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Rapid synthesis of 2′,3′-dideoxy-3′β-fluoro-pyrimidine nucleosides from 2′-deoxypyrimidine nucleosides

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ABSTRACT

A rapid synthesis of 2′,3′-dideoxy-3′-fluoro-β-D-*threo*-nucleosides bearing the pyrimidine canonical bases of nucleic acids has been developed in order to discover new nucleoside derivatives as potential antiviral drugs. However, when evaluated for their antiviral activity in cell culture experiments, none of these compounds showed any significant antiviral activity.

1. Introduction

Nucleoside analogs are an important class of biologically active compounds. Currently, nucleoside analogs are prominent drugs for the treatment of several viral infections [1–3]. These nucleoside analogs share a common mechanism of action. They are metabolized by cellular kinases to their 5′-triphosphate forms, which then exert their biological effect as virus-specific polymerase competitive inhibitors or chain terminators because they lack a hydroxyl group at the C-3′ position. In the search for new antiviral nucleoside analogs, structural modifications of the heterocyclic bases and/or modifications on the sugar moiety of natural nucleosides can be attempted. In the latter, the main modifications involved changes in the D-ribofuranose or 2-deoxy-D-ribofuranose moiety like inversion of hydroxyl group configurations, elimination leading to dideoxy- or dideoxy-didehydro-nucleosides, substitution/functionalization by various synthetic groups [4].

Among these functionalities, introduction of a fluorine atom into the glycon moiety has been investigated in the search for nucleoside analogs endowed with potent biological properties [5–7]. This tremendous work led, for instance, to the discovery of 2′,3′-dideoxy-3′-fluorothymidine [8]. The interest in the synthesis of fluorine containing nucleoside analogs is derived from the stability of the carbon–fluorine bond, chemically and enzymatically, and from the strong electronegativity of fluorine which affect the stereoelectronic properties of the whole molecule. Structural studies on glycon fluorinated nucleosides have demonstrated the possibility to use fluorine as a good mimic of hydrogen (similar size) or hydroxyl group (similar polarity) that can exert a powerful influence on the stability of the glycosyl bond on acid-sensitive nucleosides as well as on the sugar puckering. Such influences have been clearly established in the case of β-FddA [9] and β-FddC [10] for increasing the stability of the glycosyl bond. Furthermore, the presence of a fluorine atom in position 2′ or 3′ of dideoxynucleosides, and in a particular configuration (up or down), can drive the puckering equilibrium toward a specific distribution of the north/south [11].

In the present article, we describe the direct preparation of 2′,3′-dideoxy-3′β-fluoro-pyrimidine nucleosides 9–**11** (Fig. 1) using as model compounds their corresponding natural 2′-deoxynucleoside derivatives.

2. Experimental

2.1. General methods

Evaporation of solvents was carried out on a rotary evaporator under reduced pressure. Melting points were determined in open capillary tubes on a Gallenkamp MFB-595-010M apparatus and are uncorrected. UV spectra were recorded on an Uvikon 931 (Kontron) spectrophotometer. ^{1}H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra at 100 MHz and ^{19}F NMR at 235 MHz in $(CD_3)_2SO$ at ambient temperature with a Brüker DRX 400. Chemical shifts (δ) are quoted in parts per million (ppm) referenced to the residual solvent peak $((CD_3)CD_2H)SO$ being set at δ-$_H$ 2.49 and δ-$_C$ 39.5 relative to tetramethylsilane (TMS). ^{19}F chemical shifts are reported using trichlorofluoromethane as external reference. Deuterium exchange and COSY experiments were performed in order to confirm proton assignments. Coupling constants, *J*, are reported in Hertz. 2D ^{1}H–^{13}C heteronuclear COSY were recorded for the attribution of ^{13}C signals. Specific rotations were measured on a Perkin–Elmer

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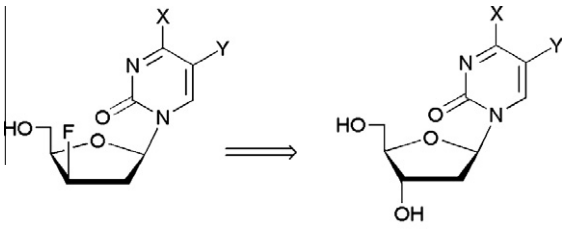

9 (X = OH, Y = H)
10 (X = OH, Y = CH_3)
11 (X = NH_2, Y = H)

X = OH, Y = H
X = OH, Y = CH_3

Fig. 1. 2′,3′-Dideoxy-3′β-fluoro-pyrimidine nucleosides.

Model 241 spectropolarimeter (path length 1 cm), and are given in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were carried out by the Service de Microanalyses du CNRS, Division de Vernaison (France). Thin layer chromatography was performed on precoated aluminum sheets of Silica Gel 60 F_{254} (Merck, Art. 5554), visualization of products being accomplished by UV absorbency followed by charring with 5% ethanolic sulfuric acid and heating. Column chromatography was carried out on Silica Gel 60 (Merck, Art. 9385). All moisture-sensitive reactions were carried out under rigorous anhydrous conditions under an argon atmosphere using oven-dried glassware. Solvents were dried and distilled prior to use and solids were dried over P_2O_5 under reduced pressure.

*2.2. Synthesis of 2′-deoxy-3-nitro-uridine (**1**) and 2′-deoxy-3-nitro-thymidine (**2**)*

Compounds **1** and **2** were obtained from commercially available 2′-deoxyuridine and 2′-deoxythymidine following a procedure initially developed by Gorchs et al. [12]. The physico-chemicals properties were similar to those previously described. (**1**): ^{1}H NMR (DMSO-d_6): δ 8.13 (d, J = 8.4, 1H), 6.07–6.14 (m, 2H), 5.23 (br s, 2H), 4.26 (m, 1H), 3.86 (m, 1H), 3.60 (m, 2H), 2.32 (m, 2H). ^{13}C NMR: δ 155.4, 145.3, 141.5, 100.1, 88.0, 86.2, 69.7, 60.7, 39.9. (**2**): ^{1}H NMR (DMSO-d_6): 7.98 (s, 1H), 6.11 (t, J = 6.5 Hz, 1H), 5.1–5.4 (br s, 2H), 4.27 (m, 1H), 3.82 (m, 1H), 3.67–3.54 (m, 2H), 2.29–2.12 (m, 2H), 1.92 (s, 3H). ^{13}C NMR (DMSO-d_6): 155.3, 144.0, 135.9, 107.6, 86.7, 84.7, 68.7, 59.7, 38.6, 11.2.

*2.3. General procedure for the preparation of 5′-O-acetyl-2′-deoxy-3-nitro-uridine (**3**) and 5′-O-acetyl-2′-deoxy-3-nitro-thymidine (**4**)*

To a solution of nucleoside (**1**, **2**) (1 mmol) in dioxane (10 cm^3) were added PPh_3 (1.5 mmol) and glacial acetic acid (9.9 mmol). The resulting mixture was stirred at 60 °C, and a solution of diethyl azodicarboxylate (1.5 mmol) in dioxane (1 cm^3) was added dropwise. The solution was stirred at 60 °C for 1 h. After cooling to room temperature and evaporation of the solvent, the oily residue was purified by silica gel chromatography using as eluent $CHCl_3$/Acetone (9/1:v/v) to give the title compounds. (**3**) (yield 75%): $[\alpha]_D^{20}$: +35 (c 1.06, DMSO). UV: (ethanol 95) λ_{max} 260 nm, (ε 8700). ^{1}H NMR (DMSO-d_6): δ 7.86 (d, 1H, J = 8.4), 6.08–6.15 (m, 2H), 5.52 (s, 1H), 4.13–4.24 (m, 3H), 4.01 (m, 1H), 2.27–2.42 (m, 2H), 2.04 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 170.1, 155.5, 145.3, 141.7, 100.3, 86.4, 84.3, 69.7, 63.5, 38.9, 20.6. Anal. Calcd for $C_{11}H_{13}N_3O_8$: C, 41.91, H, 4.16, N, 13.33. Found: C, 41.66, H, 4.16, N, 13.08. (**4**) (yield 74%): M.p.: 116–117 °C. $[\alpha]_D^{20}$: +17.5 (c 1.00, DMSO). UV: (ethanol 95) λ_{max} 264 nm, (ε 9700). ^{1}H NMR (DMSO-d_6): δ 7.65 (s, 1H), 6.13 (t, J = 6.5 Hz, 1H), 5.49 (d, 1H, J = 4.5 Hz), 4.28–4.16 (m, 3H), 3.96 (m, 1H), 2.39–2.12 (m, 2H,), 2.05 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (DMSO-d_6): 170.2, 156.4, 145.1, 136.9, 109.1, 85.8, 84.1, 69.7, 63.6, 38.6, 20.6, 12.1. Anal. Calcd for $C_{12}H_{15}N_3O_8$: C, 43.77, H, 4.59, N, 12.76. Found: C, 44.15, H, 4.69, N, 12.47.

*2.4. General procedure for the preparation of 1-(2,3-dideoxy-3-fluoro-5-O-acetyl-β-D-threo-pentofuranosyl)-3-nitro-uracil (**5**) and 1-(2,3-dideoxy-3-fluoro-5-O-acetyl-β-D-threo-pentofuranosyl)-3-nitro-thymine (**6**)*

To a stirred solution of nucleoside (**3**, **4**) (1 mmol) in an anhydrous CH_2Cl_2/pyridine (20 cm^3) mixture at −67 °C under argon was added DAST (5 mmol). The reaction mixture was allowed to warm up to room temperature and stirring was continued for 12 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, washed with H_2O. The organic phase was dried over Na_2SO_4, concentrated to dryness and purified by silica gel chromatography using ether as eluent to give the title compounds. (**5**) (yield 45%): $[\alpha]_D^{20}$: +13 (c 1.00, DMSO). UV: (ethanol 95) λ_{max} 260 nm, (ε 9200). ^{1}H NMR (DMSO-d_6): δ 7.75 (d, J = 8.1, 1H), 6.16 (d, J = 6.9, 1H), 6.09 (d, J = 8.4, 1H), 5.90 (d, J = 53.42, 1H), 4.25–4.47 (m, 3H), 2.87 (m, 1H), 2.46 (m, 1H), 2.07 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 170.1, 155, 145.3, 140.9, 100.4, 92.2 (d, J = 178.4 Hz), 85.8, 81.3 (d, J = 18.1 Hz), 61.1, 38.3 (d, J = 20.2 Hz), 20.5. ^{19}F NMR (DMSO-d_6): −190.75 (dddd, J = 54.1, J = 43.2, J = 31.3, J = 24.1 Hz). (**6**) (yield 43%): $[\alpha]_D^{20}$: +17 (c 1.00, DMSO). UV: (ethanol 95) λ_{max} 264 nm, (ε 8700). ^{1}H NMR (DMSO-d_6): δ 7.05 (s, 1H), 6.16 (dd, 1H, J = 8.04, 1.8 Hz), 5.4 (ddd, 1H, J = 54.2, J = 4.3, J = 2.4 Hz), 4.42 (m, 2H), 4.3 (m, 1H), 2.74 (m, 1H), 2.43 (m, 1H), 2.07 (m, 3H), 1.94 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 170.1, 156.3, 145.1, 135.99, 109.1, 92.3 (d, J = 178.3), 85.4, 80.9 (d, J = 18.25), 61.1, 38.1 (d, J = 20.2), 20.5, 12.3. ^{19}F NMR (DMSO-d_6): −190.31 (dddd, J = 54.3, J = 42.2, J = 29.8, J = 24.9 Hz).

*2.5. General procedure for the preparation of 1-(2,3-dideoxy-3-fluoro-5-O-acetyl-β-D-threo-pentofuranosyl)uracil (**7**) and 1-(2,3-dideoxy-3-fluoro-5-O-acetyl-β-D-threo-pentofurano-syl)thymine (**8**)*

A solution of nucleoside (**5**, **6**) (1 mmol), Bu_3SnH (1.1 mmol) and AIBN (0.3 mmol) in anhydrous toluene (50 cm^3) was heated at 100 °C for 2 h. The reaction mixture was cooled and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using as eluent CH_2Cl_2/Acetone (8/2:v/v) to give the title compounds. (**7**) (yield 67%): M.p.: 167–168 °C. $[\alpha]_D^{20}$: +4.5 (c 1.00, DMSO). UV: (ethanol 95) λ_{max} 260 nm (ε 9100). ^{1}H NMR (DMSO-d_6): δ 11.28 (s, 1H), 7.44 (d, J = 8.1, 1H), 6.08 (d, J = 8.1, 1H), 5.62 (d, J = 8.1, 1H), 5.29 (ddd, J = 54.6, J = 4.5, J = 2.4, 1H), 4.23 (m, 3H), 2.6 (m, 1H), 2.24 (ddd, J = 27.4, J = 16.5, J = 2.5, 1H), 2.01 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 170.1, 163.1, 150.3, 139.7, 102.1, 92.5 (d, J = 178.1 Hz), 83.8, 80.3 (d, J = 18.0 Hz), 61.2, 38.1 (d, J = 20.2), 20.5. ^{19}F (DMSO-d_6): δ −190.23 (dddd, J = 54.9, J = 41.3, J = 31.9, J = 25.3 Hz). Anal. Calcd for $C_{11}H_{13}FN_2O_5$: C, 48.53, H, 4.81, N, 10.29. Found: C, 48.33, H, 5.16, N, 9.99. (**8**) (yield 85%): M.p.: 142–143 °C. $[\alpha]_D^{20}$: +16.5 (c 1.00, DMSO). UV: (ethanol 95) λ_{max} 265 nm, (ε 8800). ^{1}H NMR (DMSO-d_6): δ 11.29 (s, 1H), 7.25 (s, 1H), 6.11 (dd, J = 8.7, 2.4 Hz, 1H), 5.29 (ddd, J = 54.6, J = 4.61, J = 2.42 Hz, 1H, H-3′), 4.36–4.22 (m, 2H), 4.12 (m, 1H), 2.74 (m, 1H), 2.18 (ddd, J = 26.0, J = 16.1, J = 2.8 Hz, 1H), 2.01 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 170.1, 163.6, 150.4, 135.1, 109.7, 92.5 (d, J = 178.2 Hz), 83.3, 79.9 (d, J = 17.9 Hz), 61.26, 37.9 (d, J = 20.17), 20.5, 12.3. ^{19}F NMR(DMSO-d_6): δ −189.84 (dddd, J = 54.9, J = 41.4, J = 31.9, J = 26.3 Hz). Anal. Calcd for $C_{12}H_{15}FN_2O_5$: C, 50.35, H, 5.28, N, 9.79. Found: C, 50.28, H, 5.40, N, 9.44.

*2.6. General procedure for the preparation of 1-(2,3-dideoxy-3-fluoro-β-D-threo-pentofuranosyl)uracil (**9**) and 1-(2,3-dideoxy-3-fluoro-β-D-threo-pentofuranosyl)thymine (**10**)*

A solution of nucleoside (**7**, **8**) (1 mmol) in methanolic ammonia (20 cm^3) (saturated beforehand at −10 °C and tightly stoppered)

was stirred in a stainless-steel bomb overnight at room temperature. The solution was evaporated to dryness under reduced pressure and co-evaporated several times with methanol. The residue was purified by silica gel column chromatography using as eluent CH_2Cl_2:MeOH (9/1:v/v)) to afford the title compounds. (**9**) (yield 74%). M.p.: 167 – 168 °C. $[\alpha]_D^{20}$: −11.25 (c 0.8, DMSO). UV: (ethanol 95) λ_{max} 260 nm, (ε 8800). ^{1}H NMR (DMSO-d_6): δ 11.34 (s, 1H), 7.48 (d, J = 8.15, 1H), 6.14 (d, J = 8.0 Hz, 1H), 5.69 (d, J = 8.12, 1H), 5.29 (ddd, J = 54.3, J = 4.2, J = 2.4 Hz, 1H), 5.01 br (s, 1H), 4.01 (m, 1H), 3.65–3.78 (m, 2H), 2.76 (m, 1H), 2.22 (ddd, J = 28.0, J = 16.4, 2.3 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 163.1 (C-4), 150.4 (C-2), 139.7, 101.8 (C-5), 92.0 (d, J = 178.2 Hz), 83.9, 83.6 (d, J = 15.9 Hz), 58.1, 38.4 (d, J = 20.1 Hz). ^{19}F NMR (DMSO-d_6): δ −190.51 (dddd, J = 54.7, J = 43.0, J = 30.0, J = 25.4 Hz). Anal. Calcd for $C_9H_{11}FN_2O_4$: C, 46.96, H, 4.82, N, 12.17. Found: C, 47.02, H, 4.92, N, 11.99. (**10**) (yield 78%). The physico-chemicals properties of were similar to those previously described. $[\alpha]_D^{20}$: −21.2 (c 1.00, DMSO) UV: (ethanol 95) λ_{max} 266 nm (ε 10,500). ^{1}H NMR (DMSO-d_6): δ 11.34 (s, 1H), 7.31 (s, 7.31), 6.16 (dd, J = 8.1, 2.1 Hz, 1H) 5.28 (ddd, J = 54.6, J = 4.5, J = 2.4 Hz, 1H), 4.99 (s, 1H), 3.95 (m, 1H), 3.72 (m, 2H), 2.75 (m, 1H), 2.22 (ddd, J = 25.2, J = 15.9, J = 2.7 Hz, 1H), 1.78 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 162.2, 148.9, 133.8, 108.0, 90.6 (d, J = 178.4 Hz), 82.1, 81.6 (d, J = 25.1), 56.7, 38.2 (d, J = 20.6), 12.39. ^{19}F NMR (DMSO-d_6): δ −190.12 (dddd, J = 54.5, J = 42.4, J = 30.8, J = 25.1 Hz). Anal. Calcd for $C_{12}H_{15}FN_2O_5$. $0.6H_2O$: C, 47.10, H, 5.61, N, 10.98. Found: C, 46.96, H, 5.66, N, 10.63.

2.7. Synthesis of 1-(2,3-dideoxy-3-fluoro-β-D-threo-pentofuranosyl)cytosine (**11**)

Lawesson's reagent (0.296 g, 0.73 mmol) was added under argon to a solution of compound (**7**) (0.2 g, 0.73 mmol) in anhydrous 1,2-dichloroethane (25 cm^3) and the reaction mixture was stirred under reflux for 6 h. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using as eluent CH_2Cl_2/Acetone (8/2:v/v) to give the 4-thio intermediate (0.19 g). A solution of the 4-thio intermediate in methanolic ammonia (16 cm^3) (saturated beforehand at −10 °C and tightly stoppered) was heated at 100 °C in a stainless-steel bomb for 3 h, and then cooled to room temperature. The solution was evaporated to dryness under reduced pressure and co-evaporated several times with methanol. The residue was purified by silica gel column chromatography using as eluent CH_2Cl_2/MeOH (8/2:v/v) to give the title compound (**11**) (0.13 g, overall yield 77%) which was lyophilizated from water. $[\alpha]_D^{20}$: +10.8 (c 0.6, DMSO). UV: (ethanol 95) λ_{max} 272 nm, (ε 8100). ^{1}H NMR (DMSO-d_6): δ 7.5 (d, J = 7.4, 1H), 7.14 (br d, 2H), 6.09 (d, J = 7.8 Hz, 1H), 5.75 (d, J = 7.4, 1H), 5.25 (ddd, J = 54.3, J = 4.0, J = 2.4 Hz, 1H), 4.99 (t, J = 5.4 Hz, 1H), 4.00 (m, 1H), 3.78–3.69 (m, 2H), 2.69 (m, 1H), 2.09 (ddd, J = 26.4, J = 15.8, J = 2.1 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 165.3, 154.7, 139.9, 93.6, 91.8 (d, J = 177.9) 84.1, 83.6 (d, J = 18.8 Hz), 57.9, 39.1 (d, J = 19.9) ^{19}F NMR (DMSO-d_6): δ −190.99 (dddd, J = 54.5, J = 43.2, J = 30.4, J = 24.0 Hz). Anal. Calcd for $C_9H_{12}FN_3O_3$. $0.9H_2O$: C, 44.05, H, 5.67, N, 17.12. Found: C, 44.24, H, 5.38, N, 16.87.

2.8. General procedure for the preparation of 1-(2,3-dideoxy-3-fluoro-β-D-threo-pentofuranosyl)-3-nitro-uracil (**12**) and 1-(2,3-dideoxy-3-fluoro-β-D-threo-pentofuranosyl)-3-nitro-thymine (**13**)

Treatment of nucleoside (**5**, **6**) (0.5 mmol) with HCl/MeOH (0.17 M, 25 cm^3) for 12 h at room temperature. The solution was evaporated to dryness under reduced pressure and co-evaporated several times with toluene. The residue was purified by silica gel column chromatography using as eluent CH_2Cl_2/Acetone (7:3) to give the title compounds. (**12**) (yield 75%): M.p.: 168–169 °C. $[\alpha]_D^{20}$: +13.1 (c 1.00, DMSO). UV: (ethanol 95) λ_{max} 260 nm (ε 8800). ^{1}H NMR (DMSO-d_6): δ 7.67 (d, J = 8.3 Hz, 1H), 6.13 (d, J = 7.9 Hz, 1H), 6.09 (d, J = 8.4 Hz, 1H), 5.22 (ddd, J = 54.1, J = 3.99, J = 2.4 Hz, 1H), 5.06 (t, J = 5.5 Hz, 1H), 4.06 (m, 1H), 3.79 (m, 2H), 2.79 (m, 1H), 2.43 (m, 1H). ^{13}C NMR (DMSO-d_6): δ 155.4, 145.3, 140.9, 100.2, 91.8 (d, J = 178.1 Hz), 85.7, 84.7 (d, J = 18.8 Hz), 57.9, 38.5 (d, J = 20.5 Hz). ^{19}F NMR (DMSO-d_6): δ −191.05 (dddd, J = 54.2, J = 43.2, J = 31.1, J = 22.8 Hz). Anal. Calcd for $C_9H_{10}FN_3O_6$: C, 39.28, H, 3.66, N, 15.27. Found: C, 39.63, H, 4.01, N, 15.02. (**13**) (yield 71%): M.p.: 178–180 °C. $[\alpha]_D^{20}$: +3 (c 1.00, DMSO). UV: (ethanol 95) λ_{max} 264 nm, (ε 7000). ^{1}H NMR (DMSO-d_6): δ 7.49 (s, 1H), 6.14 (dd, J = 7.9, 1.6 Hz, 1H), 5.32 (ddd, J = 54.3, J = 4.2, J = 2.5 Hz, 1H), 5.05 (t, J = 5.6 Hz, 1H), 4.06 (m, 1H), 3.71–3.84 (m, 2H), 2.78 (m, 1H), 2.41 (ddd, J = 23.6, J = 16.0, J = 2.0 Hz, 1H), 1.93 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 156.3, 145.1, 136.1, 108.8, 91.8 (d, J = 178.2 Hz), 85.2, 84.4 (d, J = 18.6), 57.9, 38.3 (d, J = 20.3 Hz), 12.4. ^{19}F NMR (DMSO-d_6): δ −190.63 (dddd, J = 54.3, J = 42.5, J = 30.5, J = 24.1 Hz). Anal. Calcd for $C_{10}H_{12}FN_3O_6$: C, 41.53, H, 4.18, N, 14.53. Found: C, 41.57, H, 4.32, N, 14.82.

3. Results and discussion

So far, the 3′β-fluoro-substituted nucleosides have been synthesized through glycosylation reaction between pre-formed 3-deoxy-3-β-fluoro-D-*xylo*-furanosides with heterocyclic bases or by introduction of a fluorine atom onto 2′,3′-anhydro-β-D-ribofuranonucleosides [7]. The resulting 3-deoxy-3-β-fluoro-D-*xylo*-nucleosides were finally subjected to a Barton-type reductive deoxygenation to afford the corresponding 2′,3′-dideoxy-3′β-fluoro nucleoside analogs. These methodologies have been used to synthesize the nucleoside derivatives bearing adenine [13], guanine [14] and thymine [14] as heterocyclic bases. In order to have a rapid access to the hitherto unknown derivatives of uracil and cytosine and evaluate their antiviral properties, we envisioned their preparation from the corresponding natural 2′-deoxynucleoside derivatives. At this point, after selective protection in position 5′, a direct nucleophilic fluorination reaction using a fluorinating agent such as diethylaminosulfur trifluoride (DAST) would not give the corresponding C-3′-β-fluoro pyrimidine nucleoside [15]. Instead, the formation of a 2,3′-anhydro nucleoside would occur due to the neighboring group participation of the C-2 carbonyl function of the aglycon. Indeed, the intramolecular attack of the C-2 carbonyl group of the nucleobase on C′-3, activated with a good leaving group [C-O-$SF_2(NEt_3)$], of the sugar moiety precedes the attack of a fluorine ion from the β-face of the nucleoside. Thus, to produce the desired corresponding C-3′β-fluoro pyrimidine nucleoside, anhydronucleoside formation has to be prevented. This unwanted side-reaction can be hindered by protection of the N-3 atom of the pyrimidine base. In this regard, Serra et al. reported the use of nitro group as protective group for the N-3 position. The use of such protective electron-withdrawing group prevented the formation of anhydro nucleoside during nucleophilic substitutions upon 2′-*O*-triflyluridine [16] as well as 2′,3′-cyclic sulfate pyrimidine nucleoside [17].

The synthesis began (Fig. 2) with the preparation of the appropriate 3-nitro 2′-deoxynucleosides **1** and **2** which were obtained from commercially available 2′-deoxyuridine and thymidine following a reported procedure [12]. Regioselective 5′-*O*-acylation of **1** and **2** was achieved using a modified Mitsunobu procedure [18] and gave the key intermediates 5′-*O*-acetyl-2′-deoxy-3-nitro-uridine and -thymidine **3** and **4** after purification by silica gel chromatography in 75% and 74%, respectively.

Reaction of DAST with **3** and **4** in an anhydrous dichloromethane/pyridine mixture provided the corresponding protected C-3′β-fluoro pyrimidine nucleosides **5** and **6**. Removal of the nitro group was attempted using iodide-mediated denitration process

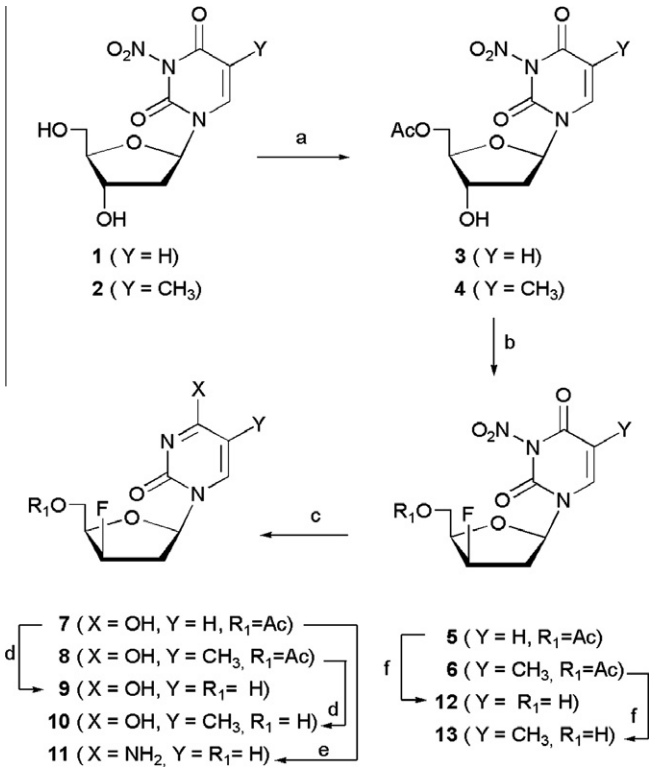

Fig. 2. *Reagents and conditions*: (a) PPh_3, AcOH, DEAD, dioxane, 60 °C; (b) DAST, CH_2Cl_2/pyridine, −67 °C; (c) Bu_3SnH, AIBN, toluene, 100 °C; (d) NH_3/MeOH, r.t.; (e) – i – Lawesson's reagent, 1,2-dichloroethane, reflux; – ii – NH_3/MeOH, 100 °C; (f) HCl/MeOH, r.t.

with NaI in Acetone. However, in our hands, no reaction occured [17]. Nevertheless, removal of the nitro group was readily achieved using a radical process for the denitration of N-nitroamines [19]. Thus, a treatment of **5** and **6** with Bu_3SnH in dry toluene in the presence of α,α′-azoisobutyronitrile (AIBN) under reflux gave the protected nucleoside derivatives **7** and **8**. Removal of the acetyl group with methanolic ammonia afforded the desired dideoxynucleosides **9** and **10** after purification on silica gel column. The structures of compounds **9** and **10** were fully established from ^1H, ^{13}C and ^{19}F NMR spectra. In particular, the physicochemical properties of compound **10** were identical to those previously reported by Gosselin et al. [14] for the 2′,3′-dideoxy-3′β-fluoro-nucleoside derivative of thymine. Compound **7** was converted into the corresponding cytidine derivative **11** *via* the formation of a 4-thioamide intermediate followed by aminolysis. Finally, in order to evaluate the potential antiviral activity of the fluorinated nucleosides obtained during the synthesis of compounds **9**–**11**, the 3-nitro fluorinated intermediates **5** and **6** were deprotected following a treatment with methanolic HCl and provided the 2′,3′-dideoxy-3′β-fluoro-3-nitro-uridine (**12**) and -thymidine (**13**).

4. Conclusion

A rapid synthesis of 2′3′-dideoxy-3′β-fluoro-nucleosides bearing the pyrimidine canonical bases of nucleic acids has been developed in order to discover new nucleoside derivatives as potential antiviral drugs. However, when the nucleosides **9**, **11**–**13** were evaluated against DNA and several RNA viruses (including HIV) in cell culture experiments, none of the nucleoside derivatives showed any antiretroviral activity nor cytotoxicity at the highest concentration tested (usually 100 μM).

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