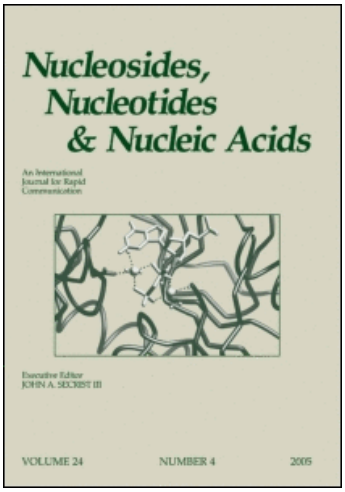

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Simple Synthesis and Anti-Hiv Activity of Novel 3'-Vinyl Branched Apiosyl Pyrimidine Nucleosides

Chang Hyun Oh[a]; Jin Woo Kim[b]; Joon Hee Hong[b]
[a] Medicinal Chemistry Research Center, Korea Institute of Science and Technology, Seoul, Republic of Korea [b] College of Pharmacy, Chosun University, Kwangju, Republic of Korea

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SIMPLE SYNTHESIS AND ANTI-HIV ACTIVITY OF NOVEL 3′-VINYL BRANCHED APIOSYL PYRIMIDINE NUCLEOSIDES

Chang Hyun Oh □ *Medicinal Chemistry Research Center, Korea Institute of Science and Technology, Seoul, Republic of Korea*

Jin Woo Kim and Joon Hee Hong □ *College of Pharmacy, Chosun University, Kwangju, Republic of Korea*

□ *Novel vinyl branched apiosyl nucleosides were synthesized in this study. Apiosyl sugar moiety was constructed by sequential ozonolysis and reductions. The bases (uracil and thymine) were efficiently coupled by glycosyl condensation procedure (persilyated base and TMSOTf). The antiviral activities of the synthesized compounds were evaluated against the HIV-1, HSV-1, HSV-2, and HCMV. Compound 10β displayed moderate anti-HIV activity (EC_{50} = 17.3 μg/mL) without exhibiting any cytotoxicity up to 100 μM.*

Keywords Antiviral Agents; Apiosyl Nucleoside; Ozonolysis

INTRODUCTION

The discovery of novel nucleosides as antiviral and anticancer agents has been the goal of nucleoside chemists for a several decades. In particular, since the emergence of the HIV pandemic, extensive efforts 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] However, side effects and the emergence of drug-resistant mutants continue to be a problem with these antiviral agents. Therefore, the development of structurally new nucleoside derivatives, which have potent antiviral activities and low toxicity as well as novel resistant profiles, are urgently needed to provide better choices for the combination chemotherapy. Furthermore, more fundamental modifications of pentofuranose moiety, such as isonucleosides and apionucleosides, have been reported to be compatible with antiviral activities. Apiosyl nucleosides

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Address correspondence to Dr. Joon Hee Hong, College of Pharmacy, Chosun University, Kwangju 501-759, Republic of Korea E-mail: hongjh@chosun.ac.kr

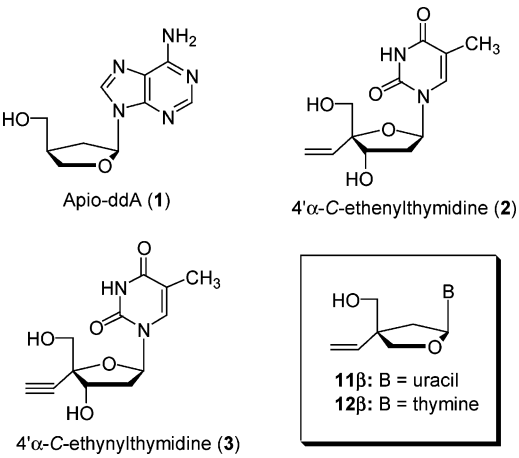
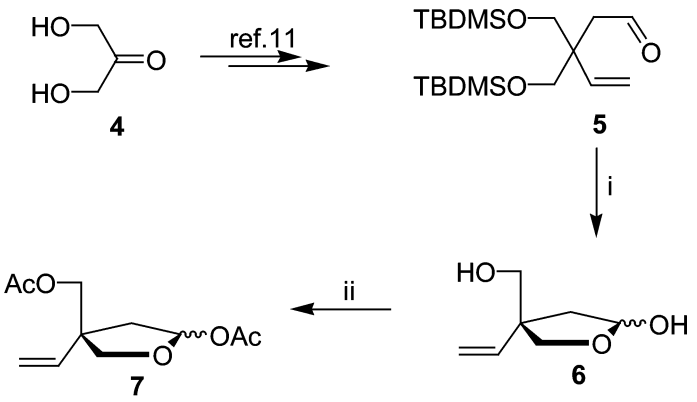


FIGURE 1 Synthesis rationale of target 3′-branched nucleosides.

are a group of compounds that are structurally similar to natural nucleosides in which the 4′-hydroxymethyl group of the classical nucleosides moves to the C3′ position. Among this type of nucleosides, adenine analogue (apio-ddA, **1**) was reported to exhibit anti-HIV activity comparable to parent 2′,3′-didieoxy adenosine.[7] Nevertheless, since systematic structure-activity relationship study in apio dideoxy nucleosides has not been fulfilled so far, it is thought that much more effort should be made in this class of nucleosides to search for new antiviral agents. For example, the compounds synthesized, 4′α-*C*-vinylthymidine **2**,[8] 4′α-*C*-ethynylthymidine **3**[9] are of particular interest as they represent a new class of compounds and exhibit significant biological activity (Figure 1). Recently, we also have reported the synthesis procedure of 4′-hydroxymethyl branched carbocyclic *C*-nucleoside.[10] In this study, we have synthesized novel 3′-vinyl branched apiosylnucleosides in order to find new lead compounds with improved biological activity.

RESULTS AND DISCUSSION

As shown in Scheme 1, the γ,δ-unsaturated aldehyde derivative **5**, which was readily synthesized from 1,3-dihydroxy acetone by a previously reported method,[11] was selected as the starting compound for the synthesis of target nucleosides. Aldehyde **5** was treated with tetrabutylammonium fluoride (TBAF) to give lactol **6**. The apiose lactol **6** was acetylated in pyridine to furnish a 1:1 mixture of key intermediate **7** as glycosyl donor (Scheme 1). For the preparation of the pyrimidine nucleosides, compound **7** was condensed with corresponding per-*O*-silylated bases (uracil and thymine) using trimethylsilyl trifluoromethanesulfonates (TMSOTf) as the catalyst in 1,2-dichloroethane (DCE) to give protected nucleosides **8**β, **8**α, **9**β, and **9**α, respectively. Each nucleoside was subjected to methanolic ammonolysis



SCHEME 1 Synthesis of apiosyl acetate.

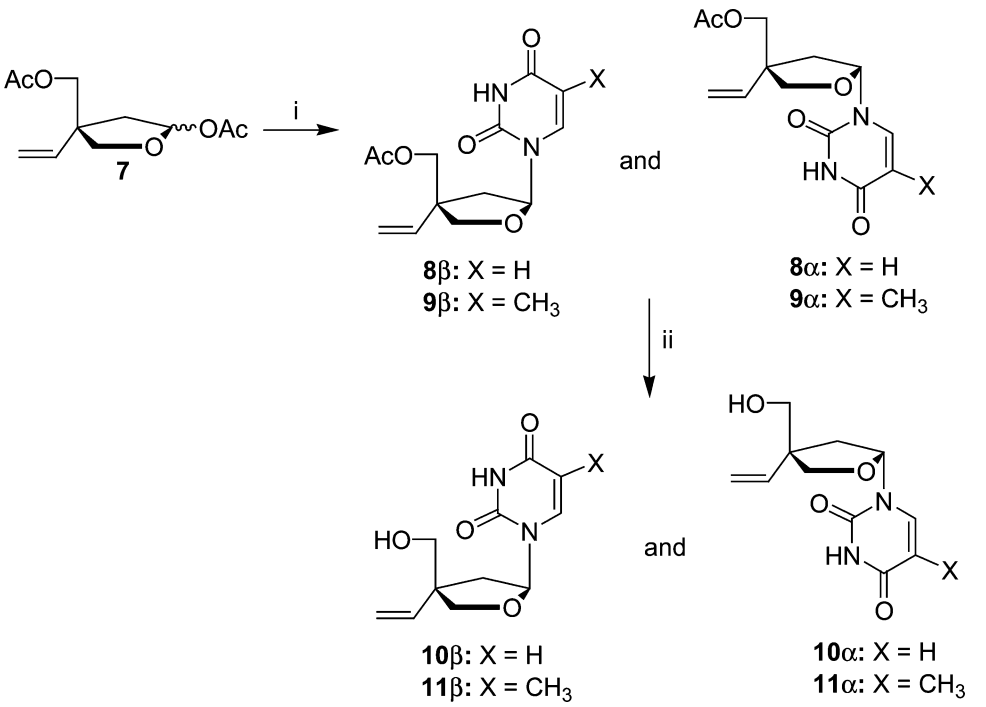
procedures to give corresponding nucleoside analogue **10β**, **10α**, **11β**, and **11α**. Stereochemical assignments of the synthesized compounds were carried out on the basis of ^{1}H NMR spectroscopy. A cross peak was found in the NOE spectrum for **10(α)** between proximal hydrogen atoms (anomeric H and CH_2OH). However, there were no cross peaks in the spectrum for **10(β)**. The stereochemistry of thymine nucleoside analogues was also similarly determined on the basis of NOE results.

Antiviral evaluation on the synthesized compounds was performed against several viruses such as the HIV-1 (MT-4 cells), HSV-1 (CCL81 cells), HSV-2 (CCL-81 cells), and HCMV (AD-169). Among compounds tested, uracil derivative **10β** was found to be potent (EC_{50} = 17.3 μg/mL) against HIV-1 without cytotoxicity up to 100 μg/mL when compared to positive control, AZT (EC_{50} = 0.007 μg/mL, in MT-4 cells) (Table 1).

TABLE 1 Antiviral activity of the synthesized compounds

	HIV-1 EC_{50} (μg/mL)	HSV-1 EC_{50} (μg/mL)	HSV-2 EC_{50} (μg/mL)	HCMV EC_{50} (μg/mL)	Cytotoxicity CC_{50} (μg/mL)
10β	17.3	>100	>100	44.7	>100
10α	78.9	>100	>100	>100	>100
11β	60.2	>100	>100	>100	>100
11α	>100	>100	>100	>100	>100
AZT	0.007	ND	ND	ND	1.5
GCV	ND	ND	ND	1.5	>10
ACV	ND	0.20	ND	ND	>100

AZT: azidothymidine; GCV: ganciclovir; ACV: acyclovir.
ND: Not determined.
EC_{50} (μg/mL): Concentration required to inhibit 50% of virus-induced cytopathicity.
CC_{50} (μg/mL): Concentration required to reduce cell viability by 50%.



Reagents: i) (a) Bases, HMDS, $(NH_4)_2SO_4$, reflux, overnight; (b) silylated bases, TMSOTf; ii) NH_3/MeOH, rt, overnight.

SCHEME 2 Synthesis of vinyl branched pyrimidine nucleosides.

It is interesting to note that the uracil analogue **10***β* exhibited moderate antiviral activity against the HIV-1, indicating that phosphorylation is carried out by intracellular enzymes of T-4 cells.

In summary, this study developed a novel synthetic method for 3′ vinyl branched apiosyl analogues from simple 1,3-dihydroxyacetone. When the synthesized compounds were tested against several viruses such as the HIV-1, HSV-1, HSV-2, and HCMV, the uracil analogue **10***β* exhibit moderate antiviral activity against the HIV-1. These results suggested that the 3′ vinyl branched sugar moiety can serve as a novel template for the development of new antiviral agents.

EXPERIMENTS

All the chemicals were of reagent grade and were used without further purification. All the moisture-sensitive reactions were performed in an inert atmosphere with either N_2 or Ar using distilled dry solvents. The melting points were determined using a Mel-temp II laboratory device and were uncorrected. The NMR spectra were recorded on a JEOL JNM-LA

300 spectrometer. The 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 elemental analyses were performed using an Elemental Analyzer System (EA1112). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. The dry THF was obtained by distillation from Na and benzophenone when the solution became purple.

(±)-(2S,4S and 2R,4S)-4-Hydroxymethyl-4-vinyl-tetrahydro-furan-2-ol (6). To a solution of **5** (290.7 mg, 0.78 mmol) in tetrahydrofurane (10 mL), tetrabutylammonium fluoride (2.34 mL, 1.0 M solution in THF) was added at 0°C. The mixture was stirred overnight at rt and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 4:1) to diastereomeric mixture **6** as a colorless oil (86.5 mg, 77%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.93–5.80 (m, 2H), 5.59–5.49 (m, 1H), 5.26–5.04 (m, 3H), 4.11 (d, J = 9.0 Hz, 1H), 3.96–3.81 (m, 2H), 3.67 (s, 2H), 3.53 (s, 1H), 2.26–2.17 (m, 2H), 2.05–1.26 (m, 2H), 0.95 (t, J = 5.8 Hz, 1H), 0.91 (t, J = 5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.06, 129.69, 115.72, 114.26, 98.97, 73.75, 72.17, 67.12, 66.77, 49.67, 43.14, 41.77.

(±)-(2S,4S and 2R,4S)-(Acetoxymethyl-4-vinyl-tetrahydro-furan-2-yl) methyl acetate (7). To a solution of compound **6** (335.9 mg, 2.33 mmol) in anhydrous pyridine (10 mL), Ac_2O (0.951 g, 9.32 mmol) was slowly added, and the mixture was stirred overnight under nitrogen. The pyridine was evaporated under reduced pressure and co-evaporated with toluene. The residue was extracted with EtOAc/H_2O, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give compound **7** (467.9 mg, 88%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.21–6.22 (m, 1H), 5.90–5.77 (m, 1H), 4.17 (dd, J = 17.7, 11.1 Hz, 2H), 4.08–3.81 (m, 3H), 2.26 (dd, J = 13.8, 5.4 Hz, 1H), 2.01–1.95 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.92, 170.30, 139.60, 138.60, 115.39, 114.81, 98.87, 75.11, 74.13, 67.18, 48.57, 48.16, 40.84, 40.41, 21.32, 20.85.

(±)-(2S,4S)-1-(Acetoxymethyl-4-vinyl-tetrahydro-furan-2-yl) uracil (8β) and (±)-(2R,4S)-1-(Acetoxymethyl-4-vinyl-tetrahydro-furan-2-yl) uracil (8α). Uracil (300 mg, 1.784 mmol), anhydrous HMDS (10 mL), and a catalytic amount of ammonium sulfate (30 mg) were refluxed to a clear solution, and the solvent was distilled under anhydrous conditions. The residue was dissolved in anhydrous 1,2-dichloroethane (10 mL). To this mixture, a solution of **7** (203.6 mg, 0.892 mmol) in dry DCE (10 mL) and TMSOTf (396 mg, 1.784 mmol) was added, and the resulting mixture was stirred at rt for 3 h. The reaction mixture was quenched with 5 mL of saturated $NaHCO_3$ and stirred for 30 min. The resulting solid was filtered through a Celite pad, and the filtrate was extracted with CH_2Cl_2 two times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated

under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 4:1) to give compound **8β** (85.86 mg, 33%) and **8α** (75.13 mg, 35%). Spectroscopical data for **8β**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.89 (br s, 1H), 7.38 (d, J = 9.8 Hz, 1H), 6.01–5.70 (m, 3H), 5.26 (dd, J = 12.8, 8.6 Hz, 2H), 4.12–3.89 (m, 4H), 2.51 (dd, J = 10.6, 6.8 Hz, 1H), 2.08–1.90 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.88, 164.21, 150.30, 138.56, 137.12, 115.54, 102.21, 86.54, 74.80, 66.43, 48.76, 39.65, 20.18; Anal calc for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.54; H, 5.82; N, 9.85. Spectroscopical data for **8α**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.09 (br s, 1H), 7.42 (dd, J = 16.8, 8.1 Hz, 1H), 6.07–5.75 (m, 3H), 5.31–5.12 (m, 2H), 4.17–3.98 (m, 4H), 2.64–2.55 (m, 1H), 2.12–1.94 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.65, 163.69, 150.33, 139.17, 137.70, 115.86, 102.02, 86.87, 74.87, 66.80, 49.11, 40.24, 20.74; Anal calc for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.89; H, 5.65; N, 10.21.

(±)-(2S,4S)-1-(Acetoxymethyl-4-vinyl-tetrahydro-furan-2-yl) thymine (9β) and (±)-(2R,4S)-1-(Acetoxymethyl-4-vinyl-tetrahydro-furan-2-yl) thymine (9α). Thymine nucleoside analogues **9β** and **9α** were synthesized from **7** by the similar procedure as described for **8β** and **8α**. Spectroscopical data for **9β**: yield 30%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.65 (br s, 1H), 7.27 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.09–6.02 (m, 1H), 5.30–5.13 (m, 2H), 4.20–3.97 (m, 4H), 2.57 (dd, J = 10.6, 6.6 Hz, 1H), 2.08 (s, 3H), 1.99–1.92 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.83, 163.97, 150.33, 137.93, 134.90, 115.95, 110.78, 86.50, 74.76, 66.82, 49.10, 40.15, 20.79, 12.66; Anal calc for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found: C, 57.01; H, 6.05; N, 9.66. Spectroscopical data for **9α**: yield 31%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.67 (br s, 1H), 7.30 (s, 1H), 7.17 (dd, J = 13.2, 8.4 Hz, 1H), 5.92–5.82 (m, 1H), 5.27–5.15 (m, 2H), 4.12–3.95 (m, 4H), 2.60–2.52 (m, 1H), 2.09–1.83 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.74, 163.88, 150.35, 138.45, 135.25, 116.34, 111.13, 87.05, 74.87, 67.14, 49.31, 40.54, 20.85, 12.68; Anal calc for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found: C, 57.26; H, 6.34; N, 9.37.

(±)-(2S,4S)-1-(Hydroxymethyl-4-vinyl-tetrahydro-furan-2-yl) uracil (10β). Compound **8β** (106.5 mg, 0.38 mmol) was dissolved in saturated methanolic ammonia (10 mL) and stirred overnight at rt. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:7) to give compound **10β** (74.2 mg, 82%) as a white solid: mp 168–170°C; UV (H_2O) λ_{max} 262.5.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.31 (br s, 1H), 7.66 (d, J = 8.1 Hz, 1H), 5.97–5.87 (m 2H), 5.65 (d, J = 8.1 Hz, 1H), 5.17 (s, 1H), 5.13 (d, J = 8.6 Hz, 1H), 5.01 (t, J = 5.4 Hz, 1H), 4.03 (d, J = 8.4 Hz, 1H), 3.83 (d, J = 8.4 Hz, 1H), 2.53 (dd, J = 13.2, 6.3 Hz, 1H), 1.99 (dd, J = 13.5, 7.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 163.33, 150.44, 140.88, 140.06, 114.91, 101.55, 86.43, 74.13, 64.58, 51.15, 38.03; Anal calc for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.57; H, 5.81; N, 11.80.

(±)-(2R,4S)-1-(Hydroxymethyl-4-vinyl-tetrahydro-furan-2-yl) uracil (10α). Compound **10α** was synthesized from **8α** by the similar procedure as described for **10β**: yield 77%: mp 165–168°C; UV (H_2O) λ_{max} 262.0 nm; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.29 (br s, 1H), 7.62 (d, J = 8.1 Hz, 1H), 6.00–5.87 (m 2H), 5.57 (d, J = 8.1 Hz, 1H), 5.15–5.01 (m, 4H), 3.96 (d, J = 8.4 Hz, 1H), 3.83 (d, J = 8.4 Hz, 1H), 2.37 (dd, J = 13.8, 6.6 Hz, 1H), 1.94 (dd, J = 13.5, 7.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 163.34, 150.67, 141.66, 140.12, 114.76, 102.12, 86.78, 74.21, 64.87, 51.23, 38.13; Anal calc for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.32; H, 6.08; N, 11.65.

(±)-(2S,4S)-1-(Hydroxymethyl-4-vinyl-tetrahydro-furan-2-yl) thymine (11β). Compound **11β** was synthesized from **9β** by the similar procedure as described for **10β**: yield 79%: mp 166–168°C; UV (H_2O) λ_{max} 267.0 nm; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.28 (br s, 1H), 7.50 (s, 1H), 7.40 (d, J = 8.8 Hz, 1H), 6.02–5.87 (m, 1H), 5.22–4.96 (m, 2H), 4.05–3.78 (m, 4H), 2.50 (dd, J = 13.2, 8.8 Hz, 1H), 1.78 (dd, J = 13.2, 6.8 Hz, 1H), 1.77 (m, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 163.87, 150.23, 138.76, 133.71, 114.76, 110.94, 87.54, 74.65, 67.54, 48.18, 39.76, 12.87; Anal calc for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.33; H, 6.50; N, 10.96.

(±)-(2R,4S)-1-(Hydroxymethyl-4-vinyl-tetrahydro-furan-2-yl) thymine (11α). Compound **11α** was synthesized from **9α** by the similar procedure as described for **10β**: yield 70%: mp 160–163°C; UV (H_2O) λ_{max} 268.0 nm; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.45 (br s, 1H), 7.45 (s, 1H), 7.32 (s, 1H), 6.00 (dd, J = 10.4, 8.2 Hz, 1H), 5.18–4.90 (m, 2H), 4.11–3.83 (m, 4H), 2.02 (dd, J = 13.2, 8.4 Hz, 1H), 1.75 (m, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 163.56, 152.65, 138.34, 133.89, 113.223, 109.42, 88.39, 74.56, 66.29, 48.81, 39.33, 12.89; Anal calc for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.09; H, 6.27; N, 11.23.

REFERENCES

1. Furman, P.A.; Fyfe, J.A.; St. Clair, M.H.; Weinhold, K.; Rideout, J.L.; Freeman, G.A.; Nusinoff-Lehrman, S.; Bolognesi, D.P.; Broder, S.; Mitsuya, H.; Barry, D.W. Phosphorylation of 3′-Azido-3′-Deoxythymidine and Selective Interaction of the 5′-Triphosphate with Human Immunodeficiency Virus Reverse Transcriptase. *Proceedings of the National Academy of Sciences USA* **1986**, 83, 8333–8337.
2. Yarchoan, R.; Thomas, R.V.; Allain, J.-P.; McAtee, N.; Dubinsky, R.; Mitsuya, H.; Lawley, T.J.; Safai, B.; Myers, C.E.; Perno, C.F.; Klecker, R.W.; Wills, R.J.; Fischl, M.A.; McNeely, M.C.; Pluda, J.M.; Leuther, M.; Collins, J.M.; Broder, S. The Phase I Studies of 2′,3′-Dideoxycytidine in Human Immunodeficiency Virus Infection as Single Agent and Alternating with Zidovudine (AZT). *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.; Johns, D.G.; Broder, S. In Vivo Activity against HIV and Favorable Toxicity Profile of 2′,3′-Dideoxyinosine. *Science* **1989**, 245, 412–415.
4. Lin, T.-S.; Schinazi, R.F.; Prusoff, W.H. Potent and Selective In Vitro Activity of 3′-Deoxy Thymidine-2′-ene (3′-Deoxy-2′,3′Dideoxydehydrothymidine) against Human Immunodeficiency Virus. *Biochemical Pharmacology* **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. Activities of the Four Optical Isomers of 2′,3′-Dideoxy-3′-Thiacytidine (BCH-189) against Human Immunodeficiency Virus Type I in Human Lymphocytes. *Antimicrobial Agents in Chemotherapy* **1992**, 36, 672–676.
6. Daluge, S.M.; Good, S.S.; Faletto, M.B.; Miller, W.H.; St. Clair, M.H.; Boone, L.R.; Tisdale, M.; Parry, N.R.; Reardon, J.E.; Dornsife, R.E.; Averett, D.R.; Krenitsky, T.A. A Novel Carbocyclic Nucleoside Analog with Potent, Selective Anti-Human Immunodeficiency Virus Activity. *Antimicrobial Agents in Chemotherapy* **1997**, 41, 1082–1093.
7. Nair, V.; Zintek, L.B.; Sells, T.B.; Jeffery, A.L.; Nuesca, Z.M.; Purdy, D.F.; Jeon, G.S.; Hamilton, R.B.; Bolon, P.J.; Malany, S. Novel Chiral Isomeric Nucleosides and Nucleotides: Synthesis, Enzymology, and Anti-HIV Activity. *Antiviral Research* **1994**, 23, 38–38.
8. Sugimoto, I.; Shuto, S.; Mori, S.; Shigeta, S.; Matuda, A. Synthesis of 4′α-Branched Thymidines as a New Type of Antiviral Agents. *Bioorganic & Medicinal Chemistry Letters* **1999**, 9, 385–388.
9. Ohrui, H.; Kohgo, S.; Kitano, K.; Sakata, S.; Kodama, E.; Yoshimura, K.; Matsuoka, M.; Shigeta, S.; Mitsuya, H. Synthesis of 4′-*C*-Ethynyl-β-D-Arabino- and 4′-*C*-Ethynyl-2′-Deoxy-β-D-ribo-Pentofuranosylpyrimidines and -Purines and Evaluation of Their Anti-HIV Activity. *Journal of Medicinal Chemistry* **2000**, 43, 4516–4525.
10. Jin, Y.L.; Hong, J.H. Synthesis and Antiviral Activity of Novel 4′-Branched Carbocyclic *C*-Nucleoside. *Bulletin of the Korean Chemical Society* **2005**, 26, 1366–1389.
11. Ko, O.H.; Hong, J.H. Efficient Synthesis of Novel Carbocyclic Nucleosides via Sequential Claisen Rearrangement and Ring-Closing Metathesis. *Tetrahedron Letters* **2002**, 43, 6399–6402.