination as a key step, but the final nucleosides did not exhibit any significant antiviral activity.

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