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Synthesis of 3′-deoxy-3′-*C*-methyl nucleoside derivatives

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ABSTRACT

2′,3′-Dideoxy-3′-*C*-methyl nucleosides bearing the five naturally occurring nucleic acid bases were synthesized. Additionally, the 3′-deoxy-3′-*C*-methyl nucleoside analogues bearing 5-aminoimidazole-4-carboxamide as well as 1,2,4-triazole-3-carboxamide moieties were prepared. The synthesis of the corresponding 2′,3′-dideoxy-3′-*C*-methyl triazole derivative was also accomplished. The dideoxynucleoside derivatives were prepared by radical deoxygenation from their 3′-deoxy-3′-*C*-methyl parent ribonucleosides. When evaluated for their antiviral activity in cell culture experiments, none of these compounds showed any significant antiviral activity.

1. Introduction

Nucleoside analogues are an important class of biologically active compounds. Currently, nucleoside analogues are prominent drugs for the treatment of several viral infections.[1] These nucleoside analogues 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. However, inherent drug resistance[2] and toxicity[3] of the currently used antiviral drugs have prompted the development of new agents possessing more potent and broad antiviral activities. In order to discover new nucleoside derivatives with antiviral activity, modifications of the base and/or sugar moiety of natural nucleosides can be attempted. As a part of our ongoing research on this topic, we have recently reported the synthesis of 3′-*C*-methyl nucleoside analogues incorporating the five canonical bases of nucleic acids from a common sugar precursor.[4] Herein, we report on the synthesis of the 2′,3′-dideoxy-3′-*C*-methyl counterparts (**14**–**18**) bearing the five naturally occurring nucleic acid bases, all of them being hitherto unknown except for **15**.[5] Additionally, the synthesis of some nucleoside derivatives bearing 5-aminoimidazole-4-carboxamide and 1,2,4-triazole-3-carboxamide moieties was also undertaken.

2. Results and discussions

The synthesis began with the preparation of an appropriate methyl sugar precursor, namely, 1,2-di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-3-*C*-methyl-β-D-ribofuranose (**1**), which was obtained from commercially available D-xylose following a procedure reported by us. The syntheses of the protected 3′-deoxy-3′-*C*-methyl nucleosides (**2**–**5**) were previously reported (Scheme 1).[4] A glycosylation reaction with heterocyclic bases, under Vorbrüggen conditions[6] using (trimethylsilyl)trifluoromethane sulfonate as a catalyst, afforded the target nucleosides. In order to prepare the target compounds **14**–**18**, regioselective 2′-*O*-deacylation with hydrazine hydrate[7] was accomplished to give the key derivatives **6**–**9**. The latter were then treated with *O*-phenyl chloro(thio)formate ($C_6H_5OC(S)Cl$) and 4-dimethylaminopyridine (DMAP) in acetonitrile. The corresponding 2′-*O*-[phenoxy-(thiocarbonyl)] intermediates were subsequently deoxygenated with tris(trimethylsilyl)silane[8] in dry toluene in the presence of α,α′-azoisobutyronitrile (AIBN) to yield the protected 2′,3′-dideoxy-3′-*C*-methyl nucleoside derivatives **10**–**13**. Removal of the benzoyl group with methanolic ammonia afforded the desired dideoxynucleosides **14**, **15** and **17**, **18** after purification on silica gel column. Compound **10** was converted into the corresponding cytidine derivative **16** via the formation of a 4-thioamide intermediate followed by aminolysis.[9]

The synthesis of the 5-aminoimidazole-4-carboxamide nucleoside **24** was envisioned from the 3′-deoxy-3′-*C*-methyl-adenosine nucleoside **19** (Scheme 2).[4] Indeed, a glycosylation reaction between 5-amino-4-carboxamide imidazole and a sugar precursor usually lead to a mixture of different regioisomers.[10] Thus, we chose, as a synthetic strategy, a methodology based upon the hydrolysis of a N^1-alkyl inosine derivative under basic conditions.[11] Conversion of adenine moiety of **19** to hypoxanthine moiety was achieved following a treatment with sodium nitrite in acetic acid to give the inosine derivative **20**. Benzoylation of **20** with benzoyl

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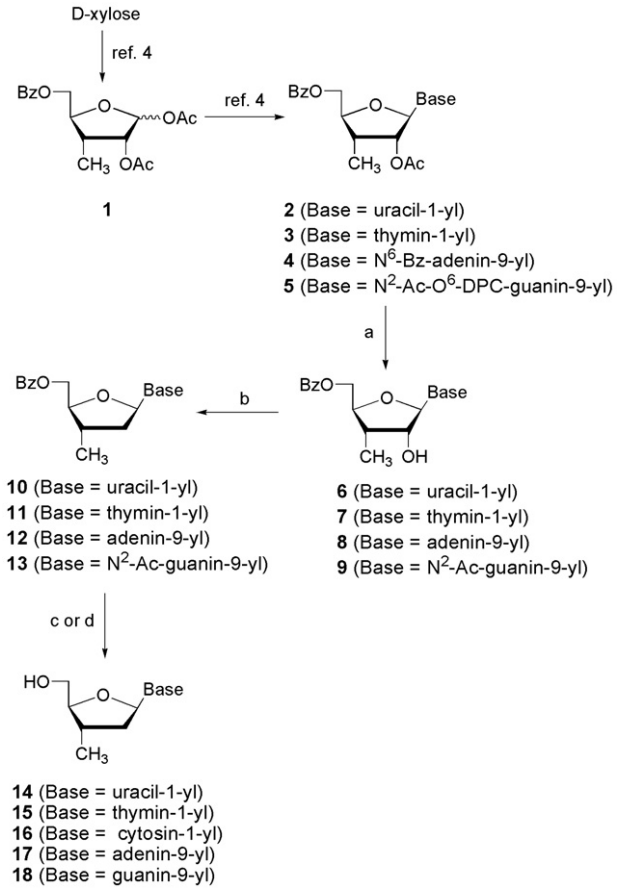
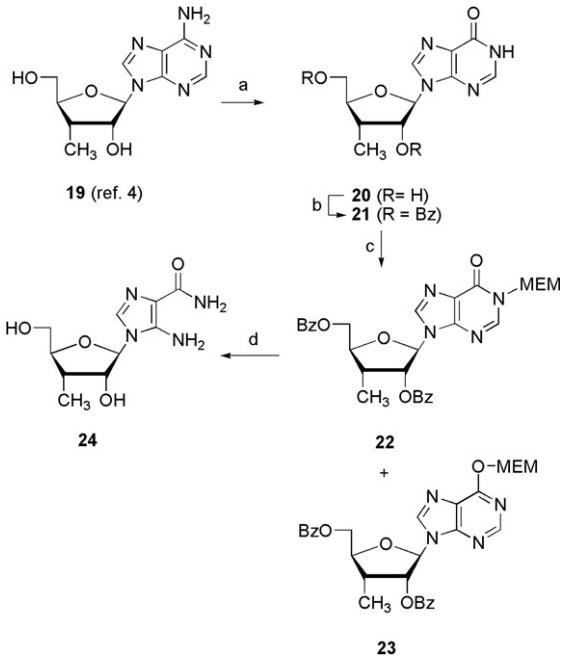
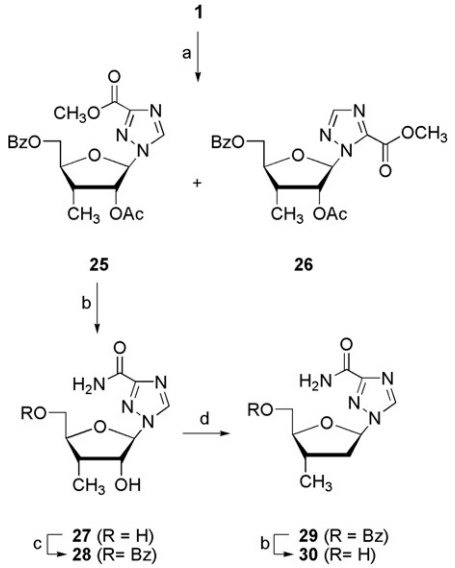


Scheme 1. Reagents and conditions: (a) $H_2NNH_2{\cdot}H_2O$, AcOH, pyridine, 100 °C (rt for **4** and **5**); (b) i—DMAP, $C_6H_5O(S)Cl$, CH_2Cl_2 (1,4-dioxane for **8**, 1,2-dichloroethane for **9**), rt; ii—$(Me_3Si)_3SiH$, AIBN, toluene, reflux; (c) for compounds **10**–**13**, NH_3/MeOH, rt; (d) for compound **16**; i—Lawesson's reagent, 1,2-dichloroethane, reflux; ii—NH_3/MeOH, 100 °C.



Scheme 2. Reagents and conditions: (a) $NaNO_2$, AcOH, H_2O, rt; (b) BzCl, pyridine, 0 °C → rt; (c) MEMCl, DBU, CH_2Cl_2, 0 °C → rt; (d) i—NH_3/MeOH, rt; ii—NaOH 0.2 M, reflux.



Scheme 3. Reagents and conditions: (a) methyl 1,2,4-triazole-carboxylate, bis-PNPP, 165 °C; (b) NH_3/MeOH, rt; (c) BzCl, pyridine, 0 °C → rt; (d) i—1-methylimidazole, $C_6H_5O(S)Cl$, CH_2Cl_2, rt; ii—$(Me_3Si)_3SiH$, AIBN, toluene, reflux.

chloride in pyridine provided more lipophilic derivative **21**, which was easily handled in organic solvent. Next, compound **21** was treated with 2-methoxyethoxymethyl chloride in the presence of DBU in dichloromethane at 0 °C. The N^1-substitution was carried out regioselectively on **21** to give compound **22** in 52% yield. The O^6-substituted side product **23** was obtained in 23% yield. The structure of compounds **22** and **23** was fully established from ^1H, ^{13}C and UV spectra according to literature data.[12] Compound **22** was initially deprotected, to increase water solubility, and treated with 0.2 M NaOH under reflux to give finally the target nucleoside **24**.

Thereafter, we were interested in the preparation of 3′-deoxy-3′-*C*-methyl nucleosides bearing the 1,2,4,-triazole-3-carboxamide moiety (Scheme 3). As in the case of the 5-aminoimidazole-4-carboxamide, a glycosylation reaction between a sugar precursor and the triazole may give a mixture of N^1- and N^2-regioisomers.[13] To prepare in a regioselective way the N^1-regioisomer, we used the acid-catalyzed fusion procedure with methyl 1,2,4-triazole-3-carboxylate and sugar **1** in the presence of bis(*p*-nitrophenyl)phosphate as a catalyst.[14] Under these conditions, the N^1-regioisomer **25** was obtained in 81% yield as well as the N^2-regioisomer **26** in 3% yield after purification on silica gel column chromatography. Treatment of **25** with methanolic ammonia provided (3*S*)-1-(3-deoxy-3-*C*-methyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (**27**). In order to prepare the 2′,3′-dideoxynucleoside counterpart, a selective 5′-*O*-benzoylation of **27** followed by a radical deoxygenation at C-2′ and removal of the protective group gave the target nucleoside **30**.

3. Conclusion

The syntheses of 2′,3′-dideoxy-3′-*C*-methyl nucleosides bearing the five canonical bases of nucleic acids were undertaken to discover new nucleoside derivatives as potential antiviral drugs. Additionally, the synthesis of some nucleoside derivatives bearing 5-aminoimidazole-4-carboxamide and 1,2,4,-triazole-3-carboxamide moieties was realized. However, when evaluated against HIV and several RNA viruses in cell culture experiments, none of the nucleoside derivatives showed any antiretroviral activity nor cytotoxicity at the highest concentration tested (usually 100 μM).

4. Experimental

4.1. 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 Büchi-545 apparatus and are uncorrected. UV spectra were recorded on an Uvikon 931 (Kontron) spectrophotometer. ^{1}H NMR spectra were recorded at 300 or 400 MHz, ^{13}C NMR spectra at 100 MHz in $CDCl_3$ or $(CD_3)_2SO$ at ambient temperature with a Brüker 300 Advance or DRX 400. Chemical shifts (δ) are quoted in parts per million (ppm) referenced to the residual solvent peak, $CHCl_3$ being set at δ_{-H} 7.26 and δ_{-C} 77 and [$(CD_3)(CD_2H)SO$] being set at δ_{-H} 2.49 and δ_{-C} 39.5, relative to tetramethylsilane (TMS). COSY experiments were performed in order to confirm proton assignments. Coupling constants *J* are reported in Hertz. 2D ^{1}H–^{13}C heteronuclear COSY experiments were recorded for the attribution of ^{13}C signals. FAB mass spectra were recorded in positive-ion or negative-ion mode on a JEOL JMS DX 300. The matrix was a mixture (50:50, v/v) of glycerol and thioglycerol (G-T). Specific rotations were measured on a Perkin-Elmer Model 341 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 aluminium 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 and under an argon atmosphere using over-dried glassware. Solvents were dried and distilled prior to use and solids were dried over P_2O_5 under reduced pressure.

4.2. General procedure for the preparation of compounds 6–9

Hydrazine hydrate (10 mmol) was added to a stirred solution of nucleosides (**2**–**5**) (1.0 mmol) in a mixture of acetic acid/pyridine (1:4, v/v, 10 ml). The reaction mixture was stirred at 100 °C for 90 min (3 days at room temperature for compound **4**, 5 days at room temperature for compound **5**). After cooling to room temperature, acetone (16 ml) was added and stirring continued for 30 min. The crude mixture was then diluted with a solution of saturated sodium hydrogen carbonate and dichloromethane (50 ml). The organic phase was washed with water (20 ml) and a solution of saturated sodium chloride (20 ml), dried over sodium sulfate and evaporated under reduced pressure and co-evaporated with toluene. Column chromatography of the residue on silica gel using as eluent a stepwise gradient of methanol (0–5%) in dichloromethane afforded the title compounds.

4.2.1. 1-(5-*O*-Benzoyl-3-deoxy-3-*C* -methyl-β-D-ribofuranosyl)-uracile (6)

The title compound **6** was obtained as a white foam (923 mg, 90%) and was crystallized from acetonitrile: mp 155–156 °C; $[\alpha]_D^{20}$ +16.5 (*c* 1.09 in DMSO); UV λ_{max} (EtOH)/nm 263 (ε 9500), 228 (ε 13,900), λ_{min} (EtOH)/nm 245 (ε 6500); ^{1}H NMR ($CDCl_3$) δ 10.34 (1H, s, NH), 7.95 (2H, m, 2H *ortho*), 7.83 (1H, d, J_{6-5} = 8.1 Hz, H-6), 7.58–7.38 (3H, m, 2H *meta* and 1H *para*), 5.66 (1H, s, H-1′), 5.41 (1H, dd, J_{5-6} = 8.1 Hz and $J_{5\text{-NH}}$ = 2.0 Hz, H-5), 4.81 (1H, d, $J_{OH\text{-}2'}$ = 2.3 Hz, OH-2′), 4.66 (1H, dd, $J_{5'-4'}$ = 2.2 Hz and $J_{5'-5''}$ = 13.0 Hz, H-5′), 4.60 (1H, dd, $J_{5'-4'}$ = 3.1 Hz and $J_{5''-5'}$ = 13.0 Hz, H-5″), 4.33 (1H, m, H-4′), 4.21 (1H, m, H-2′), 2.03 (1H, m, H-3′), 1.10 (3H, d, $J_{CH_{3-3'}}$ = 6.7 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.1 (CO), 163.9 (C-4), 150.8 (C-2), 139.4 (C-6), 133.7–128.7 (C arom.), 101.8 (C-5), 93.2 (C-1′), 84.2 (C-4′), 78.3 (C-2′), 62.6 (C-5′), 35.9 (C-3′), 8.4 (CH_3); *m*/*z* (FAB > 0) 347 $(M+H)^+$, 235 $(S)^+$; *m*/*z* (FAB < 0) 399 $(M-H)^-$, 111 $(B)^-$.

4.2.2. 1-(5-*O*-Benzoyl-3-deoxy-3-*C* -methyl-β-D-ribofuranosyl)-thymine (7)

The title compound **7** was obtained as a white foam (341.7 mg, 90%) and was crystallized from acetonitrile: mp 171–172 °C; $[\alpha]_D^{20}$ −17.6 (*c* 1.02 in DMSO); UV λ_{max} (EtOH)/nm 267 (ε 11,100), 225 (ε 15,800), λ_{min} (EtOH)/nm 245 (ε 6100); ^{1}H NMR ($CDCl_3$) δ 10.3 (1H, br s, NH), 7.97 (2H, m, 2H *ortho*), 7.51 (1H, s, H-6), 7.56–7.36 (3H, m, 2H *meta* and 1H *para*), 5.64 (1H, s, H-1′), 4.90 (1H, br s, OH-2′), 4.71 (1H, dd, $J_{5'-4'}$ = 1.8 Hz and $J_{5'-5''}$ = 12.9 Hz, H-5′), 4.51 (1H, dd, $J_{5'-4'}$ = 3.9 Hz and $J_{5''-5'}$ = 12.9 Hz, H-5″), 4.34 (1H, m, H-4′), 4.26 (1H, m, H-2′), 2.09 (1H, m, H-3′), 1.54 (3H, s, CH_3), 1.11 (3H, d, $J_{CH_{3-3'}}$ = 6.7 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 164.8 (CO), 163.0 (C-4), 149.3 (C-2), 133.6 (C-6), 132.1–127.4 (C arom.), 108.9 (C-5), 91.9 (C-1′), 82.6 (C-4′), 76.8 (C-2′), 61.6 (C-5′), 34.8 (C-3′), 10.9 (CH_3), 7.1 (CH_3); *m*/*z* (FAB > 0) 361 $(M+H)^+$, 235 $(S)^+$, 127 $(BH_2)^+$; *m*/*z* (FAB < 0) 359 $(M-H)^-$, 125 $(B)^-$. Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.72; H, 5.45; N, 7.75.

4.2.3. 9-(5-*O*-Benzoyl-3-deoxy-3-*C* -methyl-β-D-ribofuranosyl)-adenine (8)

The title compound **8** was obtained as a white foam (193 mg, 90%) and was crystallized from ethanol: mp 202 °C; $[\alpha]_D^{20}$ −17.6 (*c* 1.01 in DMSO); UV λ_{max} (EtOH)/nm 258 (ε 13,700), 230 (ε 14,000), λ_{min} (EtOH)/nm 244 (ε 9600); ^{1}H NMR (DMSO-d_6) δ 8.18 (1H, s, H-8), 8.07 (1H, s, H-2), 7.83–7.41 (5H, m, C_6H_5CO), 7.21 (2H, s, NH_2), 5.88 (1H, d, $J_{1'-2'}$ = 1.1 Hz, H-1′), 5.71 (1H, d, $J_{OH\text{-}2'}$ = 5.0 Hz, OH-2′), 4.51 (2H, m, H-2′ and H-5′), 4.42 (1H, dd, $J_{5'-4'}$ = 5.2 Hz and $J_{5''-5'}$ = 12.4 Hz, H-5″), 4.10 (1H, m, H-4′), 2.60 (1H, m, H-3′), 1.02 (3H, d, $J_{CH_{3-3'}}$ = 6.8 Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 166.1 (CO), 156.5 (C-6), 153.1 (C-2), 149.3 (C-4), 139.5 (C-8), 133.9–129.2 (C_6H_5CO), 119.5 (C-5), 91.1 (C-1′), 83.2 (C-4′), 76.7 (C-2′), 64.9 (C-5′), 37.8 (C-3′), 9.9 (CH_3); *m*/*z* (FAB > 0) 370 $(M+H)^+$, 136 $(BH_2)^+$; *m*/*z* (FAB < 0) 368 $(M-H)^-$, 134 $(B)^-$; Anal. Calcd for $C_{18}H_{19}N_5O_4$: C, 58.53; H, 5.18; N, 18.96. Found: C, 58.32; H, 5.11; N, 18.76.

4.2.4. 9-(5-*O*-Benzoyl-3-deoxy-3-*C*-methyl-β-D-ribofuranosyl)-N_2-acetylguanine (9)

The title compound **9** (1.13 g, 90%) was precipitated from water: $[\alpha]_D^{20}$ +4.0 (*c* 1.01 in DMSO); UV λ_{max} (EtOH)/nm 260 (ε 12,600), 232 (ε 7900), λ_{min} (EtOH)/nm 240 (ε 7300); ^{1}H NMR (DMSO-d_6) δ 12.05 (1H, s, NH), 11.63 (1H, s, NH), 8.13 (1H, s, H-8), 7.90–7.49 (5H, m, C_6H_5CO), 5.83 (1H, d, $J_{1'-2'}$ = 1.3 Hz, H-1′), 5.75 (1H, d, $J_{OH\text{-}2'}$ = 5.3 Hz, OH-2′), 4.51 (3H, m, H-2′, H-5′ and H-5″), 4.15 (1H, m, H-4′), 2.58 (1H, m, H-3′), 2.18 (3H, s, CH_3CO), 1.09 (3H, d, $J_{CH_{3-3'}}$ = 6.8 Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 174.0 (CO), 166.1 (CO), 155.3 (C-6), 148.6 (C-4), 148.3 (C-2), 138.0 (C-8), 134.0–129.2 (C_6H_5CO), 120.8 (C-5), 90.7 (C-1′), 83.3 (C-4′), 76.9 (C-2′), 65.0 (C-5′), 38.0 (C-3′), 24.3 (CH_3CO), 10.1 (CH_3); *m*/*z* (FAB > 0) 428 $(M+H)^+$, 194 $(BH_2)^+$, 105 $(C_6H_5CO)^+$, 43 $(CH_3CO)^+$; *m*/*z* (FAB < 0) 426 $(M-H)^-$; Anal. Calcd for $C_{20}H_{21}N_5O_9 \cdot 1.3H_2O$: C, 53.28; H, 5.28; N, 15.53. Found: C, 52.87; H, 5.27; N, 15.91.

4.3. General procedure for the preparation of compounds 10–13

To a stirred solution of nucleosides (**6**–**9**) (1 mmol) in dichloromethane (30 ml) (1,4-dioxane for compound **8**, 1,2-dichloroethane for compound **9**) were added successively DMAP (4 mmol) and phenoxy(thiocarbonyl) chloride (2 mmol). After 30 min at room temperature (24 h for compound **8**), water was added (20 ml)

and the organic phase washed with hydrochloric acid 0.5 N (20 ml) and water (20 ml), dried over sodium sulfate, and evaporated to dryness. The resulting crude material was co-evaporated with dry toluene, then dissolved in the same solvent (20 ml) and α,α′-azoisobutyronitrile (0.5 mmol) and *tris*(trimethylsilyl)silane (2 mmol) were added. The reaction mixture was heated under reflux for 3 h. After cooling to room temperature, the solvent was removed under reduced pressure. Chromatography of the residue on a silica gel column using as eluent a stepwise gradient of methanol (0–4%) in dichloromethane afforded the title compounds.

4.3.1. 1-(5-*O*-Benzoyl-2,3-dideoxy-3-*C*-methyl-β-D-*erythro*-pentofuranosyl)uracil (10)

The title compound **10** was obtained as a white foam (692 mg, 90%): ^{1}H NMR ($CDCl_3$) δ 10.50 (1H, s, NH), 7.85 (2H, m, H *ortho*), 7.54 (1H, d, J_{6-5} = 8.1 Hz, H-6), 7.46–7.27 (3H, m, H *meta* and *para*), 5.88 (1H, dd, $J_{1'-2'} = 6.4$ Hz and $J_{1'-2''} = 1.8$ Hz, H-1′), 5.30 (1H, dd, J_{5-6} = 8.1 Hz and $J_{5\text{-NH}}$ = 2.2 Hz, H-5), 4.48 (1H, dd, $J_{5'-4'} = 2.9$ Hz and $J_{5'-5''} = 12.7$ Hz, H-5′), 4.43 (1H, dd, $J_{5'-4'} = 3.6$ Hz and $J_{5''-5'} = 12.7$ Hz, H-5″), 3.75 (1H, m, H-4′), 2.05 (3H, m, H-2′, H-2″ and H-3′), 0.99 (3H, d, $J_{CH_{3-3'}} = 5.9$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.2 (CO), 163.0 (C-4), 150.0 (C-2), 139.5 (C-6), 133.7–128.7 (C arom.), 101.6 (C-5), 85.6 (C-1′ and C-4′), 62.9 (C-5′), 41.4 (C-2′), 32.4 (C-3′), 15.6 (CH_3); *m*/*z* (FAB > 0) 331 (M+H)$^+$, 219 (S)$^+$, 113 (BH_2)$^+$; *m*/*z* (FAB < 0) 329 (M−H)$^-$, 111 (B)$^-$.

4.3.2. 1-(5-*O*-Benzoyl-2,3-dideoxy-3-*C*-methyl-β-D-*erythro*-pentofuranosyl)thymine (11)

The title compound **11** was obtained as a white foam (183.9 mg, 90%): ^{1}H NMR ($CDCl_3$) δ 10.26 (1H, s, NH), 7.98 (2H, m, 2H *ortho*), 7.57–7.36 (3H, m, 2H *meta* and 1H *para*), 7.30 (1H, d, $J_{6\text{-}CH3}$ = 1.2 Hz, H-6), 6.03 (1H, dd, $J_{1'-2'} = 7.0$ Hz and $J_{1'-2''} = 2.9$ Hz, H-1′), 4.60 (1H, dd, $J_{5'-4'} = 2.6$ Hz and $J_{5'-5''} = 12.5$ Hz, H-5′), 4.49 (1H, dd, $J_{5'-4'} = 4.4$ Hz and $J_{5''-5'} = 12.5$ Hz, H-5″), 3.86 (1H, m, H-4′), 2.22 (2H, m, H-2′ and H-3′), 2.11 (1H, m, H-2″), 1.62 (3H, s, CH_3), 1.11 (3H, d, $J_{CH_{3-3'}} = 6.2$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.3 (CO), 163.4 (C-4), 150.0 (C-2), 135.2 (C-6), 133.5 −128.6 (C arom.), 110.5 (C-5), 85.2 (C-1′), 85.1 (C-4′), 63.6 (C-5′), 40.9 (C-2′), 33.0 (C-3′), 16.2 (CH_3), 12.4 (CH_3); *m*/*z* (FAB > 0) 345 (M+H)$^+$, 219 (S)$^+$, 127 (BH_2)$^+$; *m*/*z* (FAB < 0) 343 (M−H)$^-$, 125 (B)$^-$.

4.3.3. 9-(5-*O*-Benzoyl-2,3-dideoxy-3-*C*-methyl-β-D-*erythro*-pentofuranosyl)adenine (12)

The title compound **12** was obtained as a white foam (158 mg, 56%): $[\alpha]_D^{20}$ −8.6 (*c* 1.02 in DMSO); UV λ_{max} (EtOH)/nm 259 (ε 13,300), 230 (ε 13,400); λ_{min} (EtOH)/nm 244 (ε 9300); ^{1}H NMR (DMSO-d_6) δ 8.24 (1H, s, H-8), 8.09 (1H, s, H-2), 7.83–7.45 (5H, m, C_6H_5CO), 7.21 (2H, s, NH_2), 6.25 (1H, d, $J_{1'-2''} = 7.2$ Hz, H-1′), 4.44 (2H, m, H-5′ and H-5″), 3.93 (1H, m, H-4′), 2.69 (2H, m, H-2′ and H-3′), 2.22 (1H, m, H-2″), 1.13 (3H, d, $J_{CH_{3-3'}} = 6.0$ Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 166.1 (CO), 156.5 (C-6), 153.0 (C-2), 149.3 (C-4), 139.6 (C-8), 133.9–129.2 (C_6H_5CO), 119.5 (C-5), 84.8 (C-4′), 83.7 (C-1′), 64.9 (C-5′), 39.7 (C-2′), 33.9 (C-3′), 16.3 (CH_3); *m*/*z* (FAB > 0) 354 (M+H)$^+$, 219 (S)$^+$, 136 (BH_2)$^+$; *m*/*z* (FAB < 0) 352 (M−H)$^-$, 134 (B)$^-$; Anal. Calcd for $C_{18}H_{19}N_5O_3{\cdot}0.9CH_3OH$: C, 59.39; H, 5.96; N, 18.32. Found: C, 59.55; H, 5.46; N, 17.85.

4.3.4. 9-(5-*O*-Benzoyl-2,3-dideoxy-3-*C*-methyl-β-D-*erythro*-pentofuranosyl)-N_2-acetylguanine (13)

The title compound **13** was obtained as a white foam (192 mg, 57%): UV λ_{max} (EtOH)/nm 259 (ε 8600), 236 (ε 9200), λ_{min} (EtOH)/nm 245 (ε 7400); ^{1}H NMR (DMSO-d_6) δ 11.91 (1H, s, NH), 11.51 (1H, s, NH), 8.03 (1H, s, H-8), 7.75–7.36 (5H, m, C_6H_5CO), 6.01 (1H, dd, $J_{1'-2'} = 1.8$ Hz and $J_{1'-2''} = 7.0$ Hz, H-1′), 4.39 (1H, dd, $J_{5'-4'} = 3.1$ Hz and $J_{5'-5''} = 12.2$ Hz, H-5′), 4.33 (1H, dd, $J_{5'-4'} = 5.4$ Hz and $J_{5''-5'} = 12.2$ Hz, H-5″), 3.83 (1H, m, H-4′), 2.51 (2H, m, H-2′ and H-3′), 2.11 (1H, m, H-2″), 2.05 (3H, s, CH_3CO), 1.03 (3H, d, $J_{CH_{3-3'}} = 6.0$ Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 174.0 (CO), 166.0 (CO), 155.3 (C-6), 148.5 (C-4), 148.2 (C-2), 137.9 (C-8), 134.0-129.2 (C_6H_5CO), 121.0 (C-5), 85.0 (C-4′), 83.7 (C-1′), 64.8 (C-5′), 39.9 (C-2′), 33.7 (C-3′), 24.3 (CH_3CO), 16.3 (CH_3); *m*/*z* (FAB > 0) 412 (M+H)$^+$, 219 (S)$^+$, 194 (BH_2)$^+$, 43 (CH_3CO)$^+$; *m*/*z* (FAB < 0) 410 (M−H)$^-$, 192 (B)$^-$.

4.4. General procedure for the preparation of compounds 14, 15, 17, 18, 24, 27 and 30

A solution of nucleosides (**10**–**13**, **22**, **25**, **29**) (1.0 mmol) in methanolic ammonia (previously saturated at −10 °C and tightly stoppered) (20 ml) was stirred for 12 h at room temperature, then evaporated to dryness. The residue was subjected to silica gel column chromatography.

4.4.1. 1-(2,3-Dideoxy-3-*C*-methyl-β-D-*erythro*-pentofuranosyl)-uracile (14)

Purification using as eluent a stepwise gradient of methanol (0–5%) in dichloromethane afforded the title compound **14** (275 mg, 91%), which was crystallized from ethanol: mp 173–174 °C; $[\alpha]_D^{20}$ +45 (*c* 1.00 in DMSO); UV λ_{max} (EtOH)/nm 262 (ε 10,500), λ_{min} (EtOH)/nm 229 (ε 2000); ^{1}H NMR ($CDCl_3$) δ 11.25 (1H, s, NH), 8.03 (1H, d, J_{6-5} = 8.1 Hz, H-6), 5.93 (1H, dd, $J_{1'-2'} = 7.1$ Hz and $J_{1'-2''} = 2.3$ Hz, H-1′), 5.56 (1H, d, J_{5-6} = 8.1 Hz, H-5), 5.06 (1H, t, OH-5′), 3.71 (1H, m, H-5′), 3.54 (2H, m, H-5″ and H-4′), 2.17 (2H, m, H-2′ and H-3′), 1.99 (1H, m, H-2″), 0.99 (3H, d, $J_{CH_{3-3'}} = 6.2$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 163.2 (C-4), 150.3 (C-2), 140.6 (C-6), 100.7 (C-5), 87.8 (C-4′), 84.1 (C-1′), 59.9 (C-5′), 40.4 (C-2′), 30.9 (C-3′), 15.6 (CH_3); *m*/*z* (FAB > 0) 227 (M+H)$^+$, 115 (S)$^+$, 113 (BH_2)$^+$; *m*/*z* (FAB < 0) 225 (M−H)$^-$, 111 (B)$^-$.

4.4.2. 1-(2,3-Dideoxy-3-*C*-methyl-β-D-*erythro*-pentofuranosyl)-thymine (15)

Purification using as eluent a stepwise gradient of methanol (0–5%) in dichloromethane afforded the title compound **15** (191.7 mg, 86%) which was lyophilized from water: $[\alpha]_D^{20}$ +25.2 (*c* 1.03 in DMSO); UV λ_{max} (EtOH)/nm 267 (ε 8000), λ_{min} (EtOH)/nm 233 (ε 1400); ^{1}H NMR ($CDCl_3$) δ 11.24 (1H, s, NH), 7.90 (1H, d, $J_{6\text{-}CH_3}$ = 1.1 Hz, H-6), 5.95 (1H, dd, $J_{1'-2'} = 7.1$ Hz and $J_{1'-2''} = 2.5$ Hz, H-1′), 5.10 (1H, pt, OH-5′), 3.73 (1H, m, H-5′), 3.53 (2H, m, H-4′ and H-5″), 2.26 (1H, m, H-3′), 2.11 (1H, m, H-2′), 1.96 (1H, m, H-2″), 1.76 (3H, d, $J_{CH_{3-5}}$ = 1.1 Hz, CH_3), 0.99 (3H, d, $J_{CH_{3-3'}} = 6.4$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 163.8 (C-4), 150.3 (C-2), 136.4 (C-6), 108.3 (C-5), 87.6 (C-4′), 83.7 (C-1′), 60.0 (C-5′), 40.3 (C-2′), 31.0 (C-3′), 15.8 (CH_3), 12.2 (CH_3); *m*/*z* (FAB > 0) 241 (M+H)$^+$, 127 (BH_2)$^+$, 115 (S)$^+$; *m*/*z* (FAB < 0) 239 (M−H)$^-$, 125 (B)$^-$.

4.4.3. 1-(2,3-Dideoxy-3-*C*-methyl-β-D-*erythro*-pentofuranosyl)-cytosine (16)

To a solution of **10** (600 mg, 1.82 mmol) in 1,2-dichloroethane (58 ml) was added Lawesson's reagent (514 mg, 1.27 mmol). The reaction mixture was heated under reflux for 90 min. The solvent was then removed under reduced pressure and the residue purified on silica gel column chromatography using as eluent a stepwise gradient of methanol (0–0.5%) in dichloromethane to give the corresponding 4-thio intermediate as a yellow foam. A suspension of this intermediate in methanolic ammonia (previously saturated at −10 °C and tightly stoppered) (18.5 ml) was heated at 100 °C in a stainless-steel bomb for 12 h, then cooled to room temperature and evaporated to dryness. The residue was subjected to a silica gel column chromatography using as eluent a stepwise gradient of methanol (0–15%) in dichloromethane to afford the title compound **16** (377 mg, 91%) which was lyophilized from water: $[\alpha]_D^{20}$ +69.7 (*c* 1.09 in DMSO); UV λ_{max} (EtOH)/nm 272 (ε 7500), λ_{min}

(EtOH)/nm 250 (ε 4900); ^{1}H NMR (DMSO-d_6) δ 7.99 (1H, d, J_{6-5} = 7.4 Hz, H-6), 7.04 (2H, pd, NH_2), 5.90 (1H, dd, $J_{1'-2'} = 6.1$ Hz and $J_{1'-2''} = 2.8$ Hz, H-1′), 5.66 (1H, d, J_{5-6} = 7.4 Hz, H-5), 5.03 (1H, br s, OH-5′), 3.72 (1H, m, H-5′), 3.53 (2H, m, H-5″ and H-4′), 2.11 (1H, m, H-3′), 1.97 (2H, m, H-2′ and H-2″), 0.98 (3H, d, $J_{CH_{3-3'}} = 6.3$ Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 163.8 (C-4), 153.3 (C-2), 139.2 (C-6), 91.1 (C-5), 85.9 (C-4′), 82.8 (C-1′), 58.3 (C-5′), 39.3 (C-2′), 29.0 (C-3′), 13.8 (CH_3); *m/z* (FAB > 0) 226 $(M+H)^+$, 112 $(BH_2)^+$; *m/z* (FAB < 0) 224 $(M-H)^-$.

4.4.4. 9-(2,3-Dideoxy-3-*C*-methyl-β-D-*erythro*-pentofuranosyl)-adenine (17)

Purification using as eluent a stepwise gradient of methanol (0–10%) in dichloromethane to afford the title compound **12** (64.2 mg, 77%), which was lyophilized from water: UV λ_{max} (EtOH)/nm 258 (ε 13,400); λ_{min} (EtOH)/nm 226 (ε 2100); ^{1}H NMR (DMSO-d_6) δ 8.38 (1H, s, H-8), 8.13 (1H, s, H-2), 7.23 (2H, s, NH_2), 6.24 (1H, dd, $J_{1'-2'} = 1.9$ Hz) and ($J_{1'-2''} = 7.1$ Hz, H-1′), 5.02 (1H, t, $J_{OH-5'} = J_{OH-5''} = 5.4$Hz, OH-5′), 3.62 (3H, m, H-5′, H-4′ and H-5″), 2.49 (2H, m, H-2′ and H-3′), 2.15 (1H, m, H-2″), 1.07 (3H, d, $J_{CH_{3-3'}} = 6.0$ Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 156.4 (C-6), 152.9 (C-2), 149.2 (C-4), 139.4 (C-8), 119.5 (C-5), 88.4 (C-4′), 83.8 (C-1′), 61.7 (C-5′), 40.7 (C-2′), 32.6 (C-3′), 16.6 (CH_3); *m/z* (FAB > 0) 250 $(M+H)^+$, 136 $(BH_2)^+$; *m/z* (FAB < 0) 248 $(M-H)^-$, 134 $(B)^-$.

4.4.5. 9-(2,3-Dideoxy-3-*C*-methyl-β-D-*erythro*-pentofuranosyl)-guanine (18)

Purification using as eluent a stepwise gradient of methanol (0–15%) in dichloromethane afforded the title compound **18** (78.4 mg, 83%), which was lyophilized from water: $[\alpha]_D^{20}$ −12.9 (*c* 1.03 in DMSO); UV λ_{max} (EtOH)/nm 255 (ε 14,500); ^{1}H NMR (DMSO-d_6) δ 10.58 (1H, s, NH), 7.97 (1H, s, H-8), 6.45 (1H, s, NH_2), 6.00 (1H, dd, $J_{1'-2'} = 1.9$ Hz and $J_{1'-2''} = 7.3$ Hz, H-1′), 4.95 (1H, t, $J_{OH-5'} = J_{OH-5''} = 5.5$ HzHz, OH-5′), 3.64 (1H, m, H-5′), 3.54 (2H, m, H-5″ and H-4′), 2.36 (2H, m, H-2′ and H-3′), 2.06 (1H, m, H-2″), 1.05 (3H, d, $J_{CH_{3-3'}} = 6.3$ Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 157.2 (C-6), 154.0 (C-2), 150.9 (C-4), 135.6 (C-8), 117.1 (C-5), 88.3 (C-4′), 83.1 (C-1′), 61.5 (C-5′), 40.4 (C-2′), 32.5 (C-3′), 16.5 (CH_3); *m/z* (FAB > 0) 266 $(M+H)^+$, 152 $(BH_2)^+$, 115 $(S)^+$; *m/z* (FAB < 0) 264 $(M-H)^-$, 150 $(B)^-$; Anal. Calcd for $C_{11}H_{15}N_5O_3 \cdot 0.4H_2O$: C, 48.49; H, 5.84; N, 25.70. Found: C, 48.51; H, 5.79; N, 25.14.

4.4.6. 9-(3-Deoxy-3-*C*-methyl-β-D-ribofuranosyl)hypoxanthine (20)

To a stirred solution of compound **19** (1.0 g, 3.77 mmol) in glacial acetic acid (56.9 ml) was added a solution of sodium nitrite (2.7 g, 38.7 mmol) in water (19.4 ml). The reaction mixture was stirred at room temperature for 3 days, then evaporated under reduced pressure and co-evaporated with toluene. The resulting residue was subjected to silica gel column chromatography using as eluent a stepwise gradient of methanol (0–20%) in dichloromethane to afford the title compound **20** (903 mg, 90%), which was lyophilized from water: $[\alpha]_D^{20}$ −42.1 (*c* 0.95 in DMSO); ^{1}H NMR (DMSO-d_6) δ 12.45 (1H, s, NH), 8.42 (1H, s, H-8), 8.07 (1H, s, H-2), 5.90 (1H, d, $J_{1'-2'} = 0.9$ Hz, H-1′), 5.76 (1H, br s, OH-2′), 5.09 (1H, br s, OH-5′), 4.27 (1H, d, $J_{2'-3'} = 4.8$ Hz, H-2′), 3.86 (1H, m, H-4′), 3.77 (1H, dd, $J_{5'-4'} = 2.2$ Hz and $J_{5'-5''} = 12.4$ Hz, H-5′), 3.56 (1H, dd, $J_{5'-4'} = 3.4$ Hz and $J_{5''-5'} = 12.4$ Hz, H-5″), 2.38 (1H, m, H-3′), 0.99 (3H, d, $J_{CH_{3-3'}} = 6.8$ Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 156.6 (C-6), 147.5 (C-4), 145.7 (C-2), 138.1 (C-8), 124.3 (C-5), 90.3 (C-1′), 86.2 (C-4′), 77.3 (C-2′), 60.4 (C-5′), 35.4 (C-3′), 9.4 (CH_3); *m/z* (FAB > 0) 267 $(M+H)^+$, 137 $(BH_2)^+$; *m/z* (FAB < 0) 265 $(M-H)^-$, 135 $(B)^-$; Anal. Calcd for $C_{11}H_{14}N_4O_4 \cdot 0.6H_2O$: C, 47.69; H, 5.53; N, 20.22. Found: C, 47.54; H, 5.37; N, 19.98.

4.4.7. 9-(2,5-Di-*O*-benzoyl-3-deoxy-3-*C*-methyl-β-D-ribofuranosyl)-hypoxanthine (21)

To a stirred solution of compound **20** (397 mg, 1.49 mmol) in pyridine was added dropwise benzoyl chloride (692 μl, 5.96 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 h, then diluted with water and dichloromethane. The organic phase was washed with aqueous solution of sodium hydrogenocarbonate and water, dried over sodium sulfate, evaporated under reduced pressure and co-evaporated with toluene. The residue was subjected to silica gel column chromatography using as eluent a stepwise gradient of methanol (0–3%) in dichloromethane to afford the title compound **21** as a white foam (452 mg, 64%): $[\alpha]_D^{20}$ −34.4 (*c* 0.90 in DMSO); ^{1}H NMR (DMSO-d_6) δ 12.44 (1H, s, NH), 8.30 (1H, s, H-8), 8.10–7.50 (11H, m, H-2 and 2× C_6H_5CO), 6.27 (1H, d, $J_{1'-2'} = 1.1$ Hz, H-1′), 5.94 (1H, d, $J_{2'-3'} = 5.9$ Hz, H-2′), 4.67 (1H, dd, $J_{5'-4'} = 2.6$ Hz and $J_{5'-5''} = 12.5$ Hz, H-5′), 4.55 (1H, dd, $J_{5'-4'} = 4.9$ Hz and $J_{5''-5'} = 12.5$ Hz, H-5″), 4.40 (1H, m, H-4′), 3.22 (1H, m, H-3′), 1.19 (3H, d, $J_{CH_{3-3'}} = 6.8$ Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 165.5 (CO), 165.1 (CO), 156.6 (C-6), 147.6 (C-4), 146.0 (C-2), 139.2 (C-8), 133.9–128.7 (2× C_6H_5CO), 124.6 (C-5), 88.4 (C-1′), 83.1 (C-4′), 79.5 (C-2′), 63.6 (C-5′), 36.6 (C-3′), 9.2 (CH_3); *m/z* (FAB > 0) 475 $(M+H)^+$, 339 $(S)^+$, 137 $(BH_2)^+$; *m/z* (FAB < 0) 473 $(M-H)^-$, 135 $(B)^-$; Anal. Calcd for $C_{25}H_{22}N_4O_6 \cdot 0.4CH_3OH$: C, 62.61; H, 4.88; N, 11.50. Found: C, 62.67; H, 4.84; N, 11.42.

4.4.8. 9-(2,5-Di-*O*-benzoyl-3-deoxy-3-*C*-methyl-β-D-ribofuranosyl)-1-[(2-methoxyethoxy)-methyl]hypoxanthine (22) and 9-(2,5-di-*O*-benzoyl-3-deoxy-3-*C*-methyl-β-D-ribofuranosyl)-6-*O*-[(2-methoxyethoxy)methyl]hypoxanthine (23)

To a solution of compound **21** (369 mg, 0.78 mmol) in dichloromethane (7.8 ml) were successively added dropwise DBU (1.16 ml, 7.8 mmol) and (2-methoxyethoxy)methyl chloride (445 μl, 3.9 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 30 min, then diluted with water and dichloromethane. After decantation, the organic phase was washed with aqueous solution of sodium chloride and water, dried over sodium sulfate and evaporated to dryness. The residue was subjected to silica gel column chromatography using as eluent a mixture of acetone and hexane (1:1, v/v) to afford in order of elution the title compounds **23** (99.2 mg, 23%) and **22** (228 mg, 52%) as white foams: Compound **23**: mp 68 °C; $[\alpha]_D^{20}$ −26.2 (*c* 0.92 in DMSO); ^{1}H NMR (DMSO-d_6) δ 8.61 (1H, s, H-8), 8.51 (1H, s, H-2), 8.11–7.47 (10H, m, 2× C_6H_5CO), 6.38 (1H, d, $J_{1'-2'} = 1.1$ Hz, H-1′), 6.06 (1H, d, $J_{2'-3'} = 5.9$ Hz, H-2′), 5.83 (2H, s, OCH_2O), 4.67 (1H, m, H-5′), 4.56 (1H, m, H-5″), 4.41 (1H, m, H-4′), 3.85 (2H, m, OCH_2-CH_2O), 3.50 (2H, m, OCH_2CH_2O), 3.32 (1H, m, H-3′), 3.23 (3H, s, OCH_3), 1.22 (3H, d, $J_{CH_{3-3'}} = 6.8$Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 165.5 (CO), 165.1 (CO), 159.1 (C-6), 151.6 (C-4 and C-2), 143.3 (C-8), 133.9–128.7 (2× C_6H_5CO), 121.2 (C-5), 91.3 (OCH_2O), 88.7 (C-1′), 83.2 (C-4′), 79.2 (C-2′), 70.9 (OCH_2CH_2O), 68.9 (OCH_2CH_2O), 63.5 (C-5′), 58.0 (OCH3), 36.6 (C-3′), 9.2 (CH_3); *m/z* (FAB > 0) 475 $(M-(CH_3O(C_2H_4)OCH_2)+H)^+$, 339 $(S)^+$; *m/z* (FAB < 0) 473 $(M-(CH_3O(C_2H_4)OCH_2)-H)^-$; Anal. Calcd for $C_{29}H_{30}N_4O_8$: C, 61.91; H, 5.38; N, 9.96. Found: C, 61.46; H, 5.38; N, 9.64; Compound **22**: mp 62 °C; $[\alpha]_D^{20}$ −37.4 (*c* 0.88 in DMSO); ^{1}H NMR (DMSO-d_6) δ 8.42 (1H, s, H-8), 8.35 (1H, s, H-2), 8.10–7.51 (10H, m, 2× C_6H_5CO), 6.28 (1H, d, $J_{1'-2'} = 1.1$ Hz, H-1′), 5.94 (1H, dd, $J_{2'-1'} = 0.9$Hz and $J_{2'-3'} = 5.9$ Hz, H-2′), 5.42 (2H, 2× d, *J* = 10.2 Hz, NCH_2O), 4.66 (1H, m, H-5′), 4.57 (1H, m, H-5″), 4.42 (1H, m, H-4′), 3.66 (2H, m, OCH_2CH_2O), 3.42 (2H, m, OCH_2CH_2O), 3.22 (1H, m, H-3′), 3.20 (3H, s, OCH_3), 1.20 (3H, d, $J_{CH_{3-3'}} = 6.8$ Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 165.5 (CO), 165.1 (CO), 155.9 (C-6), 148.9 (C-2), 146.9 (C-4), 139.8 (C-8), 133.9–128.7 (2× C_6H_5CO), 123.9 (C-5), 88.4 (C-1′), 83.2 (C-4′), 79.5 (C-2′), 74.9 (NCH_2O), 70.9 (OCH_2CH_2O), 68.3 (OCH_2CH_2O), 63.6

(C-5′), 58.0 (OCH3), 36.6 (C-3′), 9.2 (CH_3); *m/z* (FAB > 0) 563 $(M+H)^+$, 339 $(S)^+$, 225 $(BH_2)^+$; *m/z* (FAB < 0) 561 $(M-H)^-$, 223 $(B)^-$; Anal. Calcd for $C_{29}H_{30}N_4O_8\cdot 0.4CH_3OH$: C, 61.37; H, 5.54; N, 9.74. Found: C, 61.33; H, 5.52; N, 9.68.

4.4.9. 1-(3-Deoxy-3-*C*-methyl-β-D-ribofuranosyl)-5-aminoimidazole-4-carboxamide (24)

A solution of compound **22** (264 mg, 0.47 mmol) in methanolic ammonia (previously saturated at −10 °C and tightly stoppered) (14.1 ml) was stirred at room temperature for 24 h, then evaporated to dryness. A stirred solution of the resulting residue in an aqueous solution of sodium hydroxide (0.2 M, 4.7 ml) was heated under reflux for 4 h. After cooling to room temperature, the reaction mixture was neutralized with hydrochloric acid 6 N and evaporated under reduced pressure. The residue was subjected to silica gel column chromatography using as eluent a stepwise gradient of methanol (0–20%) in dichloromethane to afford the title compound **24** (69.8 mg, 58%) which was lyophilized from water: $[\alpha]_D^{20}$ −40.0 (*c* 0.85 in DMSO); ^{1}H NMR (DMSO-d_6) δ 7.45 (1H, s, H-2), 6.79 and 6,65 (2H, 2× br s, CONH_2), 5.90 (2H, s, NH_2), 5.56 (1H, d, $J_{OH\text{-}2'} = 4.1$ Hz, OH-2′), 5.47 (1H, d, $J_{1'-2'} = 1.5$ Hz, H-1′), 5.10 (1H, t, $J_{OH\text{-}5'} = J_{OH\text{-}5''} = 5.2$ Hz, OH-5′), 4.12 (1H, t, $J_{2'\text{-}OH} = J_{2'-3'} = 3.9$ Hz, H-2′), 3.78 (1H, m, H-4′), 3.73 (1H, m, H-5′), 3.53 (1H, m, H-5″), 2.29 (1H, m, H-3′), 0.97 (3H, d, $J_{CH_{3-3'}} = 6.8$ Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 167.3 (*C*ONH$_2$), 142.5 (C-5), 128.0 (C-2), 113.2 (C-4), 90.5 (C-1′), 86.2 (C-4′), 77.0 (C-2′), 60.9 (C-5′), 35.7 (C-3′), 10.1 (CH_3); *m/z* (FAB > 0) 257 $(M+H)^+$, 127 $(BH_2)^+$; *m/z* (FAB < 0) 255 $(M-H)^-$, 125 $(B)^-$; Anal. Calcd for $C_{10}H_{16}N_4O_4\cdot 0.7CH_3OH$: C, 46.11; H, 6.80; N, 20.10. Found: C, 45.79; H, 6.28; N, 19.80.

4.4.10. 1-(2-*O*-Acetyl-5-*O*-benzoyl-3-deoxy-3-*C*-methyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxylic acid methyl ester (25) and 2-(2-*O*-acetyl-5-*O*-benzoyl-3-deoxy-3-*C*-methyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxylic acid methyl ester (26)

A mixture of methyl 1,2,4-triazole-3-carboxylate (755 mg, 5.94 mmol) and 1,2-di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-3-*C*-methyl-α, β-D-ribofuranose **1** (1 g, 2.97 mmol) was heated at 160–165 °C until the sugar had melted. Bis(*p*-nitrophenyl)phosphate (catalytic amount) was added and heating at 160–165 °C was continued under diminished pressure for 90 min. After cooling to room temperature, dichloromethane was added and the organic phase washed with aqueous solution of sodium hydrogenocarbonate, dried over sodium sulfate and evaporated to dryness. The residue was subjected to silica gel column chromatography using as eluent a mixture of petroleum ether/ethyl acetate (2:3, v/v) to afford in order of elution the title compound **25** (977 mg, 81%), which was crystallized from isopropanol: mp 92 °C; $[\alpha]_D^{20}$ −13.0 (*c* 0.92 in DMSO); ^{1}H NMR (DMSO-d_6) δ 8.90 (1H, s, H-5), 7.88–7.47 (5H, m, C$_6H_5$CO), 6.24 (1H, s, H-1′), 5.52 (1H, d, $J_{2'-3'} = 5.1$ Hz, H-2′), 4.58 (1H, dd, $J_{5'-4'} = 2.6$ Hz and $J_{5'-5''} = 12.5$ Hz, H-5′), 4.43 (1H, dd, $J_{5'-4'} = 4.6$ Hz and $J_{5''-5'} = 12.5$ Hz, H-5″), 4.26 (1H, m, H-4′), 3.85 (3H, s, OCH_3), 2.90 (1H, m, H-3′), 2.16 (3H, s, CH_3CO), 1.10 (3H, d, $J_{CH_{3-3'}} = 6.8$ Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 169.9 (CO), 165.5 (CO), 159.6 (CO), 154.4 (C-3), 146.1 (C-5), 133.4–128.7 (*C*$_6$H$_5$CO), 99.5 (C-1′), 90.4 (C-4′), 78.6 (C-2′), 63.4 (C-5′), 52.3 (O*C*H$_3$), 36.1 (C-3′), 20.5 (*C*H$_3$CO), 8.9 (CH_3); *m/z* (FAB > 0) 404 $(M+H)^+$, 277 $(S)^+$, 128 $(BH_2)^+$, 105 $(C_6H_5CO)^+$, 43 $(CH_3CO)^+$; *m/z* (FAB < 0) 402 $(M-H)^-$, 126 $(B)^-$, 121 $(C_6H_5CO_2)^-$; Anal. Calcd for $C_{19}H_{21}N_3O_7$: C, 56.57; H, 5.25; N, 10.42. Found: C, 56.29; H, 5.27; N, 10.40. Compound **26** (48 mg, 3%): ^{1}H NMR (DMSO-d_6) δ 8.21 (1H, s, H-5), 7.928–7.45 (5H, m, C$_6H_5$CO), 6.65 (1H, s, H-1′), 5.51 (1H, d, $J_{2'-3'} = 5.1$ Hz, H-2′), 4.54 (1H, dd, $J_{5'-4'} = 2.7$ Hz and $J_{5'-5''} = 12.4$ Hz, H-5′), 4.38 (1H, dd, $J_{5'-4'} = 4.6$ Hz and $J_{5''-5'} = 12.4$ Hz, H-5″), 4.23 (1H, m, H-4′), 3.90 (3H, s, O*C*H$_3$), 3.03 (1H, m, H-3′), 2.18 (3H, s, CH_3CO), 1.07 (3H, d, $J_{CH_{3-3'}} = 6.8$ Hz, CH_3).

4.4.11. 1-(3-Deoxy-3-*C*-methyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (27)

Purification using as eluent a stepwise gradient of methanol (0–10%) in dichloromethane to afford the title compound **27** (481 mg, 86%) which was crystallized from acetonitrile: mp 157 °C; $[\alpha]_D^{20}$ −26.9 (*c* 0.97 in DMSO); ^{1}H NMR (DMSO-d_6) δ 8.99 (1H, s, H-5), 7.83 and 7.62 (2H, 2× br s, NH_2), 5.84 (1H, s, H-1′), 5.77 (1H, br s, OH-2′), 5.00 (1H, br s, OH-5′), 4.24 (1H, d, $J_{2'-3'} = 4.4$ Hz, H-2′), 3.89 (1H, m, H-4′), 3.62 (2H, m, H-5′ and H-5″), 2.31 (1H, m, H-3′), 0.98 (3H, d, $J_{CH_{3-3'}} = 6.8$ Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 160.5 (CO), 157.2 (C-3), 144.0 (C-5), 94.2 (C-1′), 87.0 (C-4′), 77.4 (C-2′), 60.9 (C-5′), 35.5 (C-3′), 9.2 (CH_3); *m/z* (FAB > 0) 243 $(M+H)^+$, 131 $(S)^+$, 113 $(BH_2)^+$; *m/z* (FAB < 0) 241 $(M-H)^-$, 111 $(B)^-$; Anal. Calcd for $C_9H_{14}N_4O_4$: C, 44.63; H, 5.83; N, 23.13. Found: C, 44.77; H, 5.69; N, 23.10.

4.4.12. 1-(5-*O*-Benzoyl-3-deoxy-3-*C*-methyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (28)

To a stirred solution of compound **27** (150 mg, 0.62 mmol) in pyridine (3.1 ml) was added dropwise benzoyl chloride (108 μl, 0.93 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, then diluted with water and dichloromethane. The organic phase was washed with aqueous solution of sodium hydrogenocarbonate and water, dried over sodium sulfate, evaporated under reduced pressure and co-evaporated with toluene. The residue was subjected to silica gel column chromatography using as eluent a stepwise gradient of methanol [0–7%] in dichloromethane to afford the title compound **28** as a white foam (142 mg, 66%): $[\alpha]_D^{20}$ −1.2 (*c* 0.85 in DMSO); ^{1}H NMR (DMSO-d_6) δ 8.81 (1H, s, H-5), 7.93–7.51 (7H, m, $NH_2$and C$_6H_5$CO), 5.96 (1H, s, H-1′), 5.84 (1H, br s, OH-2′), 4.53 (1H, dd, $J_{5'-4'} = 2.7$ Hz and $J_{5'-5''} = 12.3$ Hz, H-5′), 4.41 (2H, m, H-5″ and H-2′), 4.22 (1H, m, H-4′), 271 (1H, m, H-3′), 1.09 (3H, d, $J_{CH_{3-3'}} = 6.8$ Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 165.6 (CO), 160.4 (CO), 157.5 (C-3), 145.0 (C-5), 133.4–128.8 (*C*$_6$H$_5$CO), 93.3 (C-1′), 83.5 (C-4′), 76.8 (C-2′), 64.5 (C-5′), 37.2 (C-3′), 9.2 (CH_3); *m/z* (FAB > 0) 347 $(M+H)^+$, 235 $(S)^+$, 113 $(BH_2)^+$, 105 $(C_6H_5CO)^+$; *m/z* (FAB < 0) 345 $(M-H)^-$, 121 $(C_6H_5CO_2)^-$, 111 $(B)^-$; Anal. Calcd for $C_{16}H_{18}N_4O_5\cdot 0.6CH_3OH$: C, 54.54; H, 5.62; N, 15.33. Found: C, 54.22; H, 5.42; N, 15.75.

4.4.13. 1-(5-*O*-Benzoyl-2,3-dideoxy-3-*C*-methyl-β-D-*erythro*-pentofuranosyl)-1,2,4-triazole-3-carboxamide (29)

To a stirred solution of compound **28** (100 mg, 0.29 mmol) in dichloromethane (2.9 ml) were added successively 1-methylimidazole (138 μl, 1.74 mmol) and phenoxy(thiocarbonyl) chloride (161 μl, 1.16 mmol). The reaction mixture was stirred at room temperature for 24 h, then water was added. The organic phase was washed with aqueous solution of hydrochloric acid (0.5 N) and water, dried over sodium sulfate and evaporated to dryness. The resulting residue was co-evaporated with dry toluene, then dissolved in the same solvent (4.4 ml) and α,α′-azoisobutyronitrile (32.8 mg, 0.20 mmol) and *tris*(trimethylsilyl)silane (179 μl, 0.58 mmol) were added. The reaction mixture was heated under reflux for 4 h. After cooling to room temperature, the solvent was removed under reduced pressure. Chromatography of the residue on a silica gel column using as eluent a stepwise gradient of methanol (0–5%) in dichloromethane afforded the title compound **29** as a white foam (56.3 mg, 59%): $[\alpha]_D^{20}$ +13.2 (*c* 0.83 in DMSO); ^{1}H NMR (DMSO-d_6) δ 8.75 (1H, s, H-5), 7.89–7.48 (7H, m, $NH_2$and C$_6H_5$CO), 6.21 (1H, d, $J_{1'-2''} = 6.9$ Hz, H-1′), 4.46 (1H, dd, $J_{5'-4'} = 2.9$ Hz and $J_{5'-5''} = 12.2$ Hz, H-5′), 4.35 (1H, dd, $J_{5'-4'} = 5.4$ Hz and $J_{5''-5'} = 12.2$ Hz, H-5″), 3.98 (1H, m, H-4′), 2.70 (1H, m, H-3′), 2.56 (1H, m, H-2′), 2.18 (1H, m, H-2″), 1.13 (3H, d, $J_{CH_{3-3'}} = 6.5$ Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 165.6 (CO), 160.5 (CO), 157.2 (C-3), 144.7 (C-5), 133.4–128.8 (*C*$_6$H$_5$CO), 87.1 (C-1′), 85.0 (C-4′), 64.5

(C-5′), 39.6 (C-2′), 33.2 (C-3′), 15.5 (CH_3); *m*/*z* (FAB > 0) 331 $(M+H)^+$, 219 $(S)^+$, 113 $(BH_2)^+$; *m*/*z* (FAB < 0)$^-$, 111 $(B)^-$; Anal. Calcd for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 58.05; H, 5.44; N, 16.36.

4.4.14. 1-(2,3-Dideoxy-3-*C*-methyl-β-D-*erythro*-pentofuranosyl)-1,2,4-triazole-3-carboxamide (30)

Purification using as eluent a stepwise gradient of methanol (0–10%) in dichloromethane afforded the title compound **30** (20.3 mg, 74%) which was lyophilized from 1,4-dioxane: $[\alpha]_D^{20}$ −4.7 (*c* 0.85 in DMSO); ^{1}H NMR (DMSO-d_6) δ 8.83 (1H, s, H-5), 7.81 and 7.51 (2H, 2× br s, NH_2), 6.15 (1H, d, $J_{1'-2''} = 6.4$ Hz, H-1′), 4.93 (1H, br s, OH-5′), 3.62 (3H, m, H-4′, H-5′ and H-5″), 2.45 (2H, m, H-3′ and H-2′), 2.12 (1H, m, H-2″), 1.07 (3H, d, $J_{CH_{3-3'}} = 6.3$ Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 160.6 (CO), 157.0 (C-3), 144.0 (C-5), 88.7 (C-4′), 87.9 (C-1′), 61.4 (C-5′), 40.2 (C-2′), 32.1 (C-3′), 15.8 (CH_3); *m*/*z* (FAB > 0) 227 $(M+H)^+$, 115 $(S)^+$, 113 $(BH_2)^+$; *m*/*z* (FAB < 0) 225 $(M-H)^-$, 111 $(B)^-$; Anal. Calcd for $C_9H_{14}N_4O_3 \cdot 0.21$,4-dioxan: C, 48.27; H, 6.45; N, 22.98. Found: C, 48.19; H, 6.20; N, 23.00.

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References and notes

1. Mathé, C.; Gosselin, G. *Antiviral Res.* **2006**, *71*, 276.
2. Carvalho, A. P.; Fernandes, P. A.; Ramos, M. J. *Mini-Rev. Med. Chem.* **2006**, *6*, 549.
3. Lewis, W.; Day, B. J.; Copeland, W. C. *Nat. Rev. Drug Disc.* **2003**, *2*, 812.
4. Couturier, S.; Aljarah, M.; Gosselin, G.; Mathé, C.; Périgaud, C. *Tetrahedron* **2007**, *63*, 11260.
5. Agyei-Aye, K.; Baker, D. C. *Carbohydr. Res.* **1983**, *183*, 261.
6. Vorbrüggen, H. *Acc. Chem. Res.* **1995**, *28*, 509.
7. Ishido, Y.; Nakazaki, N.; Sakairi, N. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2088.
8. Marchand, A.; Lioux, T.; Mathé, C.; Imbach, J.-L.; Gosselin, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2249.
9. Griffon, J.-F.; Mathé, C.; Faraj, A.; Aubertin, A.-M.; De Clercq, E.; Balzarini, J.; Sommadossi, J.-P.; Gosselin, G. *Eur. J. Med. Chem.* **2001**, *36*, 447.
10. Chavis, C.; de Gourcy, C.; Dumont, F.; Imbach, J.-L. *Carbohydr. Res.* **1983**, *113*, 1.
11. Kohayama, N.; Yamamoto, Y. *Synthesis* **2003**, 2639.
12. Gu, X.; Yang, Z.; Zhang, L.; Kunerth, S.; Fliegert, R.; Weber, K.; Guse, A. H.; Zhang, L. *J. Med. Chem.* **2004**, *47*, 5674.
13. Kim, M.; Jeong, L. S.; Kim, J. H.; Yong, S.; Chun, S. Y.; Sang, K. L.; Chun, M. W. *Nucleosides Nucleotides Nucl.* **2004**, *35*, 715.
14. Witkowski, J. T.; Robins, R. K.; Sidwell, R. W.; Simon, L. N. *J. Med. Chem.* **1972**, *15*, 1150.