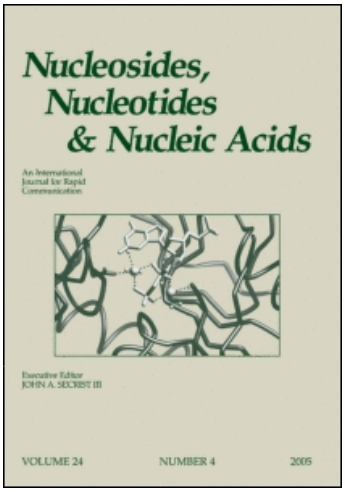

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Synthesis of a Novel Aldehyde: 4-O-Methyl-5-formylmethyl-2′-deoxyuridine

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ABSTRACT

The synthesis of the blocked nucleoside 3′,5′-di-*O*-*p*-toluoyl-4-*O*-methyl-5-formylmethyl-2′-deoxyuridine (**19**) was accomplishied in eleven steps from gamma-butyrolactone. This aldehyde, which should facilitate the synthesis of nucleosides containing ^{18}F, was converted to the corresponding blocked dithianyl nucleoside (**21**), and also to 5-(2,2-difluoroethyl)-substituted derivatives of 2′-deoxyuridine and 2′-deoxycytidine.

Key Words: Gem-difluoro; Deoxyuridine; Aldehyde; Reductive tritualation; Dithioacetals.

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Suicide gene therapy is one of the most promising clinical protocols in cancer therapy.[1] The mechanism underlying the therapy starts by delivering the suicide gene into the target cells, followed by administering the prodrugs. The presence of the suicide gene in the target cells activates the prodrugs, such as thymidine analogs, to form toxic metabolites, which then initiate the subsequent suicidal mechanism. Herpes simplex virus type 1 TK (HSV-1 TK) is the most extensively studied suicide gene. The success of this protocol relies on a predictable transfection of HSV-1 TK into cancer cells in vivo. The development of a methodology for monitoring such a process is of value. One of the most successful approaches is to use ^{18}F-radiolabeled thymidine analogs as marking substrates for HSV-1 TK on the basis of positron emission tomography (PET).[2] The previous results have shown that the syntheses of [^{18}F]-5-(2-fluoroethyl)deoxyuridine **1**[3] and [^{18}F]-5-(2-fluorovinyl)deoxyuridine **2**[4] require tosylate **3** (or triflate **4**) and organostannane **5** as precursors, respectively (Fig. 1). Radiolabeled compounds could be prepared with high specific activity using nucleophilic or electrophilic radiolabeled fluorination.[3,4] In particular, the gem-difluoro substituted thymidine analog **6** attracted the most of our attention. It is known that gem-difluoro compounds always display significant bioactivities[5] and may serve as alternative candidates of radiotracers. The recent progress in oxidative desulfurization-fluorination reaction of dithioacetals[6] and the application of [^{18}F]XeF_2[7] encouraged us to synthesize the compound **6**. Furthermore, since tritium-labeled natural products (e.g., thymidine **7**) have been widely used in enzyme-based assay in vitro, the thymidine analog **8** should be a valuable compound as well. 5-Formylmethyl deoxyuridine **9** would be a key intermediate for the facial synthesis of these radioactive molecules mentioned above (Fig. 2).

The preparation of aldehyde **9** has not been reported unlike that of 5-formylmethyl uracil **10**.[8,9] However, the attempt to repeat the reported [2 + 2] photo chemical reaction of uracil with 1,3-dioxolone was cumbersome.[10] A resulting viscous gum was obtained after evaporation of the solvent, and the product could not be successfully identified by ESI-MS spectra. Such difficulty was probably due to the attack of the 5-formyl group by the unprotected imino group during the formation of a cyclized hemiacetal **11**. Besides the cyclization, uncontrolled overoxidations were also observed during treatment of compound **12** with various oxidants[11] including MnO_2, chromium (VI) and activated DMSO. Byproducts such as 5-formyluracil **13** and 5-carboxy uracil **14** were always obtained. To prevent the cyclization and overoxidation, the 2,4-dioxo groups were protected with methyl groups, and mild oxidizing conditions were employed. However, the desired product **16** is still susceptible to the oxidants (Sch. 1).[10]

The isolation of the desired aldehyde **19** was made possible by modifying the oxidation condition using a 4-methoxy protected nucleoside **18** as the alcohol (Sch. 2).[3] The preparation of alcohol **18** was a ten-step synthesis using γ-butyrolactone as starting material and this was developed by the separate work of refs[8,12,13] and our group.[3]

The PDC oxidation in the presence of 4 Å MS was more feasible than Swern oxidation in this case. The latter reaction was observed to give a decomposed product. The successful preparation of the aldehyde **19** allowed us to synthesize the dithiane derivative **21**, gem-difluoro derivatives **6**, **23** and **24**, as well as tritium-labeled alcohol **18**. The dithiolation of aldehyde **19** was carried out by the use of 1,3-propanedithiol

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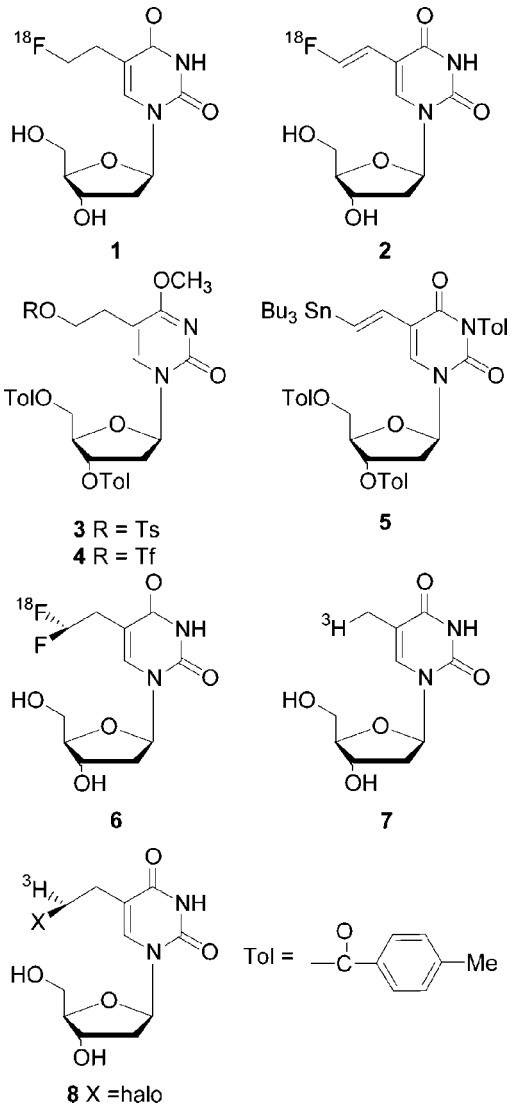


Figure 1. Biologically related radiolabeled thymidine derivatives and precursors.

and $BF_3 \cdot 2HOAc$. Treatment of aldehyde **19** with DAST provided the gem-difluoro nucleoside **22** at 80% yield within 10 min (Sch. 3). After selective deprotection, thymidine derivatives **6**, **23** and cytidine derivative **24** were obtained in high yield. Both fluorine atoms of the methyl rotamers in compound **6** and the α-anomers of compounds **23**, **24** showed different spectroscopical character in ^{19}F-NMR ($J_{F,F} = 10 \sim 15$ Hz). A hydrogen bond formation was proposed to assist the partial fixation. The reduction of aldehyde **19** with nonradioactive $NaBH_4$ provided a high yield of the alcohol **18** (10 min).

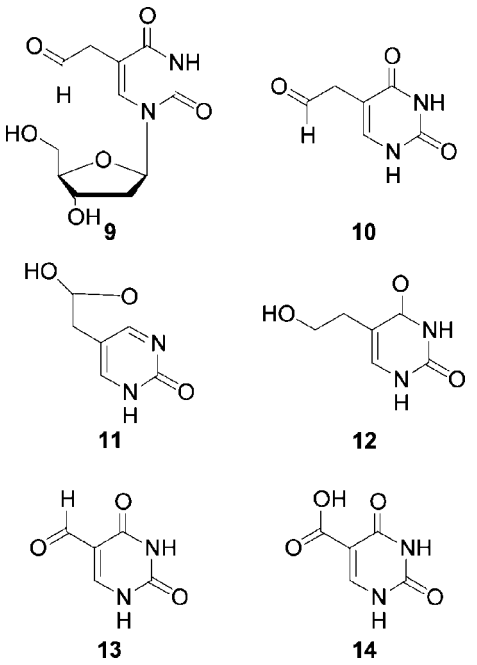
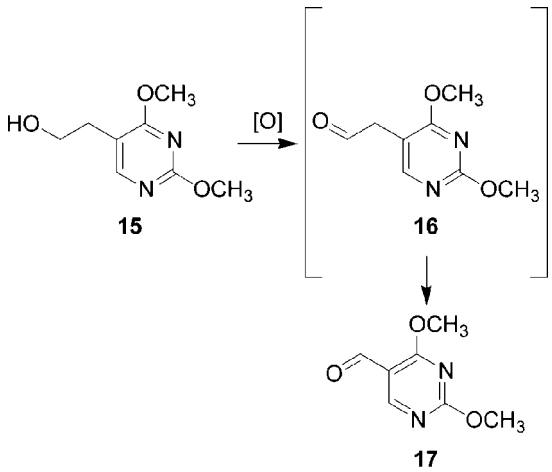


Figure 2. Aldehydes and the overoxidized by-products.



Scheme 1. Overoxidation reaction.

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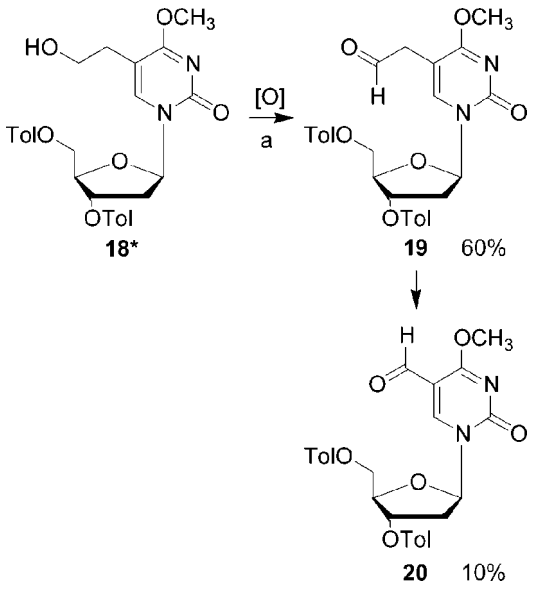

Scheme 2. *See ref [3], reagents and conditions a: 4 Å MS, PDC, CH_2Cl_2, rt, 25 min.

EXPERIMENTAL SECTION

TLC was performed on Polygram Sil G/UV 254 plates of Machery and Nagel, Düren. Detection was effective by exposure to UV light or by spraying with molybdatophosphoric acid (5% in ethanol). Column chromatography was performed on silica 60 (40–63 μm), Merck, Darmstadt, at a flow rate ranging from 2–4 mL/min under atmospheric pressure. Chemicals were purchased from Aldrich. $CHCl_3$ and CH_2Cl_2 were dehydrated by passing through a column filled with Al_2O_3 (neutral). Cation exchange resin (H^+ form, AG 50W-X8, 200–400 mesh) was purchased from Bio-Rad. Melting points were determined with a Büchi 535 apparatus and not corrected. Elemental analysis was performed at the Max Planck Institut für Medizinische Forschung in Heidelberg. NMR spectra were recorded with a Bruker AC-250 spectrometer at 250 MHz (^{1}H), 63 MHz (^{13}C) and 235 MHz (^{19}F), or AM-500 spectrometer at 500 MHz (^{1}H) and 125 MHz (^{13}C) in the Central Department of Spectroscopy of DKFZ. DFTCE ($C_2F_2Cl_4$) was used as external standard for ^{19}F-NMR. Electrospray ionization mass spectra (ESI-MS) were recorded with a Finnigan TSQ 7000 triple-quadrupole system. HRMS (FAB) experiment was carried out at Chemisches Institute der Universität Heidelberg.

1-(3,5-Di-*O*-p-toluoyl-2-deoxy-β-D-erythro-pentafuranosyl)-5-formylmethyl-4-methoxypyrimidin-2-one (19). To a flask containing CH_2Cl_2 (8 mL) was added an α and β-mixture of **18** (382 mg, 0.732 mmol) and powdered 4 Å MS (730 mg) and stirred under dry N_2. PDC (303 mg, 0.8 mmol) was added. After 20 min, the solvent was removed under reduced pressure to give a dry residue which was purified by the

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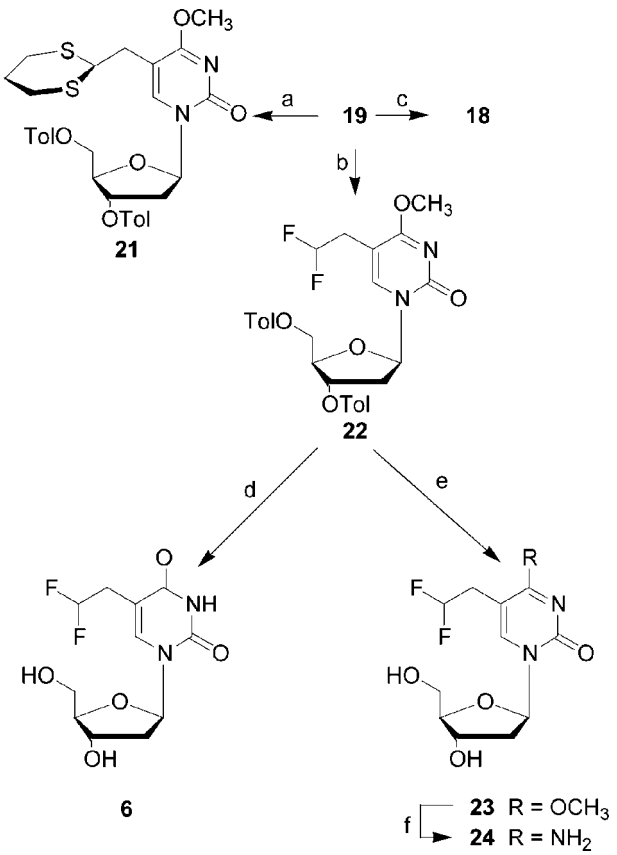

Scheme 3. Reagents and conditions: (a) 1,3-propanedithiol, $BF_3 \cdot 2HOAc$, $CHCl_3$, rt, 1 h, 65%; (b) DAST, CH_2Cl_2, rt, 1 h, 80%; (c) $NaBH_4$, THF, rt, 10 min, 90%; (d) (i) NaI, TMSCl, CH_3CN, rt, 5 min; (ii) NaOMe, MeOH, rt, 2 h, 87%; (e) NaOMe, MeOH, rt, 1 h, 64%; (f) NH_3, MeOH, 100°C, 72 h, 83%.

column chromatography with acetone/n-hexane 1:1 to afford β-form of **19** and α-form of **19** (226 mg, 60%) and **20** (41 mg, 10%). These white solids, which have a pleasant odor and are sensitive to moisture, should be carefully stored over P_4O_{10} under vacuum; mp: 181–183°C, anal. $C_{28}H_{28}N_2O_8$ calcd: C 64.62, H 5.39, N 5.39; found: C 64.76, H 5.60, N 5.42; MW: 520.54, ESI + Q1MS, $M_1 = 520$, $M_2 = 552$ (m/z); MeOH was used as solvent for ESI-MS analysis. The formyl group was attacked by MeOH. $[M_1 + H]^+ = 521.2$, $[M_2 + H]^+ = 553.2$, $[M_2 + Na]^+ = 575.2$, $[2M_1 + H]^+ = 1041.4$, $[M_1 + M_2 + H]^+ = 1073.4$, $[2M_2 + H]^+ = 1105.4$; ESI − Q1MS, $M_1 = 520$, $M_2 = 552$ (m/z) $[M_1 - H]^- = 519.1$, $[M_2 + Cl]^- = 587.1$, $[2M_1 - H]^- = 1039.4$, $[M_1 + M_2 - H]^- = 1071.4$, $[2M_2 + Cl]^- = 1139.8$ ^{1}H-NMR (250 MHz, $CDCl_3$): δ 2.24 (ddd, $J_{2'(a),2'(b)} = 14.8$, $J_{2'(a),1'} = 8.3$, $J_{2'(a),3'} = 6.6$ Hz, 1H, H-2′(a)), 2.41 (s, 3H, arom-CH_3), 2.44 (s, 3H, arom-CH_3), 2.98–3.19 (m, 3H, H-2′(b) + H-7), 3.94 (s, 3H, OCH_3), 4.58–4.59 (m, 1H, H-4′), 4.62 (dd, $J_{5'(a),5'(b)} = 11.4$, $J_{5'(a),4'} = 3.7$ Hz, 1H, H-5′(a)), 4.83 (dd, $J_{5'(b),5'(a)} = 11.4$, $J_{5'(b),4'} = 2.0$ Hz, 1H, H-5′(b)), 5.62 (d, $J = 6.6$ Hz,

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1H, H-3′), 6.45 (dd, $J_{1',2'(a)} = 8.3$, $J_{1',2'(b)} = 5.5$ Hz, 1H, H-1′), 7.22–7.30 (m, 4H, arom), 7.70 (s, 1H, H-6), 7.84–7.97 (m, 4H, arom), 9.43 (s, 1H, H-8 (CHO)). ^{13}C-NMR (62.90 MHz, $CDCl_3$): δ 21.66 (arom-$\underline{C}H_3$), 21.72 (arom-$\underline{C}H_3$), 39.31 (C-2′), 41.05 (C-7), 54.92 (4-O-CH_3), 64.14 (C-5′), 75.12 (C-3′), 83.61 (C-1′), 87.14 (C-4′), 100.52 (C-5), 126.30 ($\underline{C}$-CH_3, arom), 126.51 ($\underline{C}$-CH_3, arom), 129.28–130.27 ($\underline{C}H \times 8$, arom), 141.10 (C-6), 144.55 ($\underline{C}$-CO, arom), 144.62 ($\underline{C}$-CO, arom), 155.41 (C-2), 166.00 (arom-$\underline{C}O$), 166.17 (arom-$\underline{C}O$), 170.08 (C-4), 197.15 (C-8, CHO).

1-(3,5-Di-*O*-p-toluoyl-2-deoxy-α-D-erythro-pentafuranosyl)-5-formylmethyl-4-methoxypyrimidin-2-one (19α). White solids, pleasant odor; mp: 88–90°C, anal. $C_{28}H_{28}N_2O_8$, HRMS (FAB): m/z: calcd 521.1924 $[M+H]^+$, found 521.1894, −3.0 mmu, calcd 543.1743 $[M+Na]^+$; found 543.1733, −1.0 mmu, MW: 520.54, ESI + Q1MS, $M_1 = 520$, $M_2 = 552$ (m/z); MeOH was used as solvent for ESI-MS analysis. The formyl group of **19**α was attacked by MeOH. $[M_1+H]^+ = 521.2$, $[M_2+H]^+ = 553.2$, $[M_2+Na]^+ = 575.2$, $[2M_1+H]^+ = 1041.4$, $[M_1+M_2+H]^+ = 1073.4$, $[2M_2+H]^+ = 1105.4$; ESI − Q1MS, $M_1 = 520$, $M_2 = 552$ (m/z) $[M_1-H]^- = 519.1$, $[M_2+Cl]^- = 587.1$, $[2M_1-H]^- = 1039.4$, $[M_1+M_2-H]^- = 1071.4$, $[2M_2+Cl]^- = 1139.8$ ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.30 (s, 3H, arom-C$\underline{H}_3$), 2.36 (s, 3H, arom-C$\underline{H}_3$), 2.56–2.64 (m, 1H, H-2′(a)), 2.93 (ddd, $J_{2'(b),2'(a)} = 15.5$, $J_{2'(b),1'} = 6.7$, $J_{2'(b),3'} = 6.4$ Hz, 1H, H-2′(b)), 3.26 (m, 2H, H-7), 3.93 (s, 3H, OCH_3), 4.50 (dd, $J_{5'(a),5'(b)} = 12.1$, $J_{5'(a),4'} = 4.3$ Hz, 1H, H-5′(a)), 4.52 (dd, $J_{5'(b),5''(a)} = 12.1$, $J_{5'(b),4'} = 4.0$ Hz, 1H, H-5′(b)), 4.82–4.85 (t, $J = 4.2$ Hz, 1H, H-4′), 5.50–5.53 (d, $J = 6.0$ Hz, 1H, H-3′), 6.26–6.28 (d, $J = 6.7$, 1H, H-1′), 7.09–7.22 (m, 4H, arom), 7.58–7.60 (m, 2H, arom), 7.66 (s, 1H, H-6), 7.85–7.89 (m, 2H, arom), 9.46 (s, 1H, H-8(CHO)). ^{13}C-NMR (62.896 MHz, $CDCl_3$): δ 21.67 (arom-$\underline{C}H_3$), 38.88 (C-2′), 41.11 (C-7), 54.97 (4-O-CH_3), 64.02 (C-5′), 74.95 (C-3′), 85.87 (C-1′), 89.22 (C-4′), 99.44 (C-5), 126.17 ($\underline{C}$-CH_3, arom), 126.53 ($\underline{C}$-CH_3, arom), 129.23 ($\underline{C}$H, arom), 129.34 ($\underline{C}$H, arom), 129.47 ($\underline{C}$H, arom), 129.69 ($\underline{C}$H, arom), 141.56 (C-6), 144.28 ($\underline{C}$-CO, arom), 144.62 ($\underline{C}$-CO, arom), 155.49 (C-2), 165.54 (arom-$\underline{C}O$), 166.13 (arom-$\underline{C}O$), 170.23 (C-4), 197.19 (C-8, CHO).

1-(3,5-Di-*O*-p-toluoyl-2-deoxy-β,α-D-erythro-pentafuranosyl)-5-formyl-4-methoxypyrimidin-2-one (20β□ + 20α□ → 20β + 20α). White solids, pleasant odor; mp: 161–165°C, anal. $C_{27}H_{26}N_2O_8$, HRMS (FAB): m/z: calcd 507.1767 $[M+H]^+$, found 507.1757, −1.1 mmu, calcd 529.1587, $[M+Na]^+$; found 529.1603, 1.7 mmu, MW: 506.51, ESI + Q1MS, $M_1 = 506$, $M_2 = 538$ (m/z); $[M_1+H]^+ = 507.1$, $[M_1+Na]^+ = 529.1$, $[M_2+H]^+ = 539.1$, $[M_2+Na]^+ = 561.1$, $[2M_1+H]^+ = 1013.3$, $[2M_1+Na]^+ = 1035.3$ ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.22–2.33 (m, 1H,H-2_{β}′(a)), 2.38–2.43 (m, 12 H, arom-C$\underline{H}_3$(α,β)), 2.58–2.64 (m, 1H, H-2_{α}′(a)), 2.97–3.16 (m, 2H, H-$2_{\alpha,\beta}$′(b)), 4.07 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 4.55–4.57 (m, 2H, H-$5_{\alpha,\beta}$′(a)), 4.70–4.75 (m, 3H, H-4_{β}′ + H-$5_{\alpha,\beta}$′(b)), 5.04–5.08 (t, $J = 4.2$, 1H, H-4_{α}′), 5.58–5.66 (m, 2H, H-$3_{\alpha,\beta}$′), 6.30–6.36 (m, 2H, H-$1_{\alpha,\beta}$′), 7.12–7.30 (m, 8H, $arom_{\alpha,\beta}$), 7.64–7.86 (m, 4H, $arom_{\alpha}$), 7.92–7.96 (m, 4H, $arom_{\beta}$), 8.64 (s, 1H, H-6_{α}), 8.67 (s, 1H, H-6_{β}), 9.78 (s, 1H, H-7_{β} (C$\underline{H}$O)), 9.93 (s, 1H, H-7_{α} (C$\underline{H}$O)). ^{13}C-NMR (62.896 MHz, $CDCl_3$): δ 21.60 (arom-$\underline{C}H_3$), 21.65 (arom-$\underline{C}H_3$), 39.26 (C-2_{β}′), 39.74 (C-2_{α}′), 55.03 (4-O-$CH_{3\alpha,\beta}$), 63.86 (C-$5_{\alpha,\beta}$′), 74.53 (C-3_{α}′), 75.03 (C-3_{β}′), 84.32 (C-1_{β}′), 86.06 (C-1_{α}′), 88.35 (C-4_{β}′), 89.72 (C-4_{α}′), 106.38 (C-5_{β}), 106.99 (C-5_{α}),

125.86 (C-CH_3, arom), 126.23 (C-CH_3, arom), 126.37 (C-CH_3, arom), 126.41 (C-CH_3, arom), 129.14 (CH, arom), 129.21 (CH, arom), 129.33 (CH, arom), 129.55 (CH, arom), 129.65 (CH, arom), 129.79 (CH, arom), 144.28 (C-CO, arom), 144.31 (C-CO, arom), 144.48 (C-CO, arom), 144.59 (C-CO, arom), 146.65 (C-6_β), 146.93 (C-6_α), 154.06 (C-2_α), 154.24 (C-2_β), 165.21 (arom-CO), 165.93 (arom-CO), 165.99 (arom-CO), 169.87 (C-4_α), 170.17 (C-4_β), 183.94 (C-7_α, CHO), 184.30 (C-7_β, CHO).

1-(3,5-Di-*O*-p-toluoyl-2-deoxy-β-D-erythro-pentafuranosyl)-5-[(1,3-dithian-2-yl) methyl]-4-methoxypyrimidin-2-one (21). To a mixture of α,β form of **19** (184 mg, 0.35 mmol) in dry $CHCl_3$ (5 mL) were added 1,3-propanedithiol (76 mg, 0.70 mmol) and $BF_3{\cdot}2HOAc$ (67 mg, 0.35 mmol) sequentially. This reaction was stirred at rt for 1 h, extracted with satd $NaHCO_3$ (2×2 mL) and washed with water (1 mL). The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure at 40°C. The residue obtained was chromatographed with acetone/*n*-hexane 1:1 to give β-form of **21** and α-form of **21** (141 mg, 65%). colorless solid, mp: 64°C (dec.), anal. $C_{31}H_{34}N_2O_7S_2$, HRMS (FAB): *m/z*: calcd 611.1886 $[M+H]^+$, found 611.1874, −1.1 mmu, calcd 633.1705 $[M+Na]^+$, found 633.1711, +0.6 mmu, MW: 610.75, ESI + Q1MS, M = 610 (m/z); $[M+H]^+ = 611.0$, $[M+Na]^+ = 633.1$; ESI−Q1MS, M = 610 (m/z); $[M+{}^{35}Cl]^- = 644.9$. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.74–1.88 (m, 1H, H-10[a]), 2.02–2.11 (m, 1H, H-10[a]), 2.31 (ddd, $J_{2'(a),2'(b)} = 14.4$, $J_{2'(a),1'} = 8.3$, $J_{2'(a),3'} = 6.6$ Hz, 1H, H-2′(a)), 2.42 (s, 3H, arom-CH_3), 2–43 (s, 3H, arom-CH_3), 2.59 (d, $J_{7,8} = 7.3$ Hz, 2H, H-7), 2.71–2.79 (m, 4H, H-9 + H-11[a]), 3.00 (ddd, $J_{2'(b),2'(a)} = 14.4$, $J_{2'(b),1'} = 5.5$, $J_{2'(b),3'} = 1.5$ Hz, 1H, H-2′(b)), 3.98 (s, 3H, OCH_3), 4.05 (t, $J_{8,7} = 7.3$ Hz, H-8), 4.58–4.61 (m, 1H, H-4′), 4.65 (dd, $J_{5'(a)'5'(b)} = 12.0$, $J_{5'(a),4'} = 4.0$ Hz, 1H, H-5′(a)), 4.71–4.77 (dd, $J_{5'(b)'5'(a)} = 12.0$, $J_{5'(b),4'} = 3.2$ Hz, 1 H, H-5′(b)), 5.59–5.61 (d, $J = 6.5$ Hz, 1H, H-3′), 6.44 (dd, $J_{1',2'(a)} = 8.3$, $J_{1',2'(b)} = 5.5$ Hz, 1H, H-1′), 7.23–7.29 (m, 4 H, arom), 7.70 (s, 1H, H-6), 7.87–7.97 (m, 4H, arom). ^{13}C-NMR (62.896 MHz, $CDCl_3$): δ 21.67 (arom-CH_3), 25.58 (C-7), 29.73 (C-9 or C-11), 29.76 (C-11 or C-9), 32.37 (C-10), 39.15 (C-2′), 45.49 (C-8), 54.70 (4-O-CH_3), 64.24 (C-5′), 75.07 (C-3′), 83.35 (C-1′), 86.99 (C-4′), 104.42 (C-5), 126.35 (C-CH_3, arom), 126.61 (C-CH_3, arom), 129.21 (CH, arom), 129.40 (CH, arom), 129.59 (CH, arom), 129.83 (CH, arom), 140.51 (C-6), 144.24 (C-CO, arom), 144.41 (C-CO, arom), 155.40 (C-2), 166.06 (arom-CO), 166.08 (arom-CO), 170.16 (C-4).

1-(3,5-Di-*O*-p-toluoyl-2-deoxy-α-D-erythro-pentafuranosyl)-5-[(1,3-dithian-2-yl) methyl]-4-methoxypyrimidin-2-one (21α). Colorless solid, mp: 69°C (dec.), anal. $C_{31}H_{34}N_2O_7S_2$, MW: 610.75, ESI + Q1MS, M = 610 (m/z); $[M+H]^+ = 611.1$, $[M+Na]^+ = 633.1$, $[2M+H]^+ = 1221.5$, $[2M+Na]^+ = 1243.4$; ESI − Q1MS, M = 610 (m/z); $[M+{}^{35}Cl]^- = 645.0$; $[2M+{}^{35}Cl]^- = 1255.7$ ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.71–1.83 (m, 1H, H-10), 2.00–2.08 (m, 1H, H-10), 2.40 (s, 3H, arom-CH_3), 2.43 (s, 3H, arom-CH_3), 2.49–2.80 (m, 7H, H-7 + H-2′(a) + H-9+H-11),

[a]Protons H-9, H-10 and H-11 were identified by two-dimensional ^{1}H-NMR (COSY).

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2.96 (ddd, $J_{2'(b),2'(a)} = 15.4$, $J_{2'(b),1'} = 6.5$, $J_{2'(b),3'} = 6.4$Hz, 1H, H-2′(b)), 3.94–4.09 (m, 4H, -OCH_3 + H-8), 4.57–4.60 (d, 2 H, H-5′), 4.88–4.91 (t, $J = 3.0$ Hz, 1H, H-4′), 5.53–5.56 (d, $J = 5.2$ Hz, H-3′), 6.31 (dd, $J_{1',2'(b)} = 6.5$, $J_{1',2'(a)} = 1.4$Hz, 1H, H-1′), 7.16–7.30 (m, 4H, arom), 7.55–7.69 (m, 2 H, arom), 7.74 (s, 1H, H-6), 7.92–7.96 (m, 2H, arom). ^{13}C-NMR (62.90 MHz, $CDCl_3$): δ 21.66 (arom-$\underline{C}H_3$), 25.58 (C-7), 29.90 (C-9 or C-11), 30.05 (C-11 or C-9), 32.55 (C-10), 38.76 (C-2′), 45.79 (C-8), 54.75 (4-O-CH_3), 64.08 (C-5′), 75.00 (C-3′), 85.72 (C-1′), 89.17 (C-4′), 103.43 (C-5), 126.29 (C-CH_3, arom), 126.61 (C-CH_3, arom), 129.09 (CH, arom), 129.31 (CH, arom), 129.66 (CH, arom), 129.68 (CH, arom), 141.20 (C-6), 144.20 (C-CO, arom), 144.35 (C-CO, arom), 155.55 (C-2), 165.70 (arom-CO), 166.12 (arom-CO), 170.32 (C-4).

1-(3,5-Di-*O*-p-toluoyl-2-deoxy-β-D-erythro-pentafuranosyl)-5-(2,2-difluoroethyl)-4-methoxypyrimidin-2-one (22). A mixture of α,β form of **19** (136 mg, 0.26 mmol) dissolved in dry CH_2Cl_2 (3 mL) was stirred at rt and treated with DAST (110 mg, 0.68 mmol). The stirring was continued at rt for 1 h. CH_2Cl_2 (7 mL) was added. The organic layer was extracted with cold satd $NaHCO_3$ (2 mL), washed once with water (3 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure at 40°C. The residue obtained was chromatographed with acetone/*n*-hexane 2:3 to give β-form of **22** and α-form of **22** (112 mg, 80%). pale yellow crystals; mp: 168–169°C, anal. $C_{28}H_{28}N_2O_7F_2$, MW: 542.54, ESI + Q1MS, M = 542 (m/z); $[M + H]^+ = 543.1$, $[M + Na]^+ = 565.2$; ESI − Q1MS, M = 542 (m/z); $[M + {}^{35}Cl]^- = 577.1$. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.24 (ddd, $J_{2'(a),2'(b)} = 14.7$, $J_{2'(a),1'} = 8.4$, $J_{2'(a),3'} = 6.6$ Hz, 1H, H-2′(a)), 2.42 (s, 3H, arom-CH_3), 2.44 (s, 3H, arom-CH_3), 2.61 (ttd, $J_{7,F} = 20.9$, $J_{7(a),7(b)} = 4.7$, $J_{7,8} = 4.7$, $J_{7,6} = 0.7$ Hz, 2H, H-7(a), H-7(b)), 3.00 (ddd, $J_{2'(b),2'(a)} = 14.7$, $J_{2'(b),1'} = 5.5$, $J_{2'(b),3'} = 1.5$, 1H, H-2′(b)), 3.98 (s, 3H, OCH_3), 4.58–4.60 (m, 1H, H-4′), 4.65 (dd, $J_{5'(a),5'(b)} = 12.2$, $J_{5'(a),4'} = 3.8$ Hz, 1H, H-5′(a)), 4.79 (dd, $J_{5'(b),5'(a)} = 12.2$, $J_{5'(b),4'} = 2.9$ Hz, 1H, H-5′(b)), 5.60–5.62 (m, 1H, H-3′), 5.73 (tt, $J_{8,F} = 56.7$, $J_{8,7} = 4.7$ Hz, 1H, H-8), 6.43 (dd, $J_{1',2'(a)} = 8.4$, $J_{1',2'(b)} = 5.5$ Hz, 1H, H-1′), 7.23–7.29 (m, 4H, arom), 7.70 (t, $J_{6,\ 7} = 0.7$ Hz, 1H, H-6), 7.86–7.97 (m, 4H, arom).^{13}C-NMR (125.76 MHz, $CDCl_3$) : δ 21.65 (arom-$\underline{C}H_3$), 21.72 (arom-$\underline{C}H_3$), 31.89 (t, $J_{7,F} = 24.3$ Hz, C-7), 39.28 (C-2′), 54.95 (4-O-CH_3), 64.06 (C-5′), 75.09 (C-3′), 84.59 (C-1′), 87.05 (C-4′), 100.24 (t, $J_{5,F} = 6.9$ Hz, C-5), 114.43 (t, $J_{8,F} = 241.2$ Hz, C-8), 126.33 (C-CH_3, arom), 126.53 (C-CH_3, arom), 129.28 (CH, arom), 129.45 (CH, arom), 129.49 (CH, arom), 129.88 (CH, arom), 141.70 (C-6), 144.52 (C-CO, arom), 144.53 (C-CO, arom), 155.30 (C-2), 166.05 (arom-CO), 166.16 (arom-CO), 170.00 (C-4).^{19}F-NMR (235.34 MHz, $CDCl_3$): δ −40.77 (dt, $J_{F,H\text{-}8} = 56.7$, $J_{F,H\text{-}7} = 16.3$ Hz, CF_2H).

1-(3,5-Di-*O*-p-toluoyl-2-deoxy-α-D-erythro-pentafuranosyl)-5-(2,2-difluoroethyl)-4-methoxypyrimidin-2-one (22α). White crystals; mp: 135–138°C, anal. $C_{28}H_{28}N_2O_7F_2$ calcd: C 61.99, H 5.17, N 5.17; found: C 62.35, H 5.38, N 5.18; MW: 542.54, ESI + Q1MS, M = 542 (m/z); $[M + H]^+ = 543.2$, $[M + Na]^+ = 565.2$, $[M + K]^+ = 581.2$; ESI − Q1MS, M = 542 (m/z); $[M + {}^{35}Cl]^- = 577.1$ ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.40 (s, 3H, arom-C$\underline{H}_3$), 2.43 (s, 3H, arom-C$\underline{H}_3$), 2.68 (ddd, $J_{2'(a),2'(b)} = 15.5$,

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$J_{2'(a),1'} = 1.4$, $J_{2'(a),3'} = 0.9$ Hz, 1H, H-2′(a)), 2.82 (tt, $J_{7,F} = 16.4$, $J_{7(a),7(b)} = 3.7$, $J_{7,8} = 3.7$ Hz, 2H, H-7), 3.00 (dt, $J_{2'(b),2'(a)} = 15.5$, $J_{2'(b),1'} = 6.6$, $J_{2'(b),3'} = 6.5$ Hz, 1H, H-2′(b)), 4.03 (s, 3H, OCH_3), 4.56–4.58 (d, $J = 4.5$ Hz, 2H, H-5′), 4.88–4.91 (t, $J = 3.9$ Hz, 1H, H-4′), 5.57–5.59 (d, $J = 6.3$ Hz, 1H, H-3′), 5.75 (tt, $J_{8,F} = 56.8$, $J_{8,7} = 3.7$ Hz, 1H, H-8), 6.31 (dd, $J_{1',2'(b)} = 6.6$, $J_{1',2'(a)} = 1.4$Hz, 1H, H-1′), 7.15–7.30 (m, 4H, arom), 7.66–7.69 (m, 2H, arom), 7.73 (s, 1H, H-6), 7.93–7.96 (m, 2H, arom). ^{13}C-NMR (62.896 MHz, $CDCl_3$): δ 21.69 (arom-$\underline{C}H_3$), 32.02 (t, $J_{7,F} = 24.3$ Hz, C-7), 38.93 (C-2′), 54.97 (4-O-CH_3), 64.04 (C-5′), 74.92 (C-3′), 85.83 (C-1′), 89.25 (C-4′), 99.14 (t, $J_{5,F} = 6.8$ Hz, C-5), 114.57 (t, $J_{8,F} = 241.2$ Hz, C-8), 126.18 ($\underline{C}$-CH_3, arom), 126.56 ($\underline{C}$-CH_3, arom), 129.15 ($\underline{C}$H, arom), 129.36 ($\underline{C}$H, arom), 129.51 ($\underline{C}$H, arom), 129.71 ($\underline{C}$H, arom), 142.19 (C-6), 144.29 ($\underline{C}$-CO, arom), 144.55 ($\underline{C}$-CO, arom), 155.62 (C-2), 165.62 (arom-$\underline{C}$O), 166.13 (arom-$\underline{C}$O), 170.18 (C-4) ^{19}F-NMR (235.34 MHz, $CDCl_3$): δ −40.33 (dt, $J_{F,H\text{-}8} = 56.8$, $J_{F,H\text{-}7} = 16.4$Hz, CF_2H).

1-(2-Deoxy-β-D-erythro-pentafuranosyl)-5-(2,2-difluoroethyl)pyrimidin-2,4(3H)-dione (6). A solution of **22** (30 mg, 0.055 mmol) in dry CH_3CN (0.5 mL) was stirred under dry N_2 at rt. The reaction was subjected to the sequential addition of NaI (16.5 mg, 0.11 mmol) and Me_3SiCl (10.5 μL, 0.083 mmol). After 5 min the solvent was evaporated under reduced pressure at 40°C. To the resulting residue was added MeOH (1 mL) and NaOMe/MeOH (1 mL, 0.2 N). The mixture was stirred at rt for another 2 h. Cation exchange resin (AG 50WX-8) was added to neutralize to pH 7. After filtration and concentration under reduced pressure at 40°C, the residue (61 mg) obtained was chromatographed with silica gel column (MeOH/$CHCl_3$ 1:9) to give **6** in 87% yield (14 mg). Pale yellow crystals, mp: 166–170°C, anal. $C_{11}H_{14}N_2O_5F_2$ calcd: C 45.21, H 4.83, N 9.59; found: C 44.80, H 5.01, N 9.35; anal. $C_{11}H_{14}N_2O_5F_2$, HRMS (FAB): m/z: calcd 293.0949 $[M+H]^+$, found 293.0969, +2.0 mmu, calcd 315.0769 $[M+Na]^+$; found 315.0776, +0.8 mmu, MW: 292.24, ESI + Q1MS, M = 292 (m/z); $[M+H]^+ = 292.9$, $[M+Na]^+ = 314.9$; ESI − Q1MS, M = 292 (m/z); $[M-H]^- = 291.0$, $[2M-H]^- = 583.1$, ^{1}H-NMR (250 MHz, CD_3OD) δ 2.18 (ddd, $J_{2'(a),2'(b)} = 13.6$, $J_{2'(a),1'} = 7.0$, $J_{2'(a),3'} = 6.1$Hz, 1H, H-2′(a)), 2.28 (ddd, $J_{2'(b),2'(a)} = 13.6$, $J_{2'(b),1'} = 6.2$, $J_{2'(b),3'} = 3.8$ Hz, 1H, H-2′(b)), 2.83 (tdd, $J_{7,F} = 16.5$, $J_{7,\ 8} = 4.6$, $J_{7(a),7(b)} = 3.9$ Hz, 2H, H-7), 3.71 (dd, $J_{5'(a),5'(b)} = 12.0$, $J_{5'(a),4'} = 3.6$ Hz, 1H, H-5′(a)), 3.79 (dd, $J_{5'(b),5'(a)} = 12.0$, $J_{5'(b),4'} = 3.2$ Hz, 1H, H-5′(b)), 3.91 (ddd, $J_{4',5'(a)} = 3.6$, $J_{4',3'} = 3.4$, $J_{4',5'(b)} = 3.2$ Hz, 1H, H-4′), 4.38 (ddd, $J_{3',2'(a)} = 6.1$, $J_{3',2'(b)} = 3.8$, $J_{3',4'} = 3.4$Hz, 1H, H-3′), 5.99 (tt, $J_{8,F} = 57.1$, $J_{8,7} = 4.6$ Hz, 1H, H-8), 6.24 (dd, $J_{1',2'(a)} = 7.0$, $J_{1',2'(b)} = 6.2$ Hz, 1H, H-1′), 7.99 (s, 1H, H-6). ^{13}C-NMR (62.896 MHz, CD_3OD): δ 32.96 (t, $J_{7,F} = 24.4$ Hz, C-7), 41.47 (C-2′), 62.74 (C-5′), 72.11 (C-3′), 86.64 (C-1′), 88.98 (C-4′), 107.25 (C-5), 116.50 (t, $J_{8,F} = 239.4$Hz, C-8), 141.36 (C-6), 152.06 (C-2), 165.49 (C-4). ^{19}F-NMR (235.34 MHz, CD_3OD): δ −41.77 (dtd, $J_{F,H\text{-}8} = 57.1$, $J_{F,H\text{-}7} = 16.5$, $J_{F,F} = 10.5$ Hz, CF_2H).

1-(2-Deoxy-α-D-erythro-pentafuranosyl)-5-(2,2-difluoroethyl)pyrimidin-2,4(3H)-dione (6α). Pale yellow viscous gum, anal. $C_{11}H_{14}N_2O_5F_2$, HRMS (FAB): m/z: calcd 293.0949 $[M+H]^+$, found 293.0954, +0.5 mmu, calcd 315.0769 $[M+Na]^+$; found 315.0770, +0.1 mmu, MW: 292.24, ESI + Q1MS, M = 292 (m/z); $[M+H]^+ = 292.9$, $[M+Na]^+ = 314.9$; ESI − Q1MS, M = 292 (m/z);

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$[M-H]^- = 291.0$, $[M + {}^{35}Cl]^- = 326.9$, $[2M - H]^- = 583.1$ ^{1}H-NMR (250 MHz, CD_3OD) δ 2.05 (ddd, $J_{2'(a),2'(b)} = 14.6$, $J_{2'(a),1'} = 2.5$, $J_{2'(a),3'} = 2.0$ Hz, 1H, H-2′(a)), 2.65 (ddd, $J_{2'(b),2'(a)} = 14.6$, $J_{2'(b),1'} = 7.3$, $J_{2'(b),3'} = 6.0$ Hz, 1H, H-2′(b)), 2.85 (td, $J_{7,F} = 16.7$, $J_{7,8} = 4.6$ Hz, 2H, H-7), 3.55 (dd, $J_{5'(a),5'(b)} = 12.0$, $J_{5'(a),4'} = 4.5$ Hz, 1H, H-5′(a)), 3.60 (dd, $J_{5'(b),5'(a)} = 12.0$, $J_{5'(b),4'} = 4.3$ Hz, 1H, H-5′(b)), 4.29 (td, $J_{4',5'(a)} = 4.5$, $J_{4',5'(b)} = 4.3$, $J_{4',3'} = 2.0$ Hz, 1H, H-4′), 4.34 (dt, $J_{3',2'(b)} = 6.0$, $J_{3',2'(a)} = 2.0$, $J_{3',4'} = 2.0$ Hz, 1H, H-3′), 5.98 (tt, $J_{8,F} = 57.1$, $J_{8,7} = 4.6$ Hz, 1H, H-8), 6.17 (dd, $J_{1',2'(b)} = 7.3$, $J_{1',2'(a)} = 2.5$ Hz, 1H, H-1′), 7.89 (s, 1H, H-6). ^{13}C-NMR (62.896 MHz, CD_3OD): δ 32.96 (t, $J_{7,F} = 24.1$Hz, C-7), 41.76 (C-2′), 63.45 (C-5′), 72.43 (C-3′), 88.59 (C-1′), 91.26 (C-4′), 106.29 (t, $J_{5,F} = 7.0$ Hz, C-5), 116.49 (t, $J_{8,F} = 239.5$ Hz, C-8), 142.04 (C-6), 152.16 (C-2), 165.76 (C-4). ^{19}F-NMR (235.34 MHz, CD_3OD): δ −41.58 (dtd, $J_{F,H\text{-}8} = 57.1$, $J_{F,H\text{-}7} = 16.6$, $J_{F,F} = 9.1$Hz, CF_2H).

1-(2-Deoxy-β-D-erythro-pentafuranosyl)-5-(2,2-difluoroethyl)-4-methoxypyrimidin-2-one (23). To a methanol solution of **22** (50 mg, 0.092 mmol, 1 mL) was added NaOMe/MeOH (1 mL, 0.3 N). After 1 h, a solution of 1N HCl/ether was added to neutralize the reaction. The solvent was then evaporated under reduced pressure at 40°C. The residue obtained was chromatographed with $MeOH/CHCl_3$ (1:9) to give **23** in 64% (18 mg) yield. Colorless crystals, mp: 155–157.5°C, anal. $C_{12}H_{16}N_2O_5F_2$, HRMS (FAB): *m/z*: calcd 307.1106 $[M + H]^+$, found 307.1144, +3.9 mmu, calcd 329.0925 $[M + Na]^+$; found 329.0961, +3.6 mmu, MW: 306.25, ESI + Q1MS, M = 306 (m/z); $[M + H]^+ = 307.0$, $[M + Na]^+ = 329$, $[2M + H]^+ = 613.2$, $[2M + Na]^+ = 635.2$, $[3M + Na]^+ = 941.2$; ESI − Q1MS, M = 306 (m/z); $[M-H]^- = 304.8$, $[M+{}^{35}Cl]^- = 340.9$, $[2M-H]^- = 611.0$, $[2M + {}^{35}Cl]^- = 647.0$, $[3M-H]^- = 917.0$. ^{1}H-NMR (250 MHz, CD_3OD) δ 2.13 (ddd, $J_{2'(a),2'(b)} = 13.6$, $J_{2'(a),3'} = 6.3$, $J_{2'(a),1'} = 6.0$ Hz, 1H, H-2′(a)), 2.43 (ddd, $J_{2'(b),2'(a)} = 13.6$, $J_{2'(b),1'} = 6.2$, $J_{2'(b),3'} = 4.4$Hz, 1H, H-2′(b)), 2.92 (td, $J_{7,F} = 16.6$, $J_{7,8} = 4.5$ Hz, 2H, H-7), 3.71 (dd, $J_{5'(a),5'(b)} = 12.1$, $J_{5'(a),4'} = 3.7$ Hz, 1H, H-5′(a)), 3.79 (dd, $J_{5'(b),5'(a)} = 12.1$, $J_{5'(b),4'} = 3.2$ Hz, 1H, H-5′(b)), 3.95 (s, 3H, OCH_3), 3.98 (ddd, $J_{4',3'} = 4.1$, $J_{4',5'(a)} = 3.7$, $J_{4',5'(b)} = 3.2$ Hz, 1H, H-4′), 4.35 (ddd, $J_{3',2'(a)} = 6.3$, $J_{3',2'(b)} = 4.4$, $J_{3',4'} = 4.1$Hz, 1H, H-3′), 5.98 (tt, $J_{8,F} = 56.7$, $J_{8,7} = 4.5$ Hz, 1H, H-8), 6.19 (dd, $J_{1',2'(b)} = 6.2$, $J_{1',2'(a)} = 6.0$ Hz, H-1′), 8.30 (s, 1H, H-6). ^{13}C-NMR (62.896 MHz, CD_3OD): δ 32.66 (t, $J_{7,F} = 24.1$Hz, C-7), 42.41 (C-2′), 55.32 (4-O-CH_3), 62.38 (C-5′), 71.54 (C-3′), 88.32 (C-1′), 89.29 (C-4′), 102.05 (t, $J_{5,F} = 6.9$ Hz, C-5), 116.52 (t, $J_{8,F} = 239.6$ Hz, C-8), 144.95 (C-6), 157.87 (C-2), 171.88 (C-4). ^{19}F-NMR (235.34 MHz, CD_3OD): δ − 40.09 (dtd, $J_{F,H\text{-}8} = 56.7$, $J_{F,H\text{-}7} = 16.5$, $J_{F,F} = 1.0$ Hz, CF_2H).

1-(2-Deoxy-α-D-erythro-pentafuranosyl)-5-(2,2-difluoroethyl)-4-methoxypyrimidin-2-one (23α). Colorless foam, anal. $C_{12}H_{16}N_2O_5F_2$, HRMS (FAB): *m/z*: calcd 307.1106 $[M + H]^+$, found 307.1122, +1.6 mmu, calcd 329.0925 $[M + Na]^+$; found 329.0930, +0.5 mmu, MW: 306.25, ESI + Q1MS, M = 306 (m/z); $[M + Na]^+ = 328.8$; ESI − Q1MS, M = 306 (m/z); $[M+{}^{35}Cl]^- = 340.8$ ^{1}H-NMR (250 MHz, CD_3OD) δ 2.08 (ddd, $J_{2'(a),2'(b)} = 14.6$, $J_{2'(a),1'} = 1.9$, $J_{2'(a),3'} = 1.7$ Hz, 1H, H-2′(a)), 2.65 (ddd, $J_{2'(b),2'(a)} = 14.6$, $J_{2'(b),1'} = 7.0$, $J_{2'(b),3'} = 5.7$ Hz, 1H, H-2′(b)), 2.88 (td, $J_{7,F} = 16.6$, $J_{7,8} = 4.5$ Hz, 2H, H-7), 3.55–3.59 (m, 2H, H-5′), 3.94 (s, 3H, OCH_3), 4.31 (dt, $J_{3',2'(b)} = 5.7$, $J_{3',2'(a)} = 1.7$, $J_{3',4'} = 1.7$ Hz, 1H, H-3′), 4.36 (td, $J_{4',5'} = 4.5$,

$J_{4',3'} = 1.7$ Hz, 1H, H-4′), 5.95 (tt, $J_{8,F} = 56.8$, $J_{8,7} = 4.5$ Hz, 1H, H-8), 6.10 (dd, $J_{1',2'(b)} = 7.0$, $J_{1',2'(a)} = 1.9$ Hz, 1H, H-1′), 8.01 (s, 1H, H-6). ^{13}C-NMR (62.896 MHz, CD_3OD): δ 32.62 (t, $J_{7,F} = 24.1$Hz, C-7), 42.18 (C-2′), 55.28 (4-O-CH_3), 63.48 (C-5′), 72.53 (C-3′), 90.36 (C-1′), 91.85 (C-4′), 101.24 (t, $J_{5,F} = 6.6$ Hz, C-5), 116.63 (t, $J_{8,F} = 239.7$ Hz, C-8), 145.38 (C-6), 157.98 (C-2), 171.98 (C-4). ^{19}F-NMR (235.34 MHz, CD_3OD): δ −41.62 (dtd, $J_{F,H-8} = 56.7$, $J_{F,H-7} = 16.6$, $J_{F,F} = 16.1$Hz, CF_2H).

1-(2-Deoxy-β-D-erythro-pentafuranosyl)-4-amino-5-(2,2-difluoroethyl)pyrimidin-2-one (24). Compound **23** (14 mg, 0.046 mmol) was dissolved in the methanol solution (15 mL) which had been saturated with ammonia at 0°C. The solution was transferred to a Teflon tube which was sealed in a stainless reaction vessel. The reaction was heated at 100°C for 72 h. The solvent was then evaporated under reduced pressure at 40°C, while pale yellow crystals was formed on the inner wall of the flask. These crystals were washed with cold methanol and dried under vacuum (4 mbar). The yield of **24** was 83% (11 mg). Pale yellow crystals, mp: 185–191°C, anal. $C_{11}H_{15}N_3O_4F_2$, HRMS (FAB): m/z: calcd 292.1109 $[M+H]^+$, found 292.1099, −1.0 mmu, calcd 314.0928 $[M+Na]^+$, found 314.0930, +0.2 mmu, MW: 291.26, ESI + Q1MS, M = 291 (m/z); $[M+H]^+ = 291.8$, $[2M+H]^+ = 583.0$, $[2M+Na]^+ = 605.0$; ESI − Q1MS, M = 291 (m/z); $[M-H]^- = 289.9$, $[M+^{35}Cl]^- = 325.8$, $[2M-H]^- = 581.1$, $[2M+^{35}Cl]^- = 617.0$. ^{1}H-NMR (250 MHz, CD_3OD) δ 2.13 (ddd, $J_{2'(a),2'(b)} = 13.6$ Hz, $J_{2'(a),1'} = 6.9$ Hz, $J_{2'(a),3'} = 6.7$ Hz, 1H, H-2′(a)), 2.34 (ddd, $J_{2'(b),2'(a)} = 13.6$, $J_{2'(b),1'} = 6.1$, $J_{2'(b),3'} = 4.1$Hz, 1H, H-2′(b)), 2.92 (td, $J_{7,F} = 16.9$, $J_{7,8} = 4.3$ Hz, 2H, H-7), 3.69 (dd, $J_{5'(a),5'(b)} = 12.1$, $J_{5'(a),4'} = 3.8$ Hz, 1H, H-5′(a)), 3.79 (dd, $J_{5'(b),5'(a)} = 12.1$, $J_{5'(b),4'} = 3.2$ Hz, 1H, H-5′(b)), 3.91 (td, $J_{4',3'} = 3.8$, $J_{4',5'(a)} = 3.8$, $J_{4',5'(b)} = 3.2$ Hz, 1H, H-4′), 4.34 (ddd, $J_{3',2'(a)} = 6.7$, $J_{3',2'(b)} = 4.1$, $J_{3',4'} = 3.8$ Hz, 1H, H-3′), 5.96 (tt, $J_{8,F} = 56.4$, $J_{8,7} = 4.3$ Hz, 1H, H-8), 6.19 (dd, $J_{1',2'(a)} = 6.9$, $J_{1',2'(b)} = 6.1$Hz, 1H, H-1′), 8.00 (s, 1H, H-6). ^{13}C-NMR (62.896 MHz, CD_3OD): δ 33.11 (t, $J_{7,F} = 23.6$ Hz, C-7), 42.20 (C-2′), 62.61 (C-5′), 71.79 (C-3′), 87.66 (C-1′), 88.95 (C-4′), 99–100.5 (C-5)[b], 116.75 (t, $J_{8,F} = 240.2$ Hz, C-8), 143.64 (C-6), 157.81 (C-2)[b], 166.80 (C-4). ^{19}F-NMR (235.34 MHz, CD_3OD): δ −39.82 (dtd, $J_{F,H-8} = 56.4$, $J_{F,H-7} = 16.9$, $J_{F,F} = 3.2$ Hz, CF_2H).

1-(2-Deoxy-α-D-erythro-pentafuranosyl)-4-amino-5-(2,2-difluoroethyl)pyrimidin-2-one (24α). Colorless crystals, mp: 173–177°C, anal. $C_{11}H_{15}N_3O_4F_2$, HRMS (FAB): m/z: calcd 292.1109 $[M+H]^+$, found 292.1100, −0.8 mmu, calcd 314.0928 $[M+Na]^+$, found 314.0902, −2.6 mmu, MW: 291.26, ESI + Q1MS, M = 291 (m/z); $[M+H]^+ = 291.7$, $[M+Na]^+ = 313.7$, $[2M+H]^+ = 583.0$, $[2M+Na]^+ = 605.0$, $[3M+H]^+ = 874.1$, $[3M+Na]^+ = 896.2$; ESI − Q1MS, M = 291 (m/z); $[M-H]^- = 289.7$, $[M+^{35}Cl]^- = 325.7$, $[2M-H]^- = 581.0$, $[2M+^{35}Cl]^- = 617.0$, $[3M-H]^- = 872.1$, $[3M+^{35}Cl]^- = 907.8$ ^{1}H-NMR (250 MHz, CD_3OD) δ 2.04 (d, $J_{2'(a),2'(b)} = 14.3$ Hz, 1H, H-2′(a)), 2.64 (ddd, $J_{2'(b),2'(a)} = 14.3$, $J_{2'(b),1'} = 7.1$, $J_{2'(b),3'} = 6.3$ Hz, 1H, H-2′(b)), 2.94 (td, $J_{7,F} = 16.9$, $J_{7,8} = 4.2$ Hz, 2H, H-7), 3.52–

[b]The signal of C-5 was very broad due to coupling with the two F's. The signal of C-2 was broad.

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3.63 (m, 2H, H-5′), 4.30–4.32 (m, 2H, H-3′+H-4), 5.95 (tt, $J_{8,F} = 56.5$, $J_{8,7} = 4.3$ Hz, 1H, H-8), 6.10 (dd, $J_{1',2'(b)} = 7.1$, $J_{1',2'(a)} = 2.1$Hz, 1H, H-1′), 7.82 (s, 1H, H-6). ^{13}C-NMR (62.896 MHz, CD_3OD): δ 33.19 (t, $J_{7,F} = 23.4$Hz, C-7), 42.24 (C-2′), 63.51 (C-5′), 72.55 (C-3′), 89.57 (C-1′), 91.27 (C-4′), 98.0–99.5 (C-5)[b], 116.75 (t, $J_{8,F} = 240.3$ Hz, C-8), 144.12 (C-6), 157.89 (C-2)[b], 166.91 (C-4). ^{19}F-NMR (235.34 MHz, CD_3OD): δ −39.62 (dtd, $J_{F,H-8} = 56.5$, $J_{F,H-7} = 16.9$, $J_{F,F} = 14.8$ Hz, CF_2H).

Reduction of α,β form of aldehyde19 to α,β form of alcohol 18 with $NaBH_4$

A α and β-mixture of **19** (10 mg, 0.019 mmol) in THF (1 mL) under dry N_2 was treated with $NaBH_4$ (0.3 mg, 0.007 mmol). The solution color changed from colorless to pale yellow. The stirring was continued at rt for 10 min. TLC (acetone/*n*-hexane 1:1) indicated consumption of the starting material **19** ($R_f = 0.45$) and **19**α ($R_f = 0.41$) and formation of the product **18** ($R_f = 0.31$) and **18**α ($R_f = 0.24$).[3] After completion of the reaction, the solvent was evaporated under reduced pressure at 40°C. The residue obtained was chromatographed with acetone/*n*-hexane 1:1 to give **18** and **18**α (90%, 9 mg). The analytical data[10] of ^{1}H- and ^{13}C-NMR spectra and mass spectra was consistent with the published data.

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