

Synthesis and Antiviral Evaluation of Novel Acyclic Nucleosides

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A very short and concise synthetic route for a novel acyclic version of d4T is described. The required quaternary carbon was successfully installed using a [3,3]-sigmatropic rearrangement. The condensation of the mesylates **16-18** with an adenine base under standard nucleophilic substitution conditions (K_2CO_3 , 18-Crown-6, DMF) in addition to deblocking afforded the target acyclic nucleosides **22-24**. In addition, the antiviral evaluations against various viruses were performed.

Key Words : Acyclic nucleosides, [3,3]-Sigmatropic rearrangement, Antiviral agents

Introduction

The discovery of acyclovir¹ as an antiherpes agent ignited the search for new antiviral nucleosides with a disconnected chain resulting from the omission of bonds from the pentose or cyclopentane rings. During the past twenty years, many new synthetic schemes for various acyclic nucleoside² analogues have been reported and many of these molecules have exhibited promising antiviral activities.³ Among them, deciclovir,⁴ ganciclovir,⁵ penciclovir,⁶ famciclovir⁷ have exhibited potent antiviral activity against HBV, HIV, as well as the herpes virus. Furthermore, the recent approval of bis(POC)PMPA⁸ by the FDA as an anti-HIV agent warrants further searches for acyclic nucleosides as chemotherapeutic agents (Figure 1).

Nevertheless, the utility of these drugs is limited due to their toxicity and side effects, as well as the emergence of drug resistant viral strains. Therefore, it is essential to search

for less toxic and more effective antiviral agents, which do not have any cross-resistance with existing drugs. In view of the stimulating results reported for acyclic nucleosides and as a part of our ongoing drug discovery efforts, this study aimed to synthesize novel 1',2'-seco-4'-C-branched nucleosides. This paper reports their synthetic routes from the simple acyclic ketone derivatives **1-3**.

Results and Discussions

As shown in Scheme 1, the synthetic route is straightforward. It was envisaged that a [3,3]-sigmatropic rearrangement of compounds **7-9** would produce the desired quaternary carbon compounds **10-12** with the required functional groups. Subjecting compounds **16-18** to nucleophilic substitution conditions and desilylation gave the desired nucleosides **22-24**.

Silyl protection of the hydroxyl group of the commercially available starting materials **1-3**, followed by a Horner-Wadsworth-Emmons (HWE) reaction,⁹ provided the unsaturated ethyl ester **4** and the cis/trans isomeric mixtures of compounds **5, 6**. It was not necessary to separate the isomers of compounds **5** and **6**, as they merged into one isomer in the subsequent reactions.

The α,β -unsaturated ethyl esters **4-6** were reduced by DIBALH at $-20^\circ C$ in CH_2Cl_2 to give the allylic alcohols **7-9** in an 83-97% yield, which were subjected to a standard Johnson ortho ester Claisen rearrangement¹⁰ using triethyl orthoacetate to produce the γ,δ -unsaturated esters **10-12** in 81-86% yield. The slow addition of DIBALH to a solution of the esters **10-12** in CH_2Cl_2 at $-20^\circ C$ furnished desired alcohols **13-15** in an 89-91% yield. The hydroxyl group of compounds **13-15** were mesylated by treating them with methanesulfonyl chloride (MsCl) in an anhydrous CH_2Cl_2 to give the key intermediates **16-18**, which were coupled with the nucleobase (adenine) under well-known standard conditions (K_2CO_3 , 18-C-6, DMF)¹¹ to give the acyclic adenine derivatives **19-21** in a 42-48% two step yield. Although a small amount of the *N*⁷-isomer¹² (less than 5%) of the adenine base were present, they could be readily differentiated [UV (MeOH) λ_{max} 279 nm]. The removal of the *t*-butyldimethyl-

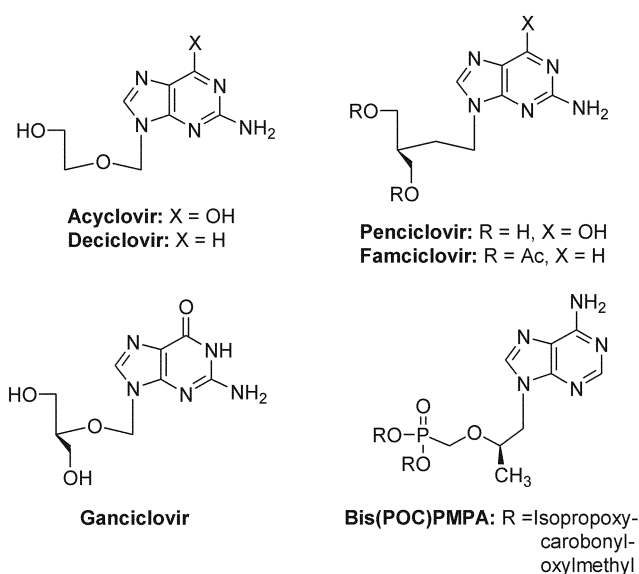
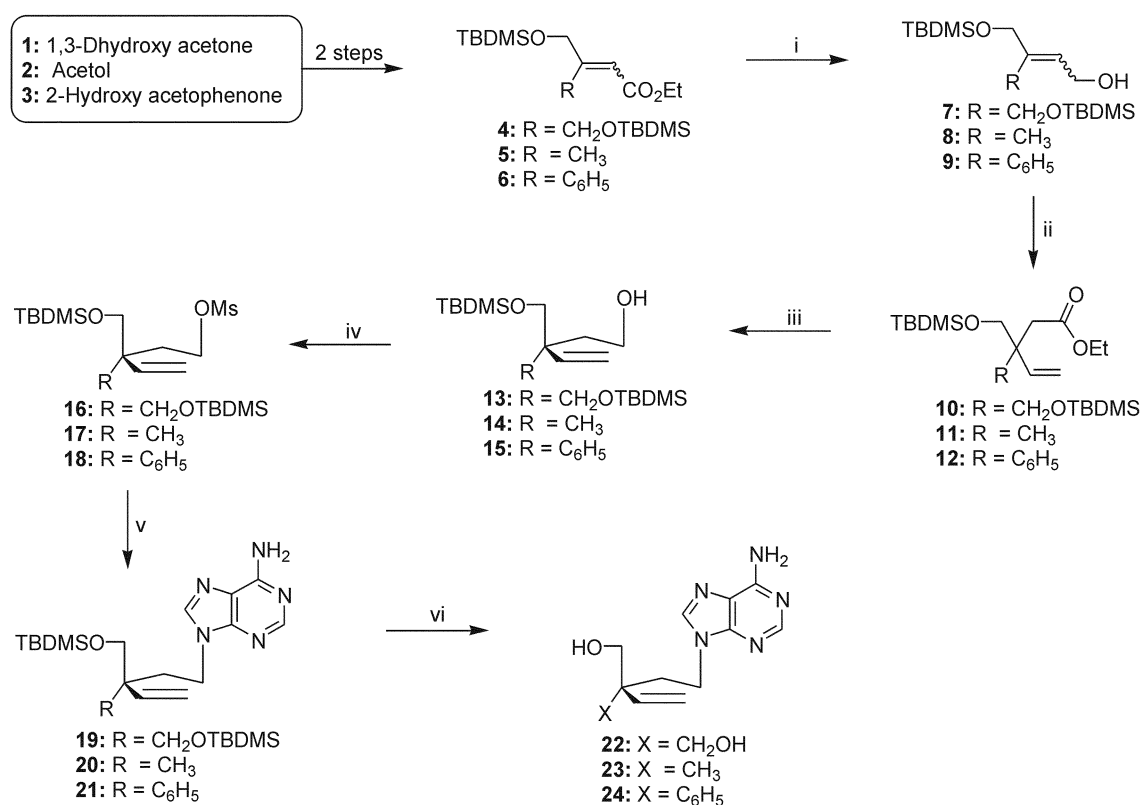


Figure 1.

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Scheme 1. Reagents: i) DIBALH, CH₂Cl₂, -20 °C, 2 h, 83-97%; ii) Triethyl orthoacetate, Propionic acid, overnight, 130 °C, 81-86%; iii) DIBALH, CH₂Cl₂, -20 °C, 1 h, 89-91%; iv) MsCl, CH₂Cl₂, TEA, 0 °C, 2 h, 83-89%; v) adenine, K₂CO₃, 18-C-6, DMF, 90 °C, overnight, 50-54%; vi) TBAF, THF rt, 3 h, 81-90%.

Table 1. The antiviral activities of the synthesized compounds

	HIV-1 EC ₅₀ (μg/mL)	HSV-1 EC ₅₀ (μg/mL)	HCMV EC ₅₀ (μg/mL)	CoxB3 EC ₅₀ (μg/mL)	cytotoxicity IC ₅₀ (μg/mL)
22	10.40	>100	62.16	>100	>100
23	>100	>100	>100	53.49	>100
24	>100	>100	>100	>100	>100
AZT	0.0005	ND	ND	ND	0.5
Ganciclovir	ND	1.21	ND	ND	>10
Ribavirin	ND	ND	ND	30.96	>300

ND: Not Determined.

silyl (TBDMS) group of compounds **19-21** was accomplished by tetrabutylammonium fluoride (TBAF) to give the final nucleosides **22-24** in an 81-90% yield.

Antiviral assays of the synthesized nucleosides **22-24** against the human immunodeficiency virus 1 (HIV-1), the herpes simplex virus 1 (HSV-1), human cytomegalovirus (HCMV) and CoxB3 virus were performed. Although the tested compounds did not display any exceptional antiviral activity, the hydroxymethyl branched nucleoside **22** exhibited moderate anti-HIV activity in MT-4 cells (EC₅₀ = 10.4 μmol) without any cytotoxicity up to 100 μmol (Table 1). This result strongly suggests that this structure for the novel nucleosides might be a candidate for a new lead compound for the development of new antiviral agents.

Conclusion

Novel acyclic nucleosides were successfully synthesized starting from very simple ketone derivatives. This synthetic method is highly efficient and convenient, and can be further applied to the synthesis of geminally substituted novel acyclic nucleosides. Based on this strategy, the syntheses of the other 4'-modified acyclic nucleosides with different bases are in progress.

Experimental Section

The melting points were determined on a Mel-tem II laboratory device and are uncorrected. The NMR spectra were recorded on a Bruker 300 Fourier transform spectro-

meter. The chemical shifts are reported as 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 (Profile HV-3). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. All reactions were carried out under N_2 unless otherwise specified. Dry dichloromethane, benzene and pyridine were obtained by distillation from CaH_2 . The dry THF was obtained by distillation from Na and benzophenone immediately prior to use.

4,4-Bis(*t*-butyldimethylsilyloxy)-iso-pent-2-en-1-ol (7): To a solution of **4** (10 g, 51.45 mmol) in CH_2Cl_2 (200 mL), DIBALH (108 mL, 1.0 M solution in hexane) was added slowly at $-20^\circ C$, and stirred for 2 h at $0^\circ C$. To the mixture, methanol (108 mL) was then added. The mixture was stirred at room temperature for 2 h, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under vacuum, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 4) to give the allylic alcohol **3** (16.78 g, 97%) as a colorless oil: 1H NMR ($CDCl_3$, 300 MHz) δ 5.82 (t, $J = 8.4$ Hz, 1H), 4.23 (s, 4H), 4.16 (s, 2H), 0.92 (s, 18H), 0.00 (s, 12H).

(*E,Z*)-4-(*t*-Butyldimethylsilyloxymethyl)-3-methyl-but-2-en-1-ol (8) and **(*E,Z*)-4-(*t*-Butyldimethylsilyloxymethyl)-3-phenyl-but-2-en-1-ol (9):** Compound **8** and **9** were prepared from **5** and **6**, respectively as described for compound **7**. Compound **8**: yield 89%; 1H NMR ($CDCl_3$, 300 MHz) δ 5.68 (br s, 1H), 4.21 (d, $J = 6.6$ Hz, 2H), 4.03 (s, 2H), 1.77, 1.64 (s, s, 3H), 0.91 (s, 9H), 0.07 (s, 6H); compound **9**: yield 83%; 1H NMR ($CDCl_3$, 300 MHz) δ 7.32-7.07 (m, 5H), 5.99, 5.91 (dt, $J = 6.6, 6.6$ Hz, 1H), 4.31 (d, $J = 6.6$ Hz, 1H), 4.27 (s, 1H), 0.85, 0.81 (s, s, 9H), 0.02 (m, 6H).

Ethyl 3,3-bis(*t*-butyldimethylsilyloxymethyl)-pent-4-enoate (10): A solution of 15 g (43.27 mmol) of allylic alcohol **7**, 150 mL of triethyl orthoacetate, 0.78 mL of propionic acid was heated at $130-135^\circ C$ overnight with constant stirring under conditions for the removal of ethanol by distillation. The excess triethyl orthoacetate was distilled off and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 15) to give compound **10** (15.5 g, 86%) as a colorless oil; 1H NMR ($CDCl_3$, 300 MHz) δ 5.87 (dd, $J = 18.0, 11.4$ Hz, 1H), 5.09 (d, $J = 11.1$ Hz, 1H), 4.98 (d, $J = 19.5$ Hz, 1H), 4.05 (q, $J = 7.5$ Hz, 2H), 3.64 (dd, $J = 15.6, 9.0$ Hz), 2.40 (s, 2H), 1.22 (t, $J = 7.5$ Hz, 3H), 0.85 (s, 18H), 0.01 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 1171.92, 139.76, 114.48, 64.67, 59.88, 45.98, 36.84, 25.85, 18.25, 14.25, -5.56 ; Anal calc for $C_{21}H_{44}O_4Si_2$: C, 60.52; H, 10.64. Found: C, 60.39; H, 10.87.

(\pm)-3-(*t*-Butyldimethylsilyloxymethyl)-3-methyl-pent-4-enoic acid ethyl ester (11) and **(\pm)-3-(*t*-Butyldimethylsilyloxymethyl)-3-phenyl-pent-4-enoic acid ethyl ester (12):** Compound **11** and **12** were prepared from compounds **8** and **9**, respectively as described for compound **10**. Compound **11**: yield 83%; 1H NMR ($CDCl_3$, 300 MHz) δ 5.91 (d, $J =$

10.8 Hz, 1H), 5.89 (d, $J = 11.4$ Hz, 1H), 5.05 (d, $J = 1.2$ Hz, 1H), 5.02 (d, $J = 7.5$ Hz, 1H), 4.01 (q, $J = 7.2$ Hz, 2H), 3.46 (d, $J = 9.3$ Hz, 1H), 3.41 (d, $J = 9.3$ Hz, 1H), 2.40 (d, $J = 3.3$ Hz, 2H), 1.23 (t, $J = 7.5$ Hz, 3H), 1.21 (s, 3H), 1.11 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.94, 143.11, 112.99, 69.91, 59.83, 41.39, 29.25, 25.66, 20.70, 14.26, -5.58 ; Anal calc for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 62.60; H, 10.45.

Compound **12**: yield 81%; 1H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.25 (m, 5H), 6.26 (dd, $J = 18.0, 11.1$ Hz, 1H), 5.31 (dd, $J = 11.4, 1.2$ Hz, 1H), 5.16 (dd, $J = 17.7, 0.6$ Hz, 1H), 4.10-3.99 (m, 4H), 3.00 (s, 2H), 1.18 (t, $J = 6.9$ Hz, 3H), 0.99 (s, 9H), 0.02 (d, $J = 8.1, 6H$); ^{13}C NMR ($CDCl_3$) δ 171.51, 143.17, 142.33, 127.82, 127.34, 126.30, 114.34, 67.73, 59.94, 48.70, 39.74, 25.76, 18.19, 14.07, -5.71 ; Anal calc for $C_{20}H_{32}O_3Si$: C, 68.92; H, 9.25. Found: C, 68.69; H, 9.05.

3,3-Bis(*t*-butyldimethylsilyloxymethyl)-4-penten-1-ol (13): To a solution of compound **10** (5 g, 11.99 mmol) in CH_2Cl_2 (100 mL), DIBALH (25.2 mL, 1.0 M solution in hexane) was added slowly at $-20^\circ C$, and stirred for 1 h at $0^\circ C$. To the mixture, methanol (25.2 mL) was then added. The mixture was stirred at room temperature for 1 h, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 5) to give the alcohol **5** (4.09 g, 91%) as a colorless oil: 1H NMR ($CDCl_3$, 300 MHz) δ 5.72 (dd, $J = 17.5, 11.5$ Hz, 1H), 5.15 (d, $J = 11.0$ Hz, 1H), 5.12 (d, $J = 18.0$ Hz, 1H), 3.98 (t, $J = 7.0$ Hz, 2H), 3.61 (d, $J = 9.0$ Hz, 4H), 1.83 (t, $J = 8.1$ Hz, 2H, H-2), 0.88 (s, 18H), 0.01 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 149.28, 109.21, 69.78, 58.78, 37.78, 33.45, 20.19, 15.07, -5.72 ; Anal calc for $C_{19}H_{42}O_3Si_2$: C, 60.90; H, 11.30. Found: C, 60.67; H, 10.95.

(\pm)-3-(*t*-Butyldimethylsilyloxymethyl)-3-methyl-pent-4-en-1-ol (14) and **(\pm)-3-(*t*-Butyldimethylsilyloxymethyl)-3-phenyl-pent-4-en-1-ol (15):** Compound **14** and **15** were prepared from compounds **11** and **12**, respectively as described for compound **13**. Compound **14**: yield 90%; 1H NMR ($CDCl_3$, 300 MHz) δ 5.89 (dd, $J = 17.7, 11.4$ Hz, 1H), 5.06 (dd, $J = 4.5, 1.2$ Hz, 1H), 5.02 (dd, $J = 10.5, 0.9$ Hz, 1H), 3.67 (dd, $J = 11.7, 6.3$ Hz, 1H), 3.46 (d, $J = 9.6$ Hz, 1H), 3.38 (d, $J = 9.6$ Hz, 1H), 1.69 (t, $J = 5.7$ Hz, 2H), 1.00 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 144.45, 112.80, 70.81, 59.34, 41.18, 25.84, 21.04, 18.29, -5.52 ; Anal calc for $C_{13}H_{28}O_2Si$: C, 63.87; H, 11.55. Found: C, 63.74; H, 11.61; compound **15**: yield 89%; 1H NMR ($CDCl_3$, 300 MHz) δ 7.33-7.28 (m, 5H), 5.82 (dd, $J = 17.4, 10.8$ Hz, 1H), 5.33 (d, $J = 10.7$ Hz, 1H), 5.13 (d, $J = 10.5$ Hz, 1H), 4.24 (t, $J = 6.9$ Hz, 2H), 3.80 (s, 2H), 1.72 (m, 2H), 0.90 (s, 9H), -0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 142.48, 141.65, 128.20, 127.32, 126.60, 115.09, 68.80, 67.72, 48.59, 34.18, 25.74, 18.13, -5.71 ; Anal calc for $C_{18}H_{30}O_2Si$: C, 70.53; H, 9.87. Found: C, 70.26; H, 9.66.

1-O-Mesy-3,3-bis(*t*-butyldimethylsilyloxymethyl)-4-pentene (16): To a solution of the alcohol **13** (350 mg, 0.93 mmol) in anhydrous CH_2Cl_2 , anhydrous triethylamine (0.24

mL) and MsCl (130 mg, 1.12 mmol) was added at 0 °C. The mixture was stirred at the same temperature for 1 h, and quenched by a cold saturated NaHCO₃ solution (0.5 mL). The mixture was extracted with CH₂Cl₂ (20 mL) and water (20 mL). The organic layer was dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under vacuum, and the residue (376 mg, 89%) was then subjected to the subsequent coupling reaction without further purification. In order to obtain spectroscopic data, a small amount of sample was purified by flash silica gel column chromatography (EtOAc/hexane, 1 : 3): ¹H NMR (CDCl₃, 300 MHz) δ 5.77 (dd, *J* = 18.0, 11.7 Hz, 1H), 5.17 (d, *J* = 10.5 Hz), 5.06 (d, *J* = 18.0 Hz, 1H), 4.30 (t, *J* = 7.5 Hz, 2H), 3.56 (d, *J* = 9.0 Hz, 4H), 2.97 (s, 3H), 1.90 (t, *J* = 8.1 Hz, 2H), 0.89 (s, 18H), 0.04 (s, 12H).

(±)-1-*O*-Methanesulfonic acid-3-(*t*-butyldimethylsilyloxymethyl)-3-methyl-pent-4-enyl ester (17) and (±)-1-*O*-Methanesulfonic acid-3-(*t*-butyldimethylsilyloxymethyl)-3-phenyl-pent-4-enyl ester (18): Compound **17** and **18** were prepared from compounds **14** and **15**, respectively as described for compounds **16**. Compound **17**: yield 88%; ¹H NMR (CDCl₃, 300 MHz) δ 5.82 (d, *J* = 10.8 Hz, 1H), 5.76 (d, *J* = 11.1 Hz, 1H), 5.11 (dd, *J* = 10.8, 0.9 Hz, 1H), 5.00 (dd, *J* = 17.7, 0.9 Hz, 1H), 4.25 (t, *J* = 7.8 Hz, 2H), 3.36 (dd, *J* = 18.9, 9.3 Hz, 2H), 2.98 (s, 3H), 1.91-1.85 (m, 2H), 1.02 (s, 3H), 0.90 (s, 9H), 0.04 (s, 6H); compound **18**: yield 83%; ¹H NMR (CDCl₃, 300 MHz) δ 7.35-7.29 (m, 5H), 6.02 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.34 (d, *J* = 9.9 Hz, 1H), 5.17 (d, *J* = 17.7 Hz, 1H), 4.25 (t, *J* = 6.9 Hz, 2H), 3.83 (s, 2H), 2.93 (s, 3H), 2.44 (m, 2H), 0.95 (s, 9H), -0.02 (s, 6H).

9-[3,3-Bis(*t*-butyldimethylsilyloxymethyl)-4-penten-1-yl] adenine (19): A solution of the mesylate **16** (376 mg, 0.83 mmol), K₂CO₃ (231 mg, 1.67 mmol), 18-crown-6 (329 mg, 1.26 mmol), and adenine (113.5 mg, 0.84 mmol) in dry DMF (6.7 mL) was stirred overnight at 90 °C. The mixture was cooled to room temperature and concentrated under vacuum. The residue was diluted with brine (20 mL) and extracted with CH₂Cl₂ (10 mL × 4). The combined organic layer was dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH₂Cl₂, 1 : 10) to give compound **19** (220 mg, 54%) as a white solid: mp 168-170 °C; ¹H NMR (CDCl₃, 300 MHz) δ 8.31 (s, 1H), 7.71 (s, 1H), 5.76 (dd, *J* = 18.0, 11.1 Hz, 1H), 5.61 (br s, 2H), 5.17 (d, *J* = 11.1 Hz, 1H), 5.10 (d, *J* = 18.0 Hz, 1H), 4.17 (t, *J* = 8.4 Hz, 2H), 3.56 (dd, *J* = 13.2, 9.3 Hz, 4H), 1.97 (dd, *J* = 17.1, 8.7 Hz, 2H), 0.84 (s, 18H), 0.02 (s, 12H); ¹³C NMR (CDCl₃) δ 155.28, 152.88, 140.29, 139.78, 115.24, 64.84, 45.90, 39.93, 32.44, 25.85, 18.22, -5.52; Anal calc for C₂₄H₄₅N₅O₂Si₂: C, 58.61; H, 9.22; N, 14.24. Found: C, 58.62; H, 9.16; N, 14.36.

(±)-9-[3-(*t*-Butyldimethylsilyloxymethyl)-3-methyl-4-pent-1-enyl] adenine (20) and (±)-9-[3-(*t*-Butyldimethylsilyloxymethyl)-3-phenyl-4-pent-1-enyl] adenine (21): Compound **20** and **21** were prepared from compounds **17** and **18**, respectively, as described for compound **19**. Compound **20**: yield 52%; mp 160-161 °C; ¹H NMR

(CDCl₃, 300 MHz) δ 8.33 (s, 1H), 7.74 (s, 1H), 5.87 (br s, 2H), 5.83 (d, *J* = 10.8 Hz, 1H), 5.77 (d, *J* = 10.8 Hz, 1H), 5.10 (dd, *J* = 7.8, 1.2 Hz, 1H), 5.06 (dd, *J* = 14.1, 0.9 Hz, 1H), 4.14 (t, *J* = 6.3 Hz, 2H), 3.42 (d, *J* = 10.2 Hz, 1H), 3.35 (d, *J* = 10.2 Hz, 1H), 1.97 (t, *J* = 7.2 Hz, 2H), 1.04 (s, 3H), 0.85 (s, 9H), -0.03 (s, 6H); ¹³C NMR (CDCl₃) δ 155.43, 152.88, 150.07, 142.71, 140.24, 119.51, 70.48, 41.24, 40.34, 36.97, 25.84, 20.25, 18.24, -5.54; Anal calc for C₁₈H₃₁N₅OSi: C, 59.79; H, 8.64; N, 19.37. Found: C, 59.58; H, 8.72; N, 19.53; compound **21**: yield 50%; mp 167-170 °C; ¹H NMR (CDCl₃, 300 MHz) δ 8.31 (s, 1H), 7.68 (s, 1H), 7.42-7.26 (m, 5H), 6.67 (br s, 2H), 6.13 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.39 (dd, *J* = 10.8, 0.6 Hz, 1H), 5.27 (d, *J* = 18.0 Hz, 1H), 4.19 (t, *J* = 8.1 Hz, 2H), 3.90 (dd, *J* = 14.1, 9.9 Hz, 2H), 2.57-2.48 (m, 2H), 0.87 (s, 9H), -0.03 (s, 6H); ¹³C NMR (CDCl₃) δ 155.44, 152.20, 149.75, 142.51, 141.64, 140.09, 128.25, 127.42, 126.67, 115.42, 68.70, 49.02, 40.73, 25.76, 18.15, -5.70; Anal calc for C₂₃H₃₃N₅OSi: C, 65.21; H, 7.85; N, 16.53. Found: C, 65.44; H, 7.69; N, 16.32.

9-[3,3-Bis(hydroxymethyl)-4-penten-1-yl] adenine (22): To a solution of compound **19** (100 mg, 0.2 mmol) in tetrahydrofuran (3 mL), tetrabutylammonium fluoride (TBAF) (0.6 mL, 1.0 M solution in THF) was added at 0 °C. The mixture was stirred at room temperature for 3 h, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH₂Cl₂, 1 : 5) to give compound **22** (47.4 mg, 90%) as a white solid: mp 184-186 °C; UV (MeOH) λ_{max} 261.5 nm; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 8.12 (s, 1H), 7.17 (br s, 2H), 5.80 (dd, *J* = 18.3, 11.4 Hz, 1H), 5.14 (d, *J* = 8.7 Hz, 1H), 5.08 (s, 1H), 4.58 (br s, 2H), 4.12 (t, *J* = 8.4 Hz, 2H), 3.40 (s, 4H), 1.87 (t, *J* = 8.4 Hz, 2H); ¹³C NMR (DMSO-*d*₆) δ 155.92, 152.02, 149.39, 140.83, 118.72, 114.77, 63.87, 45.39, 32.39, 23.19, 19.24, 13.55, 10.21; Anal calc for C₁₂H₁₇N₅O₂: C, 54.74; H, 6.51; N, 26.60. Found: C, 54.80; H, 6.49; N, 26.78.

(±)-9-[3-(*t*-Hydroxymethyl)-3-phenyl-4-pent-1-enyl] adenine (23) and (±)-9-[3-(*t*-Hydroxymethyl)-3-phenyl-4-pent-1-enyl] adenine (24): Compound **23** and **24** were prepared from compounds **20** and **21**, respectively as described for compound **22**. Compound **23**: yield 81%; mp 180-182 °C; UV (H₂O) λ_{max} 260.5 nm; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 8.13 (s, 2H), 7.14 (br s, 2H), 5.86 (d, *J* = 11.4, 1H), 5.80 (d, *J* = 10.5 Hz, 1H), 5.08 (d, *J* = 5.1 Hz, 1H), 5.03 (s, 1H), 4.70 (br s, 1H), 4.13-3.99 (m, 2H), 3.27 (d, *J* = 5.1 Hz, 1H), 3.23 (d, *J* = 5.1 Hz, 1H), 1.89-1.80 (m, 2H), 1.00 (s, 3H); ¹³C NMR (DMSO-*d*₆) δ 149.29, 147.10, 143.59, 141.40, 140.53, 118.619, 113.36, 41.05, 36.67, 34.91, 20.45; Anal calc for C₁₂H₁₇N₅O: C, 58.28; H, 6.93; N, 28.32. Found: C, 58.57; H, 6.60; N, 28.56; compound **24**: yield 86%; mp 182-185 °C; UV (H₂O) λ_{max} 261.0 nm; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 8.12 (s, 1H, H-8), 8.08 (s, 1H), 7.41-7.15 (m, 5H), 6.05 (dd, *J* = 15.9, 11.1 Hz, 1H), 5.27 (d, *J* = 11.7, 1H), 5.17 (s, 1H), 4.87 (t, *J* = 6.4 Hz, 1H, D₂O exchangeable), 4.01 (br s, 2H), 3.76 (m, 2H), 2.36 (br d, *J* = 7.8 Hz, 2H); ¹³C NMR (DMSO-*d*₆) δ 155.91, 152.30, 149.39, 143.25, 142.46, 140.60, 128.07, 127.35, 126.10, 114.62, 66.68, 48.58, 34.67, 23.05, 13.47; Anal calc for C₁₇H₁₉N₅O:

C, 66.00; H, 6.19; N, 22.64. Found: C, 66.38; H, 6.31; N, 22.48.

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References

1. Schaeffer, H. J.; Beauchamp, L.; De Miranda, P.; Elion, G. B.; Bauer, D. J.; Collins, P. *Nature* **1978**, 272, 583.
 2. El Ashry, E. S. H.; El Kilany, Y. Acyclonucleosides: Part 1, 2, 3. in *Advances in Heterocyclic Chemistry*; Academic Press: 1997; Vol. 67, 68, 69.
 3. De Clercq, E.; Descamps, J.; De Somer, P.; Holy, A. *Science* **1978**, 200, 563. (b) Martin, J. C.; Dvorak, C. A.; Smee, D. F.; Matthew, T. R.; Verheyden, J. P. H. *J. Med. Chem.* **1983**, 26, 759. (c) Smith, K. O.; Galloway, K. S.; Kennell, W. L.; Oglivie, K. K.; Radatus, B. K. *Antimicrob. Agents Chemother.* **1982**, 22, 55. (d) Vandendriessche, F.; Snoeck, R.; Janssen, G.; Hoogmartens, J.; Van Aerschot, A.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **1992**, 35, 1458.
 4. Krenitsky, T. A.; Hall, W. W.; De Miranda, P.; Beauchamp, L. M.; Schaeffer, H. J.; Whiteman, P. D. *Proc. Natl. Acad. Sci. USA* **1984**, 81, 3209.
 5. (a) Crumpacker, C. S. *N. Engl. J. Med.* **1996**, 335, 721. (b) Hamzeh, F. M.; Lietman, P. S. *Antimicrob. Agents Chemother.* **1991**, 35, 1818.
 6. Earnshaw, D. L.; Bacon, T. H.; Darlison, S. J.; Edmonds, K.; Perkins, R. M.; Vere Hodge, R. A. *Antimicrob. Agents Chemother.* **1992**, 36, 2747.
 7. Vere Hodge, R. A.; Sutton, D.; Boyd, M. R.; Harnden, M. R.; Jarvest, R. L. *Antimicrob. Agents Chemother.* **1989**, 33, 1765.
 8. Arimilli, M. N.; Kim, C. U.; Dougherty, J.; Mulato, A.; Oliyai, R.; Shaw, J. P.; Cundy, K. C.; Bischofberger, N. *Antiviral Chem. Chemother.* **1997**, 8, 557.
 9. Jeong, L. S.; Lee, Y. A.; Moon, H. R.; Chun, M. W. *Nucleosides & Nucleotides* **1998**, 17, 1473.
 10. (a) Ko, O. H.; Hong, J. H. *Tetrahedron Lett.* **2002**, 43, 6399. (b) Hong, J. H.; Gao, M. Y.; Chu, C. K. *Tetrahedron Lett.* **1999**, 40, 231.
 11. Lee, J. Y.; Oh, C. H.; Ko, O. H.; Hong, J. H. *Nucleosides, Nucleotides & Nucleic Acids* **2002**, 21, 709. (b) Hossain, N.; Rozenski, J.; De Clercq, E.; Herdewijn, P. *Tetrahedron* **1996**, 52, 13655.
 12. (a) Panzica, R. P.; Rousseau, R. J.; Robins, R. K.; Townsend, L. B. *J. Am. Chem. Soc.* **1972**, 94, 4708. (b) Rousseau, R. J.; Robins, R. K.; Townsend, L. B. *J. Am. Chem. Soc.* **1968**, 90, 2661.
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