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Synthesis of novel apionucleosides: a short and concise synthesis of 2-deoxyapio-L-furanosyl acetate from D-lactose

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Abstract

A series of 2′-deoxyapio-L-furanosyl pyrimidine nucleosides were efficiently synthesized starting from D-lactose via condensation of lactitor acetates with silylated pyrimidine bases under standard Vorbrüggen conditions. Their structures were determined by 1D and 2D NMR spectroscopy. All the synthesized nucleosides were assayed against several viruses such as HIV-1, HBV, HSV-1, HSV-2, and HCMV. However, none of these compounds had any significant antiviral activity at concentrations up to 100 μM.

Keywords: Apionucleoside; 2-Deoxyapiose; Vorbrüggen condition

1. Introduction

The discovery of novel nucleosides as antiviral and anticancer agents has been the goal of nucleoside chemists for decades. In particular, since the emergence of the HIV pandemic, extensive effort have been concentrated on various modifications in the sugar moiety of nucleosides, resulting in FDA approved anti-HIV agents such as AZT,[1] ddC,[2] ddI,[3] d4T,[4] 3TC,[5] and Abacavir.[6] In addition, several nucleosides as anti-HBV agents including DAPD,[7] L-F-ddC,[8] and L-FMAU,[9] which are being developed at various stages, have been synthesized. Among these compounds, 3TC (lamivudine) is being clinically used as an anti-HIV as well as anti-HBV agent.[10] Although there has been considerable interest in modifications at the 2′- and 3′-position of the nucleosides, much less is known about the 4′-modified compounds.[11] However, naturally occurring antibiotics, nucleocidin[12] possessing a 4′-fluorine atom, 4′-azido thymidine (ADRT),[13] 4′-fluorinated carbocyclic nucleoside,[14] and the 3′-fluoro oxetanosin analogue[15] have demonstrated a variety of biological activities. In other approaches, more fundamental modifications to the pentofuranose moiety, resulting in isonucleosides and apionucleosides, have been reported to be compatible with antiviral activities.[16] The transposition of the base moiety to C-2′ or the C-4′ hydroxymethyl group to C-3′ leads to isonucleosides and apionucleosides, respectively. In attempts to discover new lead compounds with an improved biological activity, a number of apiosyl-nucleosides with several kinds of functional groups in the 3′-position were synthesized in previous studies.[17] In this paper, a very short and efficient synthetic route for novel 2′-deoxyapioyl-L-nucleosides (Fig. 1) from a very cheap and commercially available D-lactose and their antiviral activity is reported.

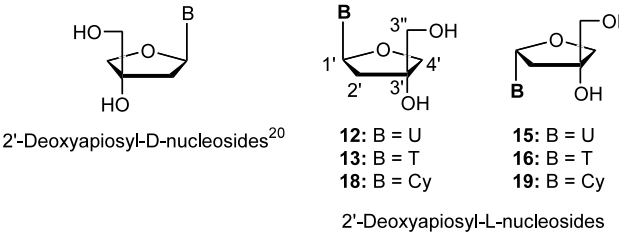

Fig. 1.

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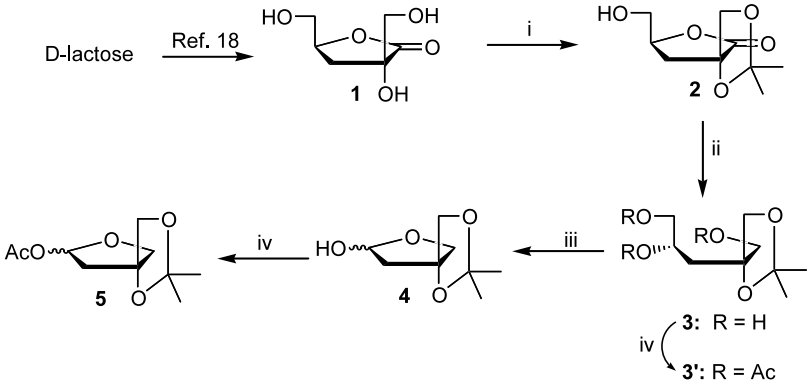
2. Results and discussion

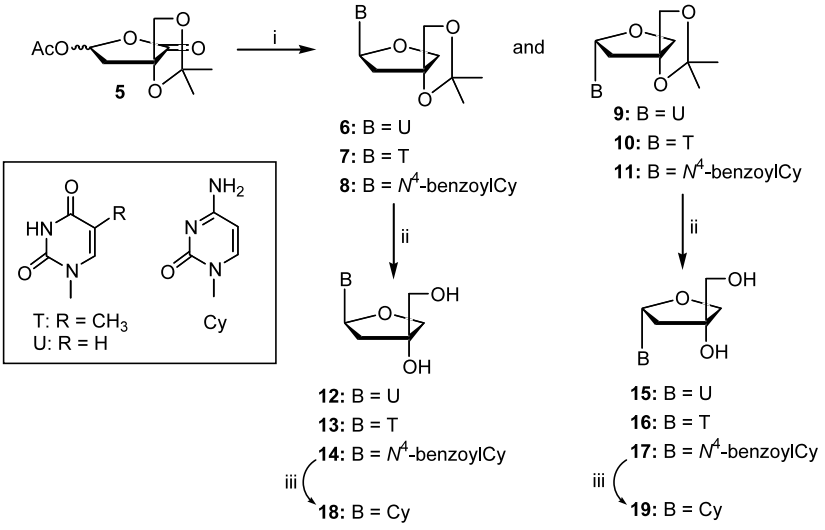
In order to reach the key intermediate **5** for the synthesis of the desired nucleosides, commercially available D-lactose was used as a carbohydrate chiral template starting material. α-D-Isosaccharino-1,4-lactone (**1**) could be made from D-lactose by the well-known method.[18] Following previously described methodologies we have synthesized lactol derivative **4** (Scheme 1).[19] The vicinal diol **1** was protected in a mixed solvent of 2,2-dimethoxypropane and acetone with a catalytic amount of *p*-TsOH to give an isopropylidene protected **2** in an 86% yield. Treatment of **2** with lithium aluminum hydride ($LiAlH_4$) in anhydrous THF furnished **3**, of which the vicinal diol moiety was readily cleaved by sodium metaperiodate ($NaIO_4$) to give compound **4** in the cyclized lactol form in a 64% yield for the two steps. The lactol derivative **4** was acetylated by acetic anhydride in an anhydrous pyridine solvent to give a glycosyl donor **5** in a 85% yield.

Condensation of **5** with silylated uracil under the standard Vorbrüggen conditions gave separable stereoisomers, **6** and **9** (Scheme 2) which were separated by silica gel chromatography and treated with 80% acetic acidic solution to give the deprotected uracil derivatives, **12** and **15**, respectively. For the synthesis of the thymine nucleosides, the glycosyl donor **5** was condensed with persilylated thymine under similar condensation conditions to give the anomeric mixtures, **7** and **10**, which were difficult to separate by normal silica gel column chromatography. Without separation, the anomeric mixture of **7** and **10** was subjected to similar acidic hydrolysis conditions as described for uracil to give the separable nucleosides, **13** and **16**, respectively.

For the synthesis of the cytosine nucleosides, the key intermediate **5** was condensed with silylated N^4-benzoyl cytosine under same conditions as described for the thymine nucleosides to afford the products, **8** and **11**. The anomeric mixtures were easily separated by silica gel column chromatography. To remove the isopropylidene protecting groups, nucleosides **8** and **11** were subjected to similar acidic hydrolysis conditions to fur-



Scheme 1. Reagents: (i) DMP, PTSA, acetone, rt, 2 h, 86%; (ii) $LiAlH_4$, THF, reflux, overnight, 80%; (iii) $NaIO_4$, MeOH–H_2O, rt, 2 h, 82%; (iv) Ac_2O, DMAP, pyridine, rt, overnight, 91%.



Scheme 2. Reagents: (i) persilylated pyrimidine nucleobase, TMSOTf, CH_3CN, rt, 4 h, 50–70%; (ii) 80% AcOH, 80 °C, 2–3 h, 40–60%; (iii) NH_3–MeOH, rt, overnight, 85–90%.

nish **14** and **17**, respectively. The free nucleosides **18** and **19** were obtained by treatment under debenzoylation conditions using saturated methanolic ammonia.

Stereochemical assignments of the synthesized compounds were determined on the basis of ^{1}H NMR spectroscopy. A cross peak was found in the NOESY spectrum for **18** between proximal hydrogen atoms (H-6 and H-3″β). However, there were no cross peaks in the spectrum for **19**. It should be noted that the synthetic route of the enantiomers of **12**, **13** and **18** has been previously reported.[20] As a result, the structures of the synthesized nucleosides were readily determined by a comparisons of the optical rotation values and their NMR spectra.

In summary, a very efficient synthetic route for novel 2′-deoxyapio-L-furanosyl nucleosides starting from very cheap and commercially available D-lactose was developed. All the synthesized compounds were tested against several viruses such as HIV-1 (MT-4 cells), HBV, HSV-1,2 (CCL18 cells), and HCMV (AD-169 and Davis cells). However, none of these compounds had any significant antiviral activity up to 100 μM.

3. Experimental

3.1. General

The melting points were determined on a Mel-temp II laboratory device and were uncorrected. The NMR spectra were recorded on a Bruker 300 Fourier transform spectrometer; chemical shifts are reported in parts per million (δ) and the signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). The UV spectra were obtained using a Beckman DU-7 spectrophotometer. The optical rotations were measured on an Autopol-IV digital polarimeter. Elemental analyses were performed in the Korea Basic Science Institute (KBSI). Thin layer chromatography (TLC) was performed on Uniplates (silica gel) purchased from Analtech Co. Dry 1,2-dichloro-ethane, CH_2Cl_2, MeCN, C_6H_6 and Py were distilled from CaH_2 prior to use. Dry THF was obtained by distillation from Na and benzophenone when the solution became purple.

3.2. α-D-Isosaccharino-1,4-lactone acetonide (2)

α-D-Isosaccharino-1,4-lactone (20 g, 0.123 mol) was dissolved in a 1:5 mixture of 2,2′-dimethoxypropane and acetone (60/300 mL). *p*-Toluenesulfonic acid monohydrate (950 mg) was then added to the mixture. The reaction mixture was stirred 1 h at rt and neutralized with Et_3N. The resulting solution was evaporated under reduced pressure. The residue was extracted with EtOAc, washed with brine, and dried under anhyd $MgSO_4$. Removal of solvent gave a syrup, which was purified by silica gel column chromatography (1:1.5 hexane–EtOAc) to give compound **2** (24.4 g, 98%) as a white solid: mp 54.5 °C; $[\alpha]_D^{25}$ +42.2° (*c* 1.0, $CHCl_3$) {Lit.[19] mp 56 °C; $[\alpha]_D$ +43° (*c* 1.0, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$) δ 6.71 (m, 1 H, H-4), 4.35 (d, *J* 9.3 Hz, 1 H, H-5), 4.13 (d, *J* 9.0 Hz, 1 H, H-5), 4 00 (d, *J* 12.3 Hz, 1 H, H-2′), 3. 63 (d, *J* 17.7, 1 H, H-2′), 2.46 (dd, *J* 14.1, 7.5 Hz, 1 H, H-3′a), 2.35 (dd, *J* 13.8, 6.6 Hz, 1 H, H-3′b), 1.49 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3).

3.3. 3-Deoxy-2-*C*-hydroxymethyl-2,2′-*O*-isopropylidene-D-*glycero*-pentitol (3)

To a solution of **2** (1.0 g, 4.92 mmol) in dry THF (10 mL), $LiAlH_4$ was added in small portions at 0 °C. The mixture was stirred overnight at rt and an excess of $LiAlH_4$ was destroyed by the sequential addition of water (0.4 mL), and 10% NaOH (0.6 mL) and water (1.2 mL). After filtering the slurry mixture through a pad of Celite, it was washed several times with MeOH. The combined filtrate was concentrated under reduced pressure to give a crude triol **3** as a syrup (0.88 g, 82%), which was subjected to the subsequent reaction without further purification. For the purpose of spectroscopic analyses, a small amount of crude **3** was acetylated under the standard conditions (Ac_2O, DMAP, Py). This product was described as its tri-*O*-acetylated derivative **3′** as an oil, which was purified by silica gel column chromatography (2:1 hexane–EtOAc): **3′**: $[\alpha]_D^{25}$ −16.4° (*c* 1.0, $CHCl_3$) {Lit.[19] syrup; $[\alpha]_D$ −16° (*c* 1.0, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$) δ 5.25 (m, 1 H, H-4), 4.34 (dd, *J* 12.0, 3.5 Hz, 1 H, H-5), 4.14–3.94 (m, 3 H, H-1 and H-2′a), 3 78 (d, *J* 8.7 Hz, 1 H, H-2′b), 2.19–1.90 (m, 2 H, H-3), 2.09 (s, 3 H, CH_3CO), 2.06 (s, 3 H, acetyl), 2.05 (s, 3 H, acetyl), 1.39 (s, 6 H, $2CH_3$).

3.4. 3-*C*-Hydroxymethyl-3,3′-*O*-isopropylidene-L-*glycero*-tetrose (4)

To a solution of **3** (1.5 g, 7.2 mmol) in MeOH (14 mL), a solution of sodium periodate (1.87 g, 7.36 mmol) in water (10 mL) was added slowly at rt. The mixture was stirred for 1 h and poured into a satd $NaHCO_3$ soln. The resulting solid was filtered and washed with MeOH. The combined solution was concentrated, and the residue was then extracted with EtOAc, washed with brine, and dried over anhyd magnesium sulfate. The removal of the solvent gave a syrup, which was purified by silica gel column chromatography (2:1 hexane–EtOAc) to give a diastereomeric mixture of **4** (1.03 g, 82%) as a syrup: ^{1}H NMR ($CDCl_3$) δ 5.64 (dd, *J* 4.0, 2.0 Hz, 1 H, H-1), 5.46 (d, *J* 4.0 Hz, 1 H, H-1), 4.10–3.78 (m, 4 H, H-4 and H-3′), 2.28–2.00 (m, 2 H, H-2), 1.56 (s, 6 H, $2CH_3$); Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.89; H, 8.36.

3.5. 1-*O*-Acetyl-3-*C*-hydroxymethyl-3,3′-*O*-isopropylidene-L-*glycero*-tetrose (5)

Compound **4** (1.0 g, 5.74 mmol) was dissolved in anhyd Py (10 mL). To this solution, DMAP (20 mg) and Ac_2O (0.81 mL, 8.6 mmol) was added drop wise at 0 °C. The mixture was stirred for 4 h at rt and was added cold water (1 mL) was then added. The solvent was concentrated under reduced pressure and coevaporated with toluene twice. The residue was extracted with EtOAc, washed with brine, and dried ($MgSO_4$). Removal of solvent gave a syrupy residue, which was purified by silica gel column chromatography (5:1 hexane–EtOAc) to give diastereomeric mixture of **5** (1.05 g, 85%) as an oil: ^{1}H NMR ($CDCl_3$) δ 6.36 (d, J 3.9 Hz, 0.3 H, H-1), 6.26 (t, J 4.2 Hz, 0.7 H, H-1), 4.13–3.86 (m, 4 H, H-4 and H-3′), 2.55 (dd, J 14.4, 6.0 Hz, 0.6 H, H-2), 2.17 (d, J 4.8 Hz, 1.4 H, H-2), 2.09 (s, 2.1 H, CH_3CO), 2.01 (s, 0.9 H, H-2, CH_3CO), 1.37 (s, 4.2 H, CH_3), 1.29 (s, 1.8 H, CH_3); Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.67; H, 7.35.

3.6. 1-[3-*C*-Hydroxymethyl-3,3′-*O*-isopropylidene-β-L-*glycero*-tetrafuranosyl] uracil (6) and 1-[3-*C*-hydroxymethyl-3,3′-*O*-isopropylidene-α-L-*glycero*-tetrafuranosyl] uracil (9)

The suspension of uracil (233 mg, 2.08 mmol), HMDS (15 mL), and $(NH_4)_2SO_4$ (20 mg, catalytic amount) was refluxed under a nitrogen atmosphere for 4 h and the excess HMDS was removed under high vacuum. To the residue, dry MeCN (5 mL), a solution of the acetates **5** (374 mg, 1.73 mmol) in dry MeCN (15 mL), and Me_3SiOTf (0.4 mL, 1.92 mmol) was added at rt and the resulting reaction mixture was stirred for 1 h at rt. Saturated $NaHCO_3$ (5 mL) was added to the reaction mixture and then stirred for another 30 min, which was extract with methylene chloride (10 mL × 2). The combined organic layer was washed with brine and dried over anhyd $MgSO_4$, filtered, and concentrated under vacuum. The residue of the anomeric mixture was separated by silica gel column chromatography (1:3 hexane–EtOAc) to give **6** (136.6 mg, 30%) and **9** (150 mg, 33%), respectively. **6** $[\alpha]_D^{25}$ + 31.4° (c 0.23, MeOH); ^{1}H NMR ($CDCl_3$) δ 8.31 (br s, 1 H, –NH), 7.70 (d, J 6.0 Hz, 1 H, H-6), 6.22 (dd, J 7.5, 2.7 Hz, 1 H, H-1′), 5.76 (d, J 8.1 Hz, 1 H, H-5), 4.22 (d, J 9.6 Hz, 2 H, H-4′), 3.87 (d, J 9.6 Hz, 2 H, H-3″), 2.57 (dd, J 15.0, 7.5 Hz, 1 H, H-2′), 2.29 (dd, J 12.0, 2.4 Hz, 1 H, H-2′), 1.41 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3); Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.69; H, 6.13; N, 10.37; **9** $[\alpha]_D^{25}$ + 11.1° (c 0.27, MeOH); ^{1}H NMR ($CDCl_3$) δ 8.46 (br s, 1 H, –NH), 7.34 (d, J 8.4 Hz, 1 H, H-6), 6.22 (t, J 6.6 Hz, 1 H, H-1′), 5.76 (dd, J 8.1, 2.4 Hz, 1 H, H-5), 4.11 (d, J 9.3 Hz, 1 H, H-4′), 4.04 (s, 2 H, H-3″), 4.01 (d, J 9.3 Hz, 1 H, H-4′), 2.76 (dd, J 13.8, 6.3 Hz, 2 H, H-2′), 1.42 (s, 6 H, $2CH_3$); Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.78; H, 6.10; N, 10.45.

3.7. 1-[3-*C*-Hydroxymethyl-3,3′-*O*-isopropylidene-β-L-*glycero*-tetrafuranosyl] thymine (7) and 1-[3-*C*-hydroxymethyl-3,3′-*O*-isopropylidene-α-L-*glycero*-tetrafuranosyl] thymine (10)

As a diastereomeric mixture, compound **7** and **10** were prepared by the same procedure as described for **6** and **9**: ^{1}H NMR ($CDCl_3$) δ 11.28 (br s, 2 H, –2NH), 7.76 (s, 1 H, H-6), 7.49 (s, 1 H, H-6), 6.18 (t, J 7.5, Hz, 1 H, H-1′), 6.00 (dd, J 7.0, 4.5 Hz, 1 H, H-1′), 4.19 (d, J 8.7 Hz, 1 H, H-4′), 3.90 (d, J 8.7 Hz, H-4′), 3.78 (d, J 9.0 Hz, 1 H, H-4′), 3.63 (d, J 9.0 Hz, H-4′), 3.42 (s, 2 H, H-3″), 3.34 (s, 2 H, H-3″), 2.48 (m, 2 H, H-2′), 2.04 (m, 2 H, H-2′), 1.45 (s, 6 H, $2CH_3$), 1.37 (s, 6 H, $2CH_3$); Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.49; H, 6.21; N, 9.88.

3.8. N^4-Benzoyl-1-[3-*C*-hydroxymethyl-3,3′-*O*-isopropylidene-β-L-*glycero*-tetrafuranosyl] cytosine (8) and N^4-benzoyl-1-[3-*C*-hydroxymethyl-3,3′-*O*-isopropylidene-α-L-*glycero*-tetrafuranosyl] cytosine (11)

The cytosine derivative **8** and **11** was prepared using the same method as described for the synthesis of **6** and **9**; **8**: yield: 37%; $[\alpha]_D^{25}$ − 34.8° (c 0.4, MeOH); ^{1}H NMR ($CDCl_3$) δ 8.09 (d, J 7.5 Hz, 1 H, H-6), 7.91–7.49 (m, 5 H, Ar), 7.54 (d, J 7.5 Hz, 1 H, H-5), 6.22 (dd, J 6.9, 2.1 Hz, 1 H, H-1′), 4.32 (dd, J 9.9, 1.5 Hz, 1 H, H-4′), 4.05 (s, 2 H, H-3″), 4.01 (d, J 9.9 Hz, 1 H, H-4′), 2.65 (dd, J 14.4, 6.9 Hz, 1 H, H-2′), 2.44 (dd, J 3.6, 1.8 Hz, 1 H, H-2′), 1.39 (s, 3 H, CH_3), 2.91 (s, 3 H, CH_3); Anal. Calcd for $C_{19}H_{21}N_3O_5$: C, 61.45; H, 5.70; N, 11.31. Found: C, 61.48; H, 5.61; N, 11.38; **11**: yield: 32%; $[\alpha]_D^{25}$ + 73.2° (c 0.66, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.93–7.26 (m, 7 H, Ar, H-6 and H-5), 6.1 (t, J 6.3 Hz, 1 H, H-1′), 4.35 (s, 2 H, H-4′), 4.04 (dd, J 18.0, 9.0 Hz, 2 H, H-3″), 3.06 (dd, J 14.1, 6.3 Hz, 1 H, H-2′), 2.20 (dd, J 16.2, 6.0 Hz, 1 H, H-2′), 1.42 (s, 6 H, $2CH_3$); Anal. Calcd for $C_{19}H_{21}N_3O_5$: C, 61.45; H, 5.70; N, 11.31. Found: C, 61.64; H, 5.56; N, 11.25.

3.9. 1-[3-*C*-(Hydroxymethyl)-3-deoxy-3-hydroxy-β-L-*erythro*-tetrafuranosyl] uracil (12)

To the compound **6** (100 mg, 0.37 mmol), 80% AcOH soln (3 mL) was added, and stirred for 6 h, at 80 °C. The solvent was concentrated and coevaporated with toluene twice and the residue was purified by silica gel column chromatography (10:1 CH_2Cl_2–MeOH) to give compound **12** (54.4 mg, 64%) as a white solid: mp 140–143 °C; UV (MeOH) λ_{max} 270.5 nm; $[\alpha]_D^{25}$ − 13.2° (c 0.8, MeOH)) {Lit.[20] mp 135–137 °C; $[\alpha]_D^{20}$ + 12.42°

(*c* 1.30, MeOH) for enantiomer of **12**}; ^{1}H NMR (Me_2SO-d_6) δ 11.21 (br s, 1 H, –NH), 7.73 (d, *J* 6.1 Hz, 1 H, H-6), 6.25 (dd, *J* 7.2, 1.8 Hz, 1 H, H-1′), 5.73 (d, *J* 8.1 Hz, 1 H, H-5), 3.99 (d, *J* 9.6 Hz, 2 H, H-4′), 3.87 (d, *J* 9.6 Hz, 2 H, H-3″), 2.57 (dd, *J* 15.0, 7.5 Hz, 1 H, H-2′), 2.32 (dd, *J* 12.4, 2.6 Hz, 1 H, H-2′); Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.16; H, 5.32; N, 12.11.

3.10. 1-[3-*C*-(Hydroxymethyl)-3-deoxy-3-hydroxy-β-L-*erythro*-tetrafuranosyl] thymine (13)

The compound **13** was prepared from **7** using the method described for preparing **12**: mp 171–173 °C; UV (MeOH) λ_{max} 266.0 nm; $[\alpha]_D^{25}$ +7.10° (*c* 1.0, MeOH) {Lit.[20] mp 169–172 °C; $[\alpha]_D^{20}$ −6.30° (*c* 0.09, MeOH) for enantiomer of **13**}; ^{1}H NMR (Me_2SO-d_6) δ 11.27 (br s, 1 H, –NH, D_2O exchangeable), 7.76 (s, 1 H, H-6), 6.16 (dd, *J* 7.4, 5.6 Hz, 1 H, H-1′), 5.05 (br s, 2 H, –OH, D_2O exchangeable), 3.89 (d, *J* 9.6 Hz, 1 H, H-4′), 3.77 (d, *J* 9.6 Hz, 1 H, H-4′), 3.43 (d, *J* 7.5 Hz, 2 H, H-3″), 2.03 (m, 2 H, H-2′), 1.89 (s, 3 H, CH_3); Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.56. Found: C, 49.68; H, 5.69; N, 11.46.

3.11. N^4-Benzoyl-1-[3-*C*-(Hydroxymethyl)-3-deoxy-3-hydroxy-β-L-*erythro*-tetrafuranosyl] cytosine (14)

Cytosine derivative **14** was prepared using the method described for preparing **12**: mp 176–178 °C; $[\alpha]_D^{25}$ +73.0° (*c* 1.6, MeOH); ^{1}H NMR ($CDCl_3$) δ 8.17 (d, *J* 7.2 Hz, 1 H, H-6), 8.00–7.33 (m, 6 H, Ar and H-5), 6.12 (dd, *J* 7.4, 1.5 Hz, 1 H, H-1′), 4.19 (d, *J* 9.3 Hz, 1 H, H-4′), 3.81 (d, *J* 9.0 Hz, 1 H, H-4′), 3.44 (s, 2 H, H-3″), 2.49 (dd, *J* 12.7, 6.0 Hz, 1 H, H-2′), 2.02 (dd, *J* 14.1, 6.0 Hz, 1 H, H-2′); Anal. Calcd for $C_{16}H_{17}N_3O_5$: C, 48.00; H, 5.17; N, 12.68. Found: C, 47.88; H, 5.09; N, 12.54.

3.12. 1-[3-*C*-(Hydroxymethyl)-3-deoxy-3-hydroxy-α-L-*erythro*-tetrafuranosyl] uracil (15)

Compound **15** was made from **9** using a similar procedure as described for **12**: mp 169–171 °C; UV (MeOH) λ_{max} 271.0 nm; $[\alpha]_D^{25}$ +36.7° (*c* 0.57, MeOH); ^{1}H NMR (Me_2SO-d_6) δ 11.27 (br s, 1 H, –NH), 7.28 (d, *J* 8.6 Hz, 1 H, H-6), 6.31 (*J* 6.3 Hz, 1 H, H-1′), 5.79 (dd, *J* 8.0, 2.6 Hz, 1 H, H-5), 4.10 (d, *J* 9.7 Hz, 1 H, H-4′), 4.04 (d, *J* 9.7 Hz, 1 H, H-4′), 3.98 (d, *J* 9.5 Hz, 2 H, H-3″), 2.74 (dd, *J* 12.6, 6.0 Hz, 2 H, H-2′); Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.55; H, 5.18; N, 12.45.

3.13. 1-[3-*C*-(Hydroxymethyl)-3-deoxy-3-hydroxy-α-L-*erythro*-tetrafuranosyl] thymine (16)

The thymine derivative **16** was prepared from **10** using the method described for preparing **12**: mp 172–174 °C; UV (MeOH) λ_{max} 267.5 nm; $[\alpha]_D^{25}$ −23.2° (*c* 0.7, MeOH); ^{1}H NMR (Me_2SO-d_6) δ 11.28 (br s, 1 H, –NH, D_2O exchangeable), 7.48 (s, 1 H, H-6), 6.18 (t, *J* 7.4 Hz, 1 H, H-1′), 5.12–4.96 (br d, 2 H, –OH, D_2O exchangeable), 4.08 (d, *J* 9.4 Hz, 1 H, H-4′), 3.62 (d, *J* 9.4 Hz, 1 H, H-4′), 3.34 (m, 2 H, H-3″), 2.13 (m, 2 H, H-2′), 1.82 (s, 3 H, CH_3); Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.56. Found: C, 49.36; H, 5.88; N, 11.79.

3.14. N^4-Benzoyl-1-[3-*C*-(hydroxymethyl)-3-deoxy-3-hydroxy-α-L-*erythro*-tetrafuranosyl] cytosine (17)

The compound **17** was prepared from **11** as described for the synthesis of **12**: mp 167–169 °C; $[\alpha]_D^{25}$ +26.1° (*c* 0.67, MeOH); ^{1}H NMR ($CDCl_3$) δ 8.15 (d, *J* 7.2 Hz, 1 H, H-6), 7.63 (d, *J* 7.2 Hz, 1 H, H-5), 8.00–7.33 (m, 5 H, Ar), 6.14 (t, *J* 6.6 Hz, 1 H, H-1′), 4.16 (d, *J* 9.3 Hz, 1 H, H-4′), 3.76 (d, *J* 9.0 Hz, 1 H, H-4′), 3.40 (s, 2 H, H-3″), 2.47 (dd, *J* 13.5, 6.0 Hz, 1 H, H-2′), 2.06 (dd, *J* 14.1, 7.5 Hz, 1 H, H-2′); Anal. Calcd for $C_{16}H_{17}N_3O_5$: C, 48.00; H, 5.17; N, 12.68. Found: C, 47.76; H, 5.31; N, 12.78.

3.15. 1-[3-*C*-(Hydroxymethyl)-3-deoxy-hydroxy-β-L-*erythro*-tetrafuranosyl] cytosine (18)

Compound **14** (110 mg, 0.33 mmol) was dissolved in 10 mL of a 0.5 M CH_3ONa soln and the resulting solution was stirred 2 h at rt. The reaction mixture was neutralized with cationic amberlite resin (120^+) and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (5:1 CH_2Cl_2–MeOH) to give **18** as a white solid (61 mg, 82%): mp 170–171 °C; UV (MeOH) λ_{max} 271.5 nm; $[\alpha]_D^{25}$ −37.12° (*c* 1.6, MeOH) {Lit.[20] $[\alpha]_D^{20}$ +36.23° (*c* 0.59, MeOH) for enantiomer of **18**}; ^{1}H NMR (Me_2SO-d_6) δ 8.21 (d, *J* 7.0 Hz, 1 H, H-6), 7.48 (d, *J* 7.0 Hz, 1 H, H-5), 6.15 (dd, *J* 7.2, 1.3 Hz, 1 H, H-1′), 4.19 (d, *J* 9.3 Hz, 1 H, H-4′), 3.83 (d, *J* 9.1 Hz, 1 H, H-4′), 3.47 (s, 2 H, H-3″), 2.45 (dd, *J* 12.7, 6.0 Hz, 1 H, H-2′), 2.11 (dd, *J* 13.1, 6.1 Hz, 1 H, H-2′); Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.86; H, 5.56; N, 18.73.

3.16. 1-[3-*C*-(Hydroxymethyl)-3-deoxy-3-hydroxy-α-L-*erythro*-tetrafuranosyl] cytosine (19)

Compound **19** was made from **17** using a similar procedure as described for **18**: mp 168–170 °C; UV (MeOH) λ_{max} 272.5 nm; $[\alpha]_D^{25}$ +21.7° (*c* 0.67, MeOH); ^{1}H NMR (Me_2SO-d_6) δ 8.17 (d, *J* 7.2 Hz, 1 H, H-6), 7.65 (d, *J* 7.2 Hz, 1 H, H-5), 6.10 (t, *J* 6.6 Hz, 1 H, H-1′), 4.10 (d, *J* 9.2 Hz, 1 H, H-4′), 3.77 (d, *J* 9.2 Hz, 1 H, H-4′), 3.43 (s, 2 H, H-3″), 2.45 (dd, *J* 12.0, 6.1 Hz, 1 H, H-2′), 2.06

(dd, *J* 12.5, 4.2 Hz, 1 H, H-2′); Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.30; H, 5.91; N, 18.22.

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References

1. Furman, P. A.; Fyfe, J. A.; St. Clair, M. H.; Weinhold, K.; Rideout, J. L.; Freeman, G. A.; Lehrman, S. N.; Bolognesi, D. P.; Broder, S.; Mitsuya, H.; Barry, D. W. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 8333–8337.
2. Yarchoan, R.; Perno, C. F.; Thomas, R. V.; Klecker, R. W.; Allain, J.-P.; Wills, R. J.; McAtee, N.; Fischl, M. A.; Dubinsky, R.; McNeely, M. C.; Mitsuya, H.; Lawley, T. J.; Safai, B.; Myers, C. E.; Pluda, J. M.; Leuther, M.; Collins, J. M.; Broder, S. *Lancet* **1988**, *1*, 76–81.
3. Yarchoan, R.; Mitsuya, H.; Thomas, R. V.; Pluda, J. M.; Hartman, N. R.; Perno, C. F.; Marczyk, K. S.; Allain, J.-P.; Johns, D. G.; Broder, S. *Science* **1989**, *245*, 412–415.
4. Lin, T.-S.; Schinazi, R. F.; Prusoff, W. H. *Biochem. Pharmacol.* **1987**, *36*, 2713–2718.
5. Schinazi, R. F.; Chu, C. K.; Peck, A.; McMillan, A.; Mathis, R.; Cannon, D.; Jeong, L. S.; Beach, J. W.; Choi, W. B.; Yeola, S.; Liotta, D. C. *Antimicrob. Agents Chemother*. **1992**, *36*, 672–676.
6. Daluge, S. M.; Good, S. S.; Faletto, M. B.; Miller, W. H.; StClair, M. H.; Boone, L. R.; Tisdale, M.; Parry, N. R.; Reardon, J. E.; Dornsife, R. E.; Averett, D. R.; Krenitsky, T. A. *Antimicrob. Agents Chemother*. **1997**, *41*, 1082–1093.
7. Schinazi, R. F.; McClure, H. M.; Boudinot, F. D.; Xiang, Y.-J.; Chu, C. K. *Antiviral Res.* **1994**, *23* (Suppl.), 81–89.
8. Lin, T. S.; Luo, M. Z.; Liu, M. C.; Pai, S. B.; Dutschman, G. E.; Cheng, Y.-C. *J. Med. Chem*. **1994**, *37*, 798–803.
9. Chu, C. K.; Ma, T. W.; Shanmuganathan, K.; Wang, C.-G.; Xiang, Y.-J.; Pai, S. B.; Yao, G.-Q.; Sommadossi, J.-P.; Cheng, Y.-C. *Antimicrob. Agents Chemother*. **1995**, *39*, 979–981.
10. Dienstag, J. L.; Perrillo, R. P.; Schiff, E. R.; Bartholomew, M.; Vicary, C.; Rubin, M. *N. Engl. J. Med.* **1995**, *333*, 1657–1661.
11. (a) Chen, M. S.; Suttmann, R. T.; Papp, E.; Cannon, P. D.; McRobert, M. J.; Bach, C.; Copeland, W. C.; Wang, T. S. F. *Biochemistry* **1993**, *32*, 6002–6010;
(b) Maag, H.; Nelson, J. T.; Rios-Steiner, J. L.; Prisbe, E. J. *J. Med. Chem*. **1994**, *37*, 431–438;
(c) Nomura, M.; Shuto, S.; Tanaka, M.; Sasaki, T.; Mori, S.; Shigeta, S.; Matsuda, A. *J. Med. Chem*. **1999**, *42*, 2901–2908;
(d) Sugimoto, I.; Shuto, S.; Mori, S.; Shigeta, S.; Matuda, A. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 385–388.
12. (a) Jenkins, I. D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Am. Chem. Soc*. **1976**, *98*, 3346–3357;
(b) Maguire, A. R.; Meng, W. D.; Roberts, S. M.; Willetts, A. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1795–1808.
13. Maag, H.; Rydzewski, R. M.; McRoberts, M. J.; Crawford-Ruth, D.; Verheyden, J. P. H.; Prisbe, E. J. *J. Med. Chem*. **1992**, *35*, 1440–1451.
14. Biggadike, K.; Borthwick, A. D. *J. Chem. Soc., Chem. Commun*. **1990**, 1380–1382.
15. Sato, Y.; Maruyama, T. *Chem. Pharm. Bull*. **1995**, *43*, 91–95.
16. Nair, V.; Jahnke, T. S. *Antimicrob. Agents Chemother*. **1995**, *39*, 1017–1029.
17. (a) Hong, J. H.; Lee, K.; Choi, Y.; Chu, C. K. *Tetrahedron Lett*. **1998**, *39*, 3443–3446;
(b) Hong, J. H.; Gao, M. Y.; Chu, C. K. *Tetrahedron Lett*. **1999**, *40*, 231–234;
(c) Hong, J. H.; Gao, M. Y.; Choi, Y.; Cheng, Y.-C.; Schinazi, R. F.; Chu, C. K. *Carbohydr. Res*. **2000**, *328*, 37–48;
(d) Hong, J. H.; Kim, H. O.; Moon, H. R.; Jeong, L. S. *Arch. Pharm. Res*. **2001**, *24*, 95–99;
(e) Jeong, L. S.; Kim, H. O.; Moon, H. R.; Hong, J. H.; Yoo, S. J.; Choi, W. J.; Chun, M. W.; Lee, C. K. *J. Med. Chem*. **2001**, *44*, 806–813;
(f) Jeong, L. S.; Moon, H. R.; Hong, J. H.; Yoo, S. J.; Choi, W. J.; Kim, H. O.; Ahn, H. S.; Baek, H. W.; Chun, M. W.; Kim, H. D.; Choi, J. R. *Nucleosides Nucleotides Nucleic Acids* **2001**, *20*, 657–660.
18. Whistler, R. L.; BeMiller, J. N. *Methods in Carbohydrate Chemistry*; Academic Press: New York, 1963; Vol. II, pp 477–479.
19. Bennani, F.; Florent, J.-C.; Koch, M.; Monneret, C. *Tetrahedron* **1984**, *40*, 4669–4676.
20. Hammerschmidt, F.; Őhler, E.; Polsteer, J.-P.; Zbiral, E.; Balzarini, J.; De Clercq, E. *Liebigs Ann*. **1995**, 551–558.