Arch Pharm Res Vol 26, No 12, 990-996, 2003

Archives of Pharmacal Research
http://apr.psk.or.kr

Synthesis of Novel Carboacyclic Nucleosides with Vinyl Bromide Moiety as Open-chain Analogues of Neplanocin A

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(Received August 25, 2003)

A novel carboacyclic nucleoside analogue, 9-[2-bromo-4-hydroxy-3-hydroxymethyl-2-butenyl] adenine, and its derivatives were designed and synthesized as open-chain analogues of neplanocin A. The syntheses were accomplished via the coupling of adenine or pyrimidine bases to the key intermediate allylic bromide **7**. The bromide **7** was prepared from epichlorohydrin in a seven step process in a 54% overall yield. The synthesized compounds were evaluated for their antiviral activity against the polio virus, HSV and HIV.

Key words: Carboacyclic nucleoside, Neplanocin A, Antiviral, Open-chain analog

INTRODUCTION

The discovery of the potent and selective antiherpes agents, acyclovir and ganciclovir, has led to an extensive search for novel nucleoside analogues with improved properties. More recently, the fermentation product neplanocin A, which is a novel cyclic carba analogue of adenosine with a cyclopentene ring, has generated considerable attention both synthetically and biologically due to the effect of the double bond on the compound activity and potency (Marquez, 1996). Penciclovir is an acyclic carba analogue of guanosine, and has been approved as an antiviral drug for treating diseases caused by HSV and VZV (Harnden *et al.*, 1987). Because of the unusual presence of a double bond in neplanocin A and the acyclic nature of penciclovir, these two compounds have stimulated extensive research in the synthesis of new cyclic and acyclic carba-nucleoside analogues that mimick the sugar portion of naturally occurring nucleosides. (Fig. 1) However, with relatively few exceptions, the activity of most conventional carbocyclic nucleosides has been poorer than those of the corresponding ribosides. The loss of the furan oxygen in the carba-nucleosides is believed to have a critical effect on their antiviral activity. The incorporation of halogen atoms into organic molecules has often been associated with profound changes in the biological profiles of the halogenated analogues compared to their hydrocarbon counterparts. In order to search for stable and effective carba-nucleosides, compound **9a** was designed as an open-chain analogue of neplanocin A.

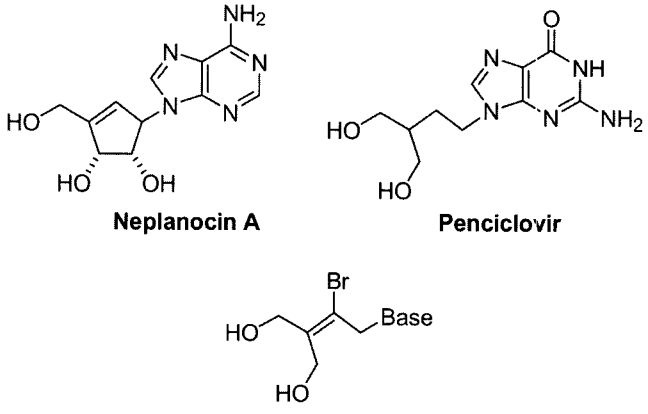

Fig. 1. Structures of neplanocin A, penciclovir, and target molecules

A number of pyrimidine bases have conferred activity to nucleoside analogues. Halogens present at the 5-position of uracil (e.g. 5-fluorouracil and 5-iodouracil) have induced antitumor and antiviral activity to nucleoside analogues. 5-Methyluracil arabinonucleosides have been reported to selectively inhibit HSV-1 and HSV-2 (Ogilvie *et al.*, 1984). Cyclopentenyl cytosine also has significant antitumor and antiviral activity (Marquez *et al.*, 1988). This report descri-

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bes the syntheses of compound **9a** and its pyrimidine derivatives.

MATERIALS AND METHODS

The melting points were obtained using a hot-stage microscope and were uncorrected. The ^{1}H-NMR spectra were obtained on a Brucker WP 80 SY spectrometer and a GEMINI 300 spectrometer and the chemical shifts are reported as values in parts per million (δ) relative to tetramethylsilane (TMS) as an internal standard. The UV spectra were recorded using a Shimadzu UV-2101PC spectrophotometer. The infrared spectra (IR) were recorded on a Shimadzu IR-435 spectrophotometer. The EI mass (EIMS) spectra were run on VG Trio-2 GC-MS spectrometer at 70 eV. Thin layer chromatography (TLC) was carried out on 0.25 mm E. Merck precoated silica gel glass plates ($60F_{254}$). Column chromatography was performed using the forced flow of indicated solvent on Merck Kieselgel 60 (230~400 mesh). Unless otherwise noted, the materials were obtained from commercially available sources and were used without further purification. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl under an argon atmosphere. Methylene chloride, benzene, dimethylformamide (DMF), triethylamine (TEA) and toluene were freshly distilled under a nitrogen atmosphere with calcium hydride.

1,3-Dibenzyloxy-2-propanol (1)

A solution of benzyl alcohol (9.6 mL, 93.0 mmol) in DMF (60 mL) was treated with sodium hydride (3.3 g, 60% oil dispersion, 83.0 mmol) and stirred for 2 h and then epichlorohydrin (3.6 mL, 46.0 mmol) was added. The reaction mixture was stirred for 2 days and quenched by the addition of a saturated ammonium chloride solution. The mixture was then extracted with ethyl acetate, the organic phase was washed with water several times and brine, dried over anhydrous sodium sulfate, filtered and then concentrated. The crude product was purified by column chromatography (eluted with 20% ethyl acetate in hexane) to afford 11.1 g (88%) of **1** as a pale yellow liquid: R*f* 0.44 (Hexane/EtOAc, 2:1); IR (neat) cm^{-1} 3400, 3045, 3005, 2845, 735, 700; ^{1}H-NMR δ 7.35~7.20 (m, 10H), 4.50 (s, 4H), 4.03~3.95 (m, 1H), 3.55~3.45 (m, 4H), 2.79 (s, 1H).

Bis(benzyloxy)acetone (2)

N-chlorosuccinimide (NCS, 6.3 g, 47.0 mmol) was suspended in toluene (150 mL) and the mixture was cooled in an ice bath. Methyl sulfide (5.9 mL, 79.0 mmol) was added and a white precipitate formed immediately. The solution was stirred for 30 min at 0°C and then cooled to -25°C. A solution of alcohol **1** (8.6 g, 32.0 mmol) in toluene (50 mL) was added to the mixture *via* a cannula. The mixture was kept under nitrogen for 3 h, whereupon TEA (6.6 mL, 47.0 mmol) was added, the solution was allowed to warm to room temperature and was then stirred for 2 h. The mixture was extracted with ethyl acetate, washed with 1 N-HCl, water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 10% ethyl acetate in hexane) to afford 7.2 g (83%) of **2** as a pale yellow liquid : R*f* 0.67 (Hexane/EtOAc, 2:1); IR (neat) cm^{-1} 3050, 3020, 2845, 1730, 735, 700; ^{1}H-NMR ($CDCl_3$, 80 MHz) δ 7.30 (s, 10H), 4.54 (s, 4H), 3.53 (s, 4H); Elms *m/z* (relative intensity) 179 (M^+-$CH_2C_6H_5$, 2), 133 (8), 107 (8), 91 (100), 77 (3), 65 (12).

Ethyl 4-benzyloxy-3-[(benzyloxy)methyl]-2-butenoate (3)

A suspension of sodium hydride (1.6 g, 60% oil dispersion, 54.0 mmol) in THF (200 mL) was cooled to 0°C, and triethyl phosphonoacetate (11.2 mL, 54.0 mmol) was added and stirred for 1 h at room temperature. A solution of ketone **2** (12.2 g, 45.0 mmol) in THF (200 mL) was added to the mixture *via* a cannula and stirred for 6 h. The reaction was quenched with water, extracted with ethyl acetate, washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oil, which was purified by column chromatography (eluted with 5% ethyl acetate in hexane) to afford 14.7 g (96%) of **3** as a pale yellow liquid: R*f* 0.76 (Hexane/EtOAc, 5:1); IR (neat) cm^{-1} 3050, 3010, 2960, 2910, 2850, 1710, 1650, 735, 700; ^{1}H-NMR ($CDCl_3$, 80 MHz) δ 7.33~7.29 (m, 10H), 6.13 (s, 1H), 4.69 (s, 2H), 4.59 (s, 2H), 4.49 (s, 2H), 4.28 (s, 2H), 4.15 (q, *J*=7.1, 2H), 1.26 (t, *J*=7.1, 3H); Elms *m/z* (relative intensity) 341 (MH^+), 234 (7), 143 (18), 105 (6), 91 (100).

Ethyl 4-benzyloxy-3-[(benzyloxy)methyl]-2,3-dibromobutanoate (4)

To a solution of the ester **3** (14.7 g, 43.0 mmol) in acetic acid (70 mL), lithium bromide (14.9 g, 0.2 mol) was added and stirred for 30 min. Bromine (4.4 mL, 86.0 mmol) was added dropwise at 0°C and stirred for 1 day at room temperature. The reaction was quenched with water, extracted with ethyl acetate and the organic phase was washed with sodium thiosulfate solution, sodium carbonate solution, water and brine sequentially. The solvent was dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 3% ethyl acetate in hexane) to afford 19.8 g (92%) of compound **4** as a pale yellow liquid: R*f* 0.48 (Hexane/EtOAc, 10:1); IR (neat) cm^{-1} 3050, 3010, 2950, 2890, 2850, 1735, 730, 690; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.36~7.25 (m, 10H), 5.00 (s, 1H), 4.64~4.58 (m, 4H), 4.28 (d, *J*=11.2, 1H), 4.19 (q, *J*=7.1, 2H), 4.09 (d, *J*=11.2, 1H),

4.07 (d, *J*=11.2, 1H), 3.89 (d, *J*=11.2, 1H), 1.26 (t, *J*=7.1, 3H); Elms *m/z* (relative intensity) 419 (M^+-Br), 171 (18), 107 (11), 91 (100).

Ethyl 4-benzyloxy-3-[(benzyloxy)methyl]-2-bromo-2-butenoate (5)

The ester **4** (10.2 g, 20.0 mmol) was dissolved in benzene (200 mL) and treated with TEA (14.2 mL, 0.1 mol). The next day, the reaction was quenched by the addition of water, extracted with ethyl acetate, and washed sequentially with 1N-HCl, sodium bicarbonate solution, water and brine. The solvent was dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 5% ethyl acetate in hexane) to afford 8.0 g (93%) of compound **5** as a pale yellow liquid : R*f* 0.27 (Hexane/EtOAc, 10:1); IR (neat) cm^{-1} 3050, 3010, 2970, 2910, 2850, 1725, 1640, 740, 700; ^{1}H-NMR ($CDCl_3$, 80 MHz) δ 7.30 (s, 10H), 4.54 (s, 2H), 4.49 (s, 2H), 4.35 (s, 4H), 4.20 (q, *J*=7.1, 2H), 1.26 (t, *J*=7.1, 3H); Elms *m/z* (relative intensity) 327 (M^+-$CH_2C_6H_5$), 105 (10), 91 (100), 77 (6).

4-Benzyloxy-3-[(benzyloxy)methyl]-2-bromo-2-buten-1-ol (6)

To a solution of the ester **5** (4.3 g, 10.0 mmol) in CH_2Cl_2 (70 mL) at -60°C under a nitrogen atmosphere, diisobutylaluminium hydride (DIBAL-H, 2 M in CH_2Cl_2, 26.0 mL, 52.0 mmol) was added dropwise. The mixture was stirred overnight at this temperature and then cautiously quenched with methanol and then water. The colloidal suspension was filtered and the solid was washed thoroughly with ethyl acetate. Evaporation of the solvent gave an oil, which was purified by column chromatography (eluted with 10% ethyl acetate in hexane) to afford 3.6 g (92%) of compound **6** as a pale yellow liquid: R*f* 0.31 (Hexane/EtOAc, 5:1); IR (neat) cm^{-1} 3400, 3050, 3010, 2910, 2850, 1640, 740, 700; ^{1}H-NMR ($CDCl_3$, 80 MHz) δ 7.32 (s, 10H), 4.51 (s, 4H), 4.41 (s, 2H), 4.30 (s, 2H), 4.21 (s, 2H), 2.40 (brs, 1H); Elms *m/z* (relative intensity) 285 (M^+-$CH_2C_6H_5$), 173 (7), 143 (6), 107 (30), 91 (100).

4-Benzyloxy-3-[(benzyloxy)methyl]-2-bromo-2-butenyl bromide (7)

The allylic alcohol **6** (493.2 mg, 1.3 mmol) was dissolved in CH_2Cl_2 (7mL), and triphenylphosphine (705.5 mg, 2.6 mmol) was added, which was followed by the slow addition of *N*-bromosuccinimide (466.3 mg, 2.6 mmol) at 0°C. After the addition was complete, the solution was stirred for 3 h at room temperature, and diluted with CH_2Cl_2. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by quick flash column chromatography (eluted with 5% ethyl acetate in hexane) to afford 559.8 mg (97%) of compound **7** as a pale yellow liquid: R*f* 0.60 (Hexane/EtOAc, 10:1); IR (neat) cm^{-1} 3075, 3045, 3005, 2905, 2845, 730, 695.

9-[4-(Benzyloxy)-3-[(benzyloxy)methyl]-2-bromo-2-butenyl]adenine (8a)

A mixture of adenine (377.0 mg, 2.8 mmol), sodium hydride (60% in oil, 83.7 mg, 2.8 mmol) and allylic bromide **7** (327.4 mg, 0.9 mmol) in DMF (15 mL) was stirred for 2 days and quenched by the addition of water. The mixture was diluted with ethyl acetate and the organic phase was then washed several times with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 25% hexane in ethyl acetate) to afford 285.1 mg (62%) of compound **8a** as a white solid: R*f* 0.57 (Hexane/EtOAc, 1:20); mp 137°C (recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 260.5 nm; IR (KBr) cm^{-1} 3280, 3130, 2890, 2850, 1670, 1600, 730, 690; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.35 (s, 1H), 7.93 (s, 1H), 7.32~7.30 (m, 10H), 5.67 (s, 2H), 5.24 (s, 2H), 4.61 (s, 2H), 4.50 (s, 2H), 4.48 (s, 2H), 4.31 (s, 2H); Elms *m/z* (relative intensity) 414 (M^+-Br), 404 (9), 202 (28), 135 (21), 91 (100).

1-[4-(Benzyloxy)-3-[(benzyloxy)methyl]-2-bromo-2-butenyl]uracil (8b)

To a stirred solution of the allylic bromide **7** (153.9 mg, 0.4 mmol) in DMF (2 mL), uracil (78.5 mg, 0.7 mmol) and cesium carbonate (228.1 mg, 0.7 mmol) were added. The mixture was stirred at room temperature until TLC showed no starting material remaining and the reaction was then quenched by the addition of water. The mixture was diluted with ethyl acetate and the organic phase was then washed several times with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 40% ethyl acetate in hexane) to afford 134.4 mg (82%) of compound **8b** as a white solid: R*f* 0.19 (Hexane/EtOAc, 1:1); mp 76°C recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 263.7 nm; IR (KBr) cm^{-1} 3160, 3040, 2840, 1710, 1625; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.59 (s, 1H), 7.32~7.26 (m, 11H), 5.62 (d, *J*=7.8, 1H), 4.77 (s, 2H), 4.55 (s, 2H), 4.50 (s, 2H), 4.33 (s, 2H), 4.30 (s, 2H); Elms *m/z* (relative intensity) 471 (MH^+), 391 (51), 285 (37), 105 (15), 91 (100), 65 (29).

1-[4-(Benzyloxy)-3-[(benzyloxy)methyl]-2-bromo-2-butenyl]thymine (8c)

Compound **8c** was obtained from the allylic bromide **7** (126.1 mg, 0.3 mmol), thymine (73.1 mg, 0.6 mmol) and cesium carbonate (114.0 mg, 0.4 mmol) as described for compound **8b**. The crude product was purified by column chromatography (eluted with 30% ethyl acetate in hexane)

to afford 120.5 mg (87%) of compound **8c** as a white solid. : R*f* 0.21 (Hexane/EtOAc, 3:2); mp 94°C (recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 268.4 nm; IR (KBr) cm^{-1} 3120, 3000, 2820, 1685, 1635; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.87 (s, 1H), 7.32~7.26 (m, 10H), 7.14 (s, 1H), 4.76 (s, 2H), 4.55 (s, 2H), 4.50 (s, 2H), 4.34 (s, 2H), 4.31 (s, 2H), 1.79 (s, 3H); Elms *m/z* (relative intensity) 469 (M^+-CH_3), 405 (6), 126 (8), 105 (29), 91 (100).

1-[4-(Benzyloxy)-3-[(benzyloxy)methyl]-2-bromo-2-butenyl]-5-fluorouracil (8d)

Compound **8d** was obtained from the allylic bromide **7** (179.9 mg, 0.4 mmol), 5-fluorouracil (106.7 mg, 0.8 mmol), cesium carbonate (172.7 mg, 0.5 mmol) using the method described for compound **8b**. The crude product was purified by column chromatography (eluted with 30% ethyl acetate in hexane) to afford 148.7 mg (74%) of **8d** as a white solid : R*f* 0.43 (Hexane/EtOAc, 3:2); mp 120°C (recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 269.4 nm; IR (KBr) cm^{-1} 3140, 3000, 2840, 1735, 1685, 1660; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.99 (s, 1H), 7.47 (d, *J*=5.7, 1H), 7.37~7.26 (m, 10H), 4.75 (s, 2H), 4.55 (s, 2H), 4.51 (s, 2H), 4.30 (s, 4H); Elms *m/z* (relative intensity) 489 (MH^+), 303 (3), 130 (6), 105 (35), 91 (100).

1-[4-(Benzyloxy)-3-[(benzyloxy)methyl]-2-bromo-2-butenyl]-5-iodouracil (8e)

Compound **8e** was obtained from the allylic bromide **7** (144.5 mg, 0.3 mmol), 5-iodouracil (157.1 mg, 0.7 mmol), cesium carbonate (140.1 mg, 0.4 mmol) using the method described for compound **8b**. The crude product was purified by column chromatography (eluted with 30% ethyl acetate in hexane) to afford 163.9 mg (84%) of **8e** as a white solid: R*f* 0.53 (Hexane/EtOAc, 3:2); mp 111°C (recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 287.4 nm; IR (KBr) cm^{-1} 3000, 2830, 1715, 1650, 1600; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.28 (s, 1H), 7.79 (s, 1H), 7.37~7.26 (m, 10H), 4.77 (s, 2H), 4.55 (s, 2H), 4.50 (s, 2H), 4.32 (s, 2H), 4.29 (s, 2H); Elms *m/z* (relative intensity) 517 (M^+-Br), 411 (5), 238 (3), 128 (35), 105 (68), 91 (100).

1-[4-(Benzyloxy)-3-[(benzyloxy)methyl]-2-bromo-2-butenyl]-5-trifluoromethyl-uracil (8f)

Compound **8f** was obtained from the allylic bromide **7** (124.5 mg, 0.3 mmol), 5-tifluoromethyluracil (100.9 mg, 0.6 mmol), cesium carbonate (110.8 mg, 0.3 mmol) using the method described for compound **8b**. The crude product was purified by column chromatography (eluted with 25% ethyl acetate in hexane) to afford 146.1 mg (96%) of compound **8f** as a white solid : R*f* 0.38 (Hexane/EtOAc, 2:1); mp 104°C (recrystallized from hexane-ethyl acetate); UV (MeOH) δ_{max} 262.0 nm; IR (KBr) cm^{-1} 3160, 3040, 2840, 1695, 1650; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.27 (s, 1H), 7.84 (s, 1H), 7.277.19 (m, 10H), 4.75 (s, 2H), 4.47 (s, 2H), 4.41 (s, 2H), 4.25 (s, 2H), 4.21 (s, 2H); Elms *m/z* (relative intensity) 459 (M^+-Br, 10), 353 (44), 181 (14), 105 (83), 91 (100).

1-[4-(Benzyloxy)-3-[(benzyloxy)methyl]-2-bromo-2-butenyl]cytosine (8g)

Compound **8g** was obtained from the allylic bromide **7** (95.1 mg, 0.2 mmol), cytosine (48.9 mg, 0.4 mmol), cesium carbonate (84.7 mg, 0.3 mmol) using the method described for compound **8b**. The crude product was purified by column chromatography (eluted with 5% methanol in CH_2Cl_2) to afford 100.7 mg (99%) of compound **8g** as a white solid: R*f* 0.44 (CH_2Cl_2/MeOH, 10:1); mp 179°C (recrystallized from methanol); UV (MeOH) λ_{max} 274.5 nm; IR (KBr) cm^{-1} 3300, 3080, 1650, 1615, 1510, 1480; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.47 (d, *J*=7.4, 1H), 7.32~7.26 (m, 10H), 5.71 (d, *J*=7.4, 1H), 4.76 (s, 2H), 4.53 (s, 2H), 4.45 (s, 2H), 4.41 (s, 2H), 4.26 (s, 2H); Elms *m/z* (relative intensity) 470 (MH^+), 390 (3), 112 (5), 105 (74), 91 (100).

Deprotection of benzylated acyclic nucleosides

A solution of the protected nucleosides **8a~8g** (0.20.7 mmol) in dry CH_2Cl_2 was stirred at -78°C under a nitrogen atmosphere. This solution was treated with 10 equiv. of boron trichloride (BCl_3) (1.0 M in CH_2Cl_2) and stirred at -78°C for 1 h. Methanol was then added and the solution was allowed warm to room temperature. This solution was concentrated *in vacuo* and co-evaporated three times with methanol. The residue was purified by column chromatography (eluted with 5~20% methanol in CH_2Cl_2).

9-[2-Bromo-4-hydroxy-3-hydroxymethyl-2-butenyl] adenine (9a)

A white solid (93% from compound **8a**): R*f* 0.55 (MeOH/EtOAc, 1:2); mp 216°C (recrystallized from water); UV (MeOH) λ_{max} 260.6 nm; IR (KBr) cm^{-1} 3310, 3140, 2960, 2890, 1650, 1590; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.14 (s, 1H), 8.13 (s, 1H), 7.31 (bs, 2H), 5.48 (t, *J*=5.7, 1H, D_2O exchangeable), 5.31 (s, 2H), 5.06 (t, *J*=5.7, 1H, D_2O exchangeable), 4.45 (d, *J*=5.6, 2H), 4.16 (d, *J*=5.5, 2H); Elms *m/z* (relative intensity) 313 (M^+, 2), 284 (38), 234 (20), 136 (100), 108 (45), 91 (19), 81 (17), 66 (8), 53 (14).

1-[2-Bromo-4-hydroxy-3-hydroxymethyl-2-butenyl] uracil (9b)

A white solid (76% from compound **8b**): R*f* 0.15 ($CHCl_3$/MeOH, 10:1); mp 183°C (recrystallized from methanol and ethyl acetate); UV (MeOH) λ_{max} 263.4 nm; IR (KBr) cm^{-1} 3340, 3080, 2960, 2790, 1670; ^{1}H-NMR (DMSO-d_6/

$CDCl_3$,, 300 MHz) δ 11.12 (s, 1H, D_2O exchangeable), 7.45 (d, *J*=8.1, 1H), 5.63 (d, *J*=8.1, 1H), 4.81 (s, 2H), 4.63 (t, *J*=6.0, 1H, D_2O exchangeable), 4.52 (t, *J*=6.0, 1H, D_2O exchangeable), 4.43 (d, *J*=6.0, 2H), 4.34 (d, *J*=6.0, 2H); Elms *m/z* (relative intensity) 273 (M^+-OH), 211 (100), 113 (29), 82 (13), 69(16).

1-[2-Bromo-4-hydroxy-3-hydroxymethyl-2-butenyl] thymine (9c)

A white solid (95% from compound **8c**): R*f* 0.50 (CH_2Cl_2/MeOH, 10:1); mp 184°C (recrystallized from methanol); UV (MeOH) λ_{max} 268.2 nm; IR (KBr) cm^{-1} 3360, 3160, 2810, 1665, 1650; ^{1}H-NMR (DMSO-d_6,, 300 MHz) δ 11.43 (s, 1H, D_2O exchangeable), 7.43 (s, 1H), 5.02 (t, *J*=5.7, 1H, D_2O exchangeable), 4.99 (t, *J*=5.7, 1H, D_2O exchangeable), 4.76 (s, 2H), 4.28 (d, *J*=5.7, 2H), 4.16 (d, *J*=5.7, 2H), 1.77 (s, 3H); Elms *m/z* (relative intensity) 305 (MH^+, 4), 287 (6), 225 (100), 177 (28), 127 (49), 81 (44), 55(68).

1-[2-Bromo-4-hydroxy-3-hydroxymethyl-2-butenyl]-5-fluorouracil (9d)

A white solid (90% from compound **8d**): R*f* 0.21 (CH_2Cl_2/MeOH, 10:1); mp 197°C (recrystallized from methanol); UV (MeOH) λ_{max} 270.7nm; IR (KBr) cm^{-1} 3390, 2960, 2800, 1655; ^{1}H-NMR (DMSO-d_6/$CDCl_3$, 300 MHz) δ 11.86 (s, 1H, D_2O exchangeable), 7.78 (d, *J*=6.0, 1H), 4.87 (t, *J*=5.7, 2H, D_2O exchangeable), 4.82 (s, 2H), 4.39 (d, *J*=5.7, 2H), 4.31 (d, *J*=5.7, 2H); Elms *m/z* (relative intensity) 309 (MH^+, 2), 229 (100), 181 (20), 131 (51), 87 (44), 81 (52).

1-[2-Bromo-4-hydroxy-3-hydroxymethyl-2-butenyl]-5-iodouracil (9e)

A white solid (86% from compound **8e**): R*f* 0.27 (CH_2Cl_2/MeOH, 10:1); mp 180°C (recrystallized from methanol and ethyl acetate); UV (MeOH) λ_{max} 286.3 nm; IR (KBr) cm^{-1} 3360, 3000, 2810, 1685, 1655, 1610; ^{1}H-NMR (DMSO-d_6/$CDCl_3$, 300 MHz) δ 11.69 (s, 1H, D_2O exchangeable), 7.96 (s, 1H), 4.84 (s, 2H), 4.69 (t, *J*=6.0, 1H, D_2O exchangeable), 4.60 (t, *J*=6.0, 1H, D_2O exchangeable), 4.42 (d, *J*=6.0, 2H), 4.33 (d, *J*=6.0, 2H); *m/z* (relative intensity) 417 (MH^+, 1), 337 (100), 254 (58), 195 (41), 127 (82), 80 (83).

1-[2-Bromo-4-hydroxy-3-hydroxymethyl-2-butenyl]-5-trifluoromethyluracil (9f)

A white solid (83% from compound **8f**): R*f* 0.11 (CH_2Cl_2/MeOH, 10:1); mp 165°C (recrystallized from water); UV (MeOH) λ_{max} 262.1nm; IR (KBr) cm^{-1} 3320, 3000, 1685; ^{1}H-NMR (DMSO-d_6/$CDCl_3$, 300 MHz) δ 11.78 (s, 1H, D_2O exchangeable), 8.12 (s, 1H), 4.91 (s, 2H), 4.66 (s, 1H, D_2O exchangeable), 4.59 (s, 1H, D_2O exchangeable), 4.45 (s, 2H), 4.35 (s, 2H); *m/z* (relative intensity) 359 (MH^+), 279 (86), 181 (13), 161 (30), 91 (34), 81 (100).

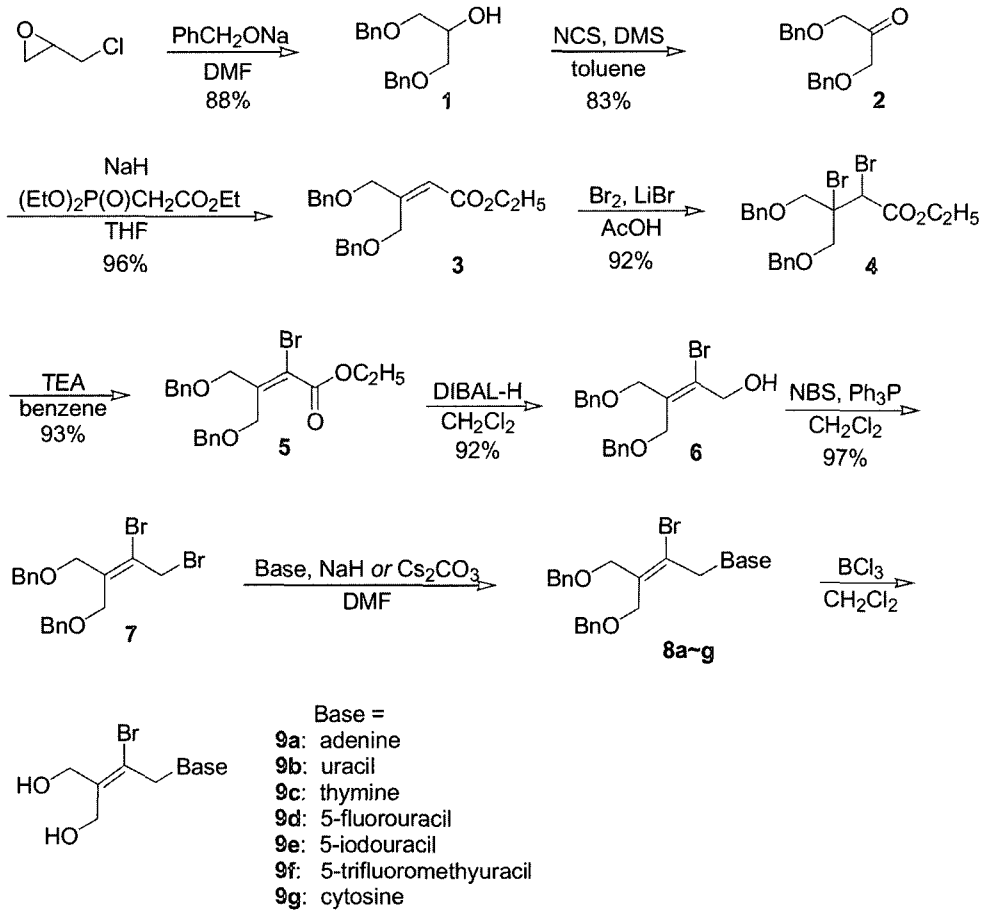
1-[2-Bromo-4-hydroxy-3-hydroxymethyl-2-butenyl] cytosine (9g)

A white solid (89% from compound **8g**): R*f* 0.53 (CH_2Cl_2/MeOH, 3:1); mp 202°C (recrystallized from methanol); UV (MeOH) λ_{max} 273.2 nm; IR (KBr) cm^{-1} 3300, 1655, 1620; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.56 (d, *J*=7.3, 1H), 7.16 (poorly resolved d, *J*=5.1, 1H, D_2O exchangeable), 7.12 (poorly resolved s, 1H, D_2O exchangeable), 5.71 (d, *J*=7.3, 1H), 5.05 (t, *J*=5.7, 1H, D_2O exchangeable), 5.02 (t, *J*=5.7, 1H, D_2O exchangeable), 4.75 (s, 2H), 4.27 (d, *J*=5.7, 2H), 4.14 (d, *J*=5.7, 2H); *m/z* (relative intensity) 290 (MH^+), 210 (34), 112 (61), 97 (100), 81 (92).

RESULTS AND DISCUSSION

The strategy for synthesizing the bromobutenyl nucleosides is based on the alkylation of either adenine or pyrimidine bases with the allylic bromide **7**. The allylic bromide **7** was prepared from epichlorohydrin *via* an efficient seven-step sequence in a 54% overall yield, as shown in Scheme 1. 1,3-Dibenzyloxy-2-propanol (**1**), which was prepared from epichlorohydrin and benzylalcohol, was easily oxidized to the ketone **2** using *N*-chlorosuccinimde and dimethyl sulfide (Corey and Kim, 1972). Other common oxidizing agents such as pyridinium chlorochromate, pyridinium dichromate, and the Jones reagent were less successful. The Horner-Emmons reaction of the ketone **2** with triethyl phosphonoacetate gave the α,β-unsaturated ester **3** in a 96% yield. The bromination of the ester **3** in basic condition was unsuccessful. However, the dibromoester **4** was obtained in acetic acid, which was then treated with TEA to yield the α,β-unsaturated bromoester **5** in an 86% yield through 2 step. The bromoester **5** was reduced with DIBAL-H to allylic alcohol **6**. Conversion of **6** to the bromide derivative **7** was accomplished by the addition of NBS to a solution of the alcohol and triphenylphosphine in CH_2Cl_2 (Borcherding *et al.*, 1988) in a 97% yield.

The coupling of the allylic bromide **7** with adenine in the presence of sodium hydride provided the desired N^9-alkylated adenine **8a** (Borcherding *et al.*, 1987; Phadtare *et al.*, 1991) in a 62% yield. Deprotection of the benzyl groups using boron trichloride in CH_2Cl_2 gave 9-[2-bromo-4-hydroxy-3-hydroxymethyl-2-butenyl]adenine (**9a**) in a 93% yield. The pyrimidine compounds were prepared by the same way as used with adenine. Direct alkylation of pyrimidines to allylic bromide **7** in DMF with cesium carbonate as a basic catalyst gave the desired N^1-alkylated products (Bronson *et al.*, 1989). The UV data was in good agreement with those of the appropriate model compounds (Cook and Holman, 1980; Ogilvie *et al.*, 1984; Hronowski and Szarek, 1992). Deprotection of the benzyl protecting groups using boron trichloride gave the bromobutenylated



Scheme 1. Synthetic scheme of carbocyclic nucleoside

pyrimidines (**9b~9g**). The structures of final products were confirmed by UV, mass, IR, and ^{1}H-NMR spectra.

Compounds **9a~9g** were evaluated for their activity against the polio virus, HSV-1, HSV-2 and HIV. However, compounds had no antiviral activity. The lack of antiviral activity of these compounds is presumably associated with their unfavorable conformations for the phosphorylation occurring during the nucleotide activation process. However, the information obtained in the present study will be useful for the development of a novel carbonucleoside. Studies toward this end and to clarify the mechanism are underway.

ACKNOWLEDGMENT

This Research was supported by the Sookmyung Women's University Research Grants 2002.

REFERENCES

Borcherding, D. R., Narayanan, S., Hasobe, M., McKee, J. G., Keller, B. T., and Borchardt, R. T., Potential inhibitors of *S*-adenosylmethionine-dependent methyltransferases. II. Molecular dissections of neplanocin A as potential inhibitors of *S*-adenosylhomocysteine hydrolase. *J. Med. Chem.*, 31, 1729-1738 (1988).

Borcherding, D. R., Scholtz, S. A., and Borchardt, R. T., Synthesis of analogues of neplanocin A: Utilization of optically active dihydroxycyclopentenones derived from carbohydrates. *J. Org. Chem.*, 52, 5457-5461 (1987).

Bronson, J. J., Ghazzouli, I., Hitchcock, M. J. M., Webb, R. R., and Martin, J. C., Synthesis and antiviral activity of the nucleotide analogue (*S*)-1-[3-hydroxy-2-(phosphonylmethoxy) propyl]cytosine. *J. Med. Chem.*, 32, 1457-1463 (1989).

Cook, A. F. and Holman, M. J., Fluorinated pyrimidine nucleosides. 4. Synthesis and antitumor testing of a series of 2',5'-dideoxy- and 2',3',5'-trideoxynucleosides of 5-fluorouracil. *J. Med. Chem.*, 23, 852-857 (1980).

Corey, E. J. and Kim, C. U., A new and highly effective method for the oxidation of primary and secondary alcohols to carbonyl compounds. *J. Am. Chem. Soc.*, 94, 7586-7587 (1972).

Harnden, M. R., Jarvest, R. L., Bacon, T. H., and Boyd M. R., Synthesis and antiviral activity of 9-[4-hydroxy-3-(hydroxymethyl)

but-1-yl]purines. *J. Med. Chem.*, 30, 1636-1642 (1987).

Hronowski, L. J. J. and Szarek, W. A., Synthesis of cyclopentane analogs of 5-fluorouracil nucleosides. *Can. J. Chem.*, 70, 1162-1169 (1992).

Marquez, V. E., *Carbocyclic nucleosides. In advances in antiviral drug design*, JAI Press, 1996, Vol. 2, pp 89-146, and references therein.

Marquez, V. E., Lim, M.-I., Treanor, S. P., Plowman, J., Priest, M. A., Markovac, A., Khan M. S., Kaskar, B., and Driscoll, J. S., Cyclopentenylcytosine. A carbocyclic nucleoside with antitumor and antiviral properties. *J. Med. Chem.*, 31, 1687-1694 (1988).

Ogilvie, K. K., Hamilton, R. G., Gillen M. F., and Radatus B. K., Uracil analogues of the acyclonucleoside 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine(BIOLF-62). *Can. J. Chem.*, 62, 16-21 (1984).

Phadtare, S., Kessel, D., Corbett, T. H., Renis, H. E., Court, B. A., and Zemlicka, J., Unsaturated and carbocyclic nucleoside analogues: synthesis, antitumor, and antiviral activity. *J. Med. Chem.*, 34, 421-429 (1991).