Arch. Pharm. Res. Vol.20, No.5, pp. 501-506, 1997

Synthesis and Biological Evaluation of 9-[2-Fluoro-4-hydroxy-3-hydroxymethyl-2-butenyl]adenine and its Related Compounds as Open-chain Analogues of Neplanocin A

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(Received July 27, 1997)

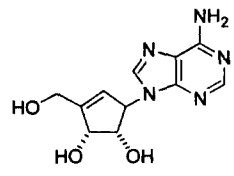
Novel 9-[2-fluoro-4-hydroxy-3-hydroxymethyl-2-butenyl]adenine and its related compounds were designed and synthesized as open-chain analogues of neplanocin A. Alkylation of adenine or pyrimidine bases with the mesylate **4** was chosen as a simple approach to the synthesis of 2-fluoro-2-butenylated nucleosides. Mesylate **4** was prepared from dihydroxyacetone dimer *via* four steps in 58% overall yield. The synthesized compounds were evaluated their antiviral activity against HSV, HIV and Polio viruses.

Key words : 9-[2-fluoro-4-hydroxy-3-hydroxymethyl-2-butenyl]adenine, open-chain analogues, neplanocin A, antiviral activity

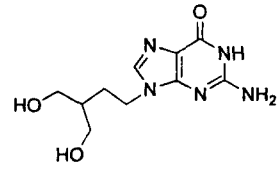
INTRODUCTION

Many cyclic and acyclic carba-nucleoside analogues, in which the furanose oxygen atom has been replaced by a carbon, have been shown to have significant antiviral activity (Marquez, 1996). The most well known carba-nucleosides to date are neplanocin A and penciclovir. Neplanocin A is a novel cyclic carba analogue of adenosine with a cyclopentene ring, and possesses potent antiviral activity against broad spectrum of viruses (De Clercq *et al.*, 1989). Penciclovir is an acyclic carba analogue of guanosine, and now approved as an antiviral drug for the treatment of diseases caused by HSV and VZV (Harnden *et al.*, 1987). Because of the unusual presence of the double bond in neplanocin A and acyclic nature of penciclovir, these two compounds have stimulated extensive research in the synthesis of new cyclic and acyclic carba-nucleoside analogues mimicking the sugar portion of naturally occurring nucleosides. However, with relatively few exceptions, the activities of most conventional carbonucleosides have been poorer than those of the corresponding ribosides. The loss of furan oxygen in carba-nucleosides is believed to have critical effects on their antiviral activity. To search for the chemically and enzymatically stable carba-nucleoside, while causing minimal structural disturbance, we designed the compound **12** as an open-chain analogue of neplanocin A (Hua *et al.*, 1987, Borcherding *et al.*, 1988).

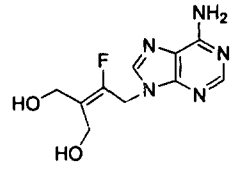
The underlying concept for the design of novel carba-nucleosides **12** is to seek C-N bond to replace the hydrolytically and enzymatically scissile glycosylic bond, while causing minimal conformational and stereoelectronical changes. The incorporation of fluorine atoms into organic molecules has often been associated with profound changes in the biological profiles of the fluorinated analogues compared to their hydrocarbon counterparts (Casara *et al.*, 1991). It has also been suggested that a fluoromethylene group is a better isostere of oxygen than the methylene group (Blackburn and Kent, 1986) and therefore carboacyclic derivatives substituted by fluorine at the 1'a-position were also at-



Neplanocin A



Penciclovir



Target Molecule(12)

Fig. 1. Structures of Carba-Nucleosides.

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tractive targets. In the present paper, we report on the syntheses of a series of 2-fluoro-4-hydroxy-3-hydroxymethyl-2-butenyl nucleosides in attempts to mimic even more closely the natural nucleoside by installing an fluoro group at 1'a-position.

MATERIALS AND METHODS

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

Bis(*t*-butyldimethylsilyloxy) acetone (1)

To a suspension of 1,3-dihydroxyacetone dimer (197.5 mg, 1.1 mmol) and imidazole (597.1 mg, 8.8 mmol) in DMF (3 ml) was added *t*-butyldimethylsilyl chloride (829.0 mg, 5.5 mmol). The mixture was stirred for 2 days and the reaction was quenched by addition of water. The mixture was diluted with hexane, and then the organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 2% ethyl acetate in hexane) to afford 625.3 mg (90%) of **1** as a colorless liquid: R*f* 0.62 (Hexane/EtOAc, 10:1); IR (neat) cm^{-1} 2950, 2930, 2890, 2850, 1740; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 4.41 (s, 4H), 0.92 (s, 18H), 0.09 (s, 12H); EIMS *m/z* (relative intensity) 319 (MH^+, 16), 261 (16), 115 (16), 103 (34), 89 (80), 73 (100).

Ethyl 4-(*t*-butyldimethylsilyloxy)-3-[(*t*-butyldimethylsilyloxy)methyl]-2-fluoro -2-butenoate (2)

To a stirred solution of triethyl 2-fluoro-2-phosphonoacetate (346.3 mg, 1.4 mmol) in THF (2 ml) at -78 °C under a nitrogen atmosphere was added n-butyllithium in hexane (1.3 ml, 1.4 mmol). The solution was stirred at -78°C for 20 min and then ketone **1** (413.2 mg, 1.3 mmol) in THF (3 ml) was added. The mixture was warmed to room temperature and was quenched by addition of water. The mixture was diluted with hexane and then the organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 2% ethyl acetate in hexane) to afford 469.2 mg (89%) of **2** as a pale yellow liquid: R*f* 0.67 (Hexane/EtOAc, 20:1); IR (neat) cm^{-1} 2930, 2900, 2860, 2830, 1725, 1660; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 4.74 (d, *J*=2.1, 2H), 4.44 (d, *J*=3.6, 2H), 4.30 (q, *J*=7.2, 2H), 1.35 (t, *J*=7.2, 3H), 0.96 ~0.84 (m, 18H), 0.16~0.03 (m, 12H); EIMS *m/z* (relative intensity) 349 (M^+-C_4H_9), 115 (5), 105 (18), 91 (100), 73 (29).

4-(*t*-butyldimethylsilyloxy)-3-[(*t*-butyldimethylsilyloxy) methyl]-2-fluoro-2-buten-1-ol (3)

To a solution of ester **2** (419.3 mg, 1.0 mmol) in CH_2Cl_2 (5 ml) at -63°C under a nitrogen atmosphere was added diisobutylaluminium hydride (DIBAH) in toluene (5.2 ml, 5.2 mmol). The mixture was stirred overnight at -63°C and the reaction was quenched by addition of methanol and then water. The resulting suspension was filtered and the solid washed thoroughly with ethyl acetate. Evaporation of the solvent gave an oil, which was purified by column chromatography (eluted with 5% ethyl acetate in hexane) to afford 314.5 mg (84%) of **3** as a pale yellow liquid: R*f* 0.28 (Hexane/EtOAc, 20:1); IR (neat) cm^{-1} 3360, 2940, 2910, 2870, 2850, 1700; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.31~4.24 (m, 7H), 0.91 (s, 9H), 0.90 (s, 9H), 0.10 (s, 6H), 0.07 (s, 6H); EIMS *m/z* (relative intensity) 347(M^+-OH), 173 (32), 100 (34), 87 (30), 72 (100).

4-(*t*-butyldimethylsilyloxy)-3-[(*t*-butyldimethylsilyloxy) methyl]-2-fluoro-2-butenyl mesylate (4)

Allylic alcohol **3** (434.1 mg, 1.2 mmol) was dissolved in CH_2Cl_2 (15 ml) and cooled to 0°C. Under nitrogen atmosphere, triethylamine (0.8 ml, 6.0 mmol) and methanesulfonyl chloride (0.1 ml, 1.4 mmol) were added sequentially with stirring. The reaction mixture was stirred at 0°C for 20 min before it was diluted with CH_2Cl_2. The solvent was 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 451.2mg (86%) of **4** as a pale yellow liquid: R*f* 0.61 (Hexane/EtOAc, 6:1); IR (neat) cm^{-1} 2940, 2900, 2860, 2840, 1700.

9-[4-(*t*-butyldimethylsilyloxy)-3-[(*t*-butyldimethylsilyloxy) methyl]-2-fluoro-2-butenyl]adenine (5)

To a suspension of adenine (539.2 mg, 4.0 mmol) in DMF (10 ml) was added sodium hydride (60% in oil, 159.6 mg, 4.0 mmol) and the mixture was stirred at room temperature for 10 min. Then allylic mesylate **4** (589.5 mg, 1.3 mmol) was added and the mixture was stirred until TLC showed no starting material remained and quenched by addition of water. The mixture was diluted with ethyl acetate and then the organic phase was washed with water several times and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 75% ethyl acetate in hexane) to afford 290.3 mg (45%) of **5** as a white solid: R*f* 0.44 (Hexane/EtOAc, 1:3); mp 127°C (recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 260.1 nm; IR (KBr) cm^{-1} 3280, 3110, 2930, 2910, 2840, 1670, 1600; ^1H NMR ($CDCl_3$, 300 MHz) 8.37 (s, 1H), 7.91 (s, 1H), 5.70 (bs, 2H), 5.09 (d, *J*=21.9, 2H), 4.46 (d, *J*=2.7, 2H), 4.32 (d, *J*=3.3, 2H), 0.91 (s, 9H), 0.87 (s, 9H), 0.13 (s, 6H), 0.03 (s, 6H); EIMS *m/z* (relative intensity) 481 (M^+), 424 (52), 147 (20), 136 (12), 89 (38), 73 (100).

1-[4-(*t*-butyldimethylsilyloxy)-3-[(*t*-butyldimethylsilyloxy) methyl]-2-fluoro-2-butenyl]thymine (6)

Compound **6** was also prepared by the same procedure as that of **5**, starting from allylic mesylate **4** (51.4 mg, 0.1 mmol), thymine (30.3 mg, 0.2 mmol) and cesium carbonate (52.1 mg, 0.2 mmol). The crude product was purified by column chromatography (eluted with 30% ethyl acetate in hexane) to afford 42.6 mg (78%) of **6** as a white solid: R*f* 0.33 (Hexane/EtOAc, 2:1); mp 165°C (recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 268.4 nm; IR (KBr) cm^{-1} 3010, 2940, 2840, 1705, 1655; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.58 (s, 1H), 7.15 (s, 1H), 4.63 (d, *J*=21.4, 2H), 4.36 (d, *J*=2.9, 2H), 4.31 (d, *J*=3.2, 2H), 1.91 (s, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.11 (s, 6H), 0.06 (s, 6H); EIMS *m/z* (relative intensity) 473 (MH^+), 415 (36), 283 (31), 183 (26), 151 (32), 115 (16), 89 (47), 73 (100).

1-[4-(*t*-butyldimethylsilyloxy)-3-[(*t*-butyldimethylsilyloxy) methyl]-2-fluoro-2-butenyl]-5-fluorouracil (7)

Compound **7** was also prepared by the same procedure as that of **5**, starting from allylic mesylate **4** (49.7 mg, 0.1 mmol), 5-fluorouracil (28.6 mg, 0.2 mmol) and cesium carbonate (45.6 mg, 0.1 mmol). The crude product was purified by column chromatography (eluted with 15% ethyl acetate in hexane) to afford 33.0 mg (62%) of **7** as a white solid: R*f* 0.50 (Hexane/EtOAc, 2:1); mp 150°C (recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 270.2 nm; IR (KBr) cm^{-1} 2920, 2900, 2840, 1720, 1705, 1675; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.06 (s, 1H), 7.56 (d, *J*=5.5, 1H), 4.66 (d, *J*=22.2, 2H), 4.36 (d, *J*=2.9, 2H), 4.32 (d, *J*=3.2, 2H), 0.92 (s, 9H), 0.89 (s, 9H), 0.12 (s, 6H), 0.06 (s, 6H); EIMS *m/z* (relative intensity) 461 (M^+-CH_3), 419 (19), 287 (20), 187 (22), 151 (44), 89 (45), 75 (100).

1-[4-(*t*-butyldimethylsilyloxy)-3-[(*t*-butyldimethylsilyloxy) methyl]-2-fluoro-2-butenyl]-5-iodouracil (8)

Compound **8** was also prepared by the same procedure as that of **5**, starting from allylic mesylate **4** (44.9 mg, 0.1 mmol), 5-iodouracil (47.6 mg, 0.2 mmol) and cesium carbonate (42.4 mg, 0.1 mmol). The crude product was purified by column chromatography (eluted with 15% ethyl acetate in hexane) to afford 45.2 mg (76%) of **8** as a white solid: R*f* 0.62 (Hexane/EtOAc, 2:1); mp 183°C (recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 286.2 nm; IR (KBr) cm^{-1} 3005, 2930, 2845, 1705, 1670, 1605; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.60 (s, 1H), 7.78 (s, 1H), 4.69 (d, *J*=21.6, 2H), 4.36 (s, 2H), 4.31 (d, *J*=3.2, 2H), 0.92 (s, 9H), 0.89 (s, 9H), 0.13 (s, 6H), 0.07 (s, 6H); EIMS *m/z* (relative intensity) 585 (MH^+), 527 (35), 395 (26), 151 (87), 89 (87), 73 (100).

1-[4-(*t*-butyldimethylsilyloxy)-3-[(*t*-butyldimethylsilyloxy) methyl]-2-fluoro-2-butenyl]-5-trifluoromethyluracil (9)

Compound **9** was also prepared by the same procedure as that of **5**, starting from allylic mesylate **4** (133.6 mg, 0.3 mmol), 5-trifluoromethyluracil (108.1 mg, 0.6 mmol) and cesium carbonate (117.3 mg, 0.4 mmol). The crude product was purified by column chromatography (eluted with 10% ethyl acetate in hexane) to afford 115.9 mg (73%) of **9** as a white solid: R*f* 0.85 (Hexane/EtOAc, 2:1); mp 172°C (recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 262.4 nm; IR (KBr) cm^{-1} 2910, 2840, 1705, 1660; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.24 (s, 1H), 7.84 (s, 1H), 4.76 (d, *J*=21.6, 2H), 4.38 (d, *J*=3.2, 2H), 4.31 (d, *J*=3.2, 2H), 0.91 (s, 9H), 0.89 (s, 9H), 0.11 (s, 6H), 0.06 (s, 6H); EIMS *m/z* (relative intensity) 527 (MH^+), 337 (28), 151 (31), 89 (97), 73 (100).

1-[4-(*t*-butyldimethylsilyloxy)-3-[(*t*-butyldimethylsilyloxy) methyl]-2-fluoro-2-butenyl]cytosine (10)

Compound **10** was also prepared by the same procedure as that of **5**, starting from allylic mesylate **4** (238.4 mg, 0.5 mmol), cytosine (120.0 mg, 1.1 mmol) and cesium carbonate (351.9 mg, 1.1 mmol). The crude product was purified by column chromatography (eluted with 5% methanol in CH_2Cl_2) to afford 242.2 mg (98 %) of **10** as a white solid: R*f* 0.69 (CH_2Cl_2/MeOH, 5:1); mp 150°C (recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 273.7 nm; IR (KBr) cm^{-1} 3290, 3160,

2940, 2920, 2880, 2840, 1630; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (d, *J*=7.2, 1H), 5.68 (d, *J*=7.2, 1H), 4.68 (d, *J*=22.3, 2H), 4.37 (d, *J*=2.1, 2H), 4.31 (d, *J*=3.1, 2H), 0.90 (s, 9H), 0.88 (s, 9H), 0.10 (s, 6H), 0.05 (s, 6H); EIms *m/z* (relative intensity) 457 (M^+, 1), 400 (96), 268 (19), 168 (100), 151 (24), 112 (14), 81 (31), 73 (88).

1-[4-(*t*-butyldimethylsilyloxy)-3-[(*t*-butyldimethylsilyloxy) methyl]-2-fluoro-2-butenyl]uracil (11)

To a stirred solution of allylic mesylate **4** (234.1 mg, 0.5 mmol) in DMF (5 ml) was added uracil (118.8 mg, 1.1 mmol) and cesium carbonate (345.4 mg, 1.1 mmol). The mixture was stirred at room temperature until TLC showed no starting material remained and quenched by addition of water. The mixture was diluted with ethyl acetate and then the organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 30% ethyl acetate in hexane) to afford 198.4 mg (82%) of **11** as a white solid: R*f* 0.29 (Hexane/EtOAc, 3:2); mp 138°C (recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 262.9 nm; IR (KBr) cm^{-1} 2930, 2910, 2870, 2840, 1700, 1675; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.67 (s, 1H), 7.37 (d, *J*=7.7, 1H), 5.70 (dd, *J*=7.7, 2.1, 1H), 4.65 (d, *J*=21.6, 2H), 4.36 (d, *J*=2.3, 2H), 4.31 (d, *J*=3.2, 2H), 0.91 (s, 9H), 0.89 (s, 9H), 0.11 (s, 6H), 0.06 (s, 6H); EIMS *m/z* (relative intensity) 443 (M^+-CH_3, 2), 401 (87), 269 (82), 169 (55), 147 (44), 89 (69), 73 (100).

Deprotection of Silylated acyclic nucleosides (12~18)

To a stirred solution of the silylated nucleoside (0.2~0.5 mmol) in THF was added 2.5 equivalent of tetrabutylammonium fluoride (TBAF) (1M in THF). The mixture was stirred at room temperature for 20 min until TLC showed no starting material remained. The solution was concentrated and the residue was purified by column chromatography (eluted with 5~15% methanol in CH_2Cl_2).

9-[2-fluoro-4-hydroxy-3-hydroxymethyl-2-butenyl] adenine (12)

A white solid (92% from **5**): R*f* 0.24 (CH_2Cl_2/MeOH, 10:1); mp 204°C (recrystallized from water); UV (MeOH) λ_{max} 260.6 nm; IR (KBr) cm^{-1} 3310, 3150, 2840, 1660, 1600; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.15 (s, 1H), 8.14 (s, 1H), 7.30 (bs, 2H, D_2O exchangeable), 5.13 (d, *J*=22.5, 2H), 5.12 (t, *J*=5.8, 1H, D_2O exchangeable), 4.79 (t, *J*=5.8, 1H, D_2O exchangeable), 4.29 (dd, *J*=5.8, 2.1, 2H), 4.04 (dd, *J*=5.8, 3.1, 2H); EIMS *m/z* (relative intensity) 254 (MH^+, 76), 253 (M^+, 29), 236 (28), 222 (98), 136 (89), 108 (100), 81 (54), 53 (46); HRMS (EI) calcd for $C_{10}H_{12}N_5O_2F$ (M^+) 253.0975, found 253.0975.

1-[2-fluoro-4-hydroxy-3-hydroxymethyl-2-butenyl]thymine (13)

A white solid (90% from **6**): R*f* 0.25 (CH_2Cl_2/MeOH, 10:1); mp 148°C (recrystallized from methanol); UV (MeOH) λ_{max} 267.4 nm; IR (KBr) cm^{-1} 3380, 3240, 3000, 2800, 1700, 1675; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.32, (s, 1H, D_2O exchangeable), 7.43 (s, 1H), 4.70 (t, *J*=4.8, 2H), 4.61 (d, *J*=21.9, 2H), 4.19 (d, *J*=4.5, 2H), 4.11 (s, 2H), 1.80 (s, 3H); EIMS *m/z* (relative intensity) 245 (MH^+, 26), 227 (30), 138 (28), 127 (100), 100 (73), 83 (49), 72 (33), 55 (55); HRMS (EI) calcd for $C_{10}H_{13}N_2O_4F$ (M^+) 244.0859, found 244.0856.

1-[2-fluoro-4-hydroxy-3-hydroxymethyl-2-butenyl]-5-fluorouracil (14)

A white solid (94% from **7**): R*f* 0.28 (CH_2Cl_2/MeOH, 10:1); mp 175°C (recrystallized from methanol-ethyl acetate); UV (MeOH) λ_{max} 269.4 nm; IR (KBr) cm^{-1} 3350, 3130, 2980, 2820, 1680; ^{1}H NMR (DMSO-d_6/$CDCl_3$, 300 MHz) δ 11.85 (s, 1H, D_2O exchangeable), 7.83 (d, *J*=6.0, 1H), 4.63 (d, *J*=21.3, 2H), 4.58 (s, 2H, D_2O exchangeable), 4.26 (s, 2H), 4.21 (s, 2H); EIMS *m/z* (relative intensity) 249 (MH^++, 5), 231 (10), 142 (15), 131 (80), 118 (25), 100 (100), 87 (84), 72 (49), 51 (20); HRMS (EI) calcd for $C_9H_{10}N_2O_4F_2$ (M^+) 248.0609, found 248.0604.

1-[2-fluoro-4-hyrdoxy-3-hydroxymethyl-2-butenyl]-5-iodouracil (15)

A white solid (98% from **8**): R*f* 0.28 (CH_2Cl_2/MeOH, 10:1); mp 181°C (recrystallized from methanol-ethyl acetate); UV (MeOH) λ_{max} 285.2 nm; IR (KBr) cm^{-1} 3450, 3270, 2945, 2795, 1710, 1680, 1610; ^{1}H NMR (DMSO-d_6/$CDCl_3$, 300 MHz) δ 11.76 (s, 1H, D_2O exchangeable), 8.09 (s, 1H), 4.68 (d, *J*=21.7, 2H), 4.64 (s, 2H, D_2O exchangeable), 4.22 (d, *J*=3.9, 2H), 4.14 (dd, *J*=5.4, 3.0, 2H); EIMS *m/z* (relative intensity) 356 (M^+, 10), 339 (10), 254 (11), 239 (100), 195 (52), 127 (58), 100 (95), 72 (37), 53 (41); HRMS (EI) calcd for $C_9H_{10}N_2O_4FI$ (M^+) 355.9669, found 355.9668.

1-[2-fluoro-4-hydroxy-3-hydroxymethyl-2-butenyl]-5-trifluoromethyluracil (16)

A white solid (93% from **9**): R*f* 0.19 (CH_2Cl_2/MeOH, 10:1); mp 190°C (recrystallized from methanol-water); UV (MeOH) λ_{max} 261.7 nm; IR (KBr) cm^{-1} 3455, 3250, 2970, 2795, 1720, 1685, 1650; ^{1}H NMR (DMSO-d_6/$CDCl_3$, 300 MHz) δ 11.89 (s, 1H, D_2O exchangeable), 8.21 (s, 1H), 4.76 (d, *J*=21.0, 2H), 4.58 (t, *J*=5.1, 2H, D_2O exchangeable), 4.28 (d, *J*=3.3, 2H), 4.21 (dd, *J*=5.1, 3.3, 2H); EIMS *m/z* (relative intensity) 299 (MH^+, 12), 281 (28), 192 (17), 181 (34), 161 (33), 118 (20),

100 (51), 72 (100), HRMS (EI) calcd for $C_{10}H_{10}N_2O_4F_4$ (M^+) 298.0577, found 298.0575.

1-[2-fluoro-4-hydroxy-3-hydroxymethyl-2-butenyl]cytosine (17)

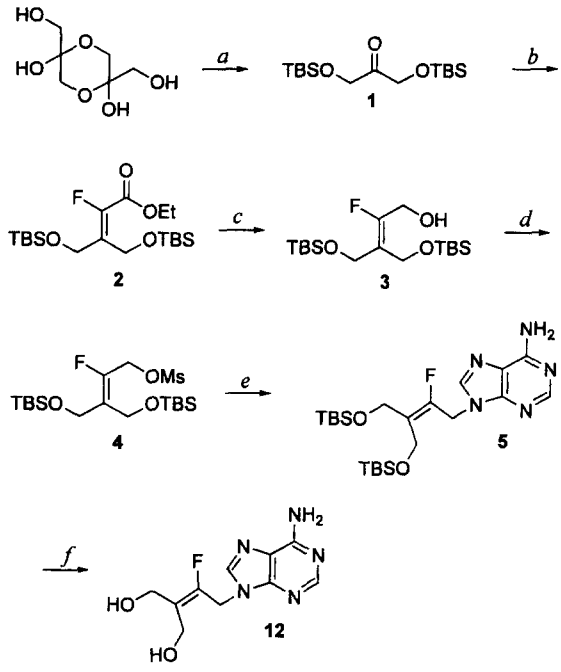
A white solid (85% from **10**): R*f* 0.34 (CH_2Cl_2/MeOH, 5:1); mp 182°C (recrystallized from ethanol); UV (MeOH) λ_{max} 272.6 nm; IR (KBr) cm^{-1} 3360, 3120, 1675, 1635, 1620; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.56 (d, *J*=7.2, 1H), 7.17 (poorly resolved s, 1H, D_2O exchangeable), 7.13 (poorly resolved s, 1H, D_2O exchangeable), 5.71 (d, *J*=7.2, 1H), 4.78~4.73 (m, 2H, D_2O exchangeable), 4.59 (d, *J*=22.2, 2H), 4.14~4.13 (m, 2H), 4.04~4.01 (m, 2H); EIMS *m/z* (relative intensity) 229 (M^+, 7), 212 (100), 112 (75), 95 (12), 83 (16), 69 (41); HRMS (EI) calcd for $C_9H_{12}N_3O_3F$ (M^+) 229.0863, found 229.0863.

1-[2-fluoro-4-hydroxy-3-hydroxymethyl-2-butenyl]uracil (18)

A white solid (84% from **11**): R*f* 0.72 (CH_2Cl_2/MeOH, 5:1)); mp 140°C (recrystallized from methanol-ethyl acetate); UV (MeOH) λ_{max} 262.7 nm; IR (KBr) cm^{-1} 3420, 3000, 1705, 1660; 1H NMR (DMSO-d_6/$CDCl_3$, 300 MHz) δ 11.14 (s, 1H, D_2O exchangeable), 7.44 (d, *J*=8.1, 1H), 5.63 (d, *J*=8.1, 1H), 4.62 (d, *J*=18.6, 2H), 4.40 (t, *J*=5.3, 2H, D_2O exchangeable), 4.31 (s, 2H), 4.27 (s, 2H); EIMS *m/z* (relative intensity) 230 (M^+, 3), 124 (51), 113 (100), 100 (80), 69 (62); HRMS (EI) calcd for $C_9H_{11}N_2O_4F$ (M^+) 230.0703, found 230.0704.

RESULTS AND DISCUSSION

As shown in Scheme 1, alkylation of adenine or pyrimidine bases with the mesylate **4** was chosen as a simple and convenient approach to the synthesis of fluorobutenyl nucleosides. Mesylate **4** was prepared from dihydroxyacetone dimer *via* an efficient four-step sequence in 58% overall yield. Standard alcohol protection of dihydroxyacetone dimer with *t*-butyldimethylsilyl chloride gave the bis(*t*-butyldimethylsilyloxy)acetone (**1**) in 90% yield. Our initial attempt to effect Horner-Emmons reaction of ketone **1** with triethyl 2-fluoro-2-phosphonoacetate by sodium hydride or LDA as a base proved unsuccessful. By switching the base to n-BuLi, however, we could get the desired compound **2** in 89% yield (Thenappan and Burton, 1991). The ester **2** was reduced with DIBAL-H to allylic alcohol **3** in 84% yield. Treatment of **3** with mesyl chloride and triethylamine to provide allylic mesylate **4** in good yield. The coupling of the allyl mesylate with adenine in the presence of sodium hydride provided the desired N^9-alkylated adenine (Borcherding *et al.*, 1987; Phadtare *et al.*, 1991) in 45% yield. Standard deprotection of the silyl protecting groups using tetrabutylammonium fluoride (TBAF) in tetrahydrofuran gave 9-[2-fluoro-4-hydroxy-3-hydroxymethyl-2-butenyl]adenine (**12**) in 92% yield.



Reagents and Conditions: *a)* TBSCl, imidazole, DMF, 90%; *b)* n-BuLi, $(EtO)_2P(O)CHFCO_2Et$, THF, 89%; *c)* DIBAL-H, CH_2Cl_2, 84%; *d)* MsCl, TEA, CH_2Cl_2, 86%; *e)* adenine, NaH, DMF, 45%; *f)* TBAF, THF, 92%

Scheme 1. Synthetic route to target molecule **12**.

By the same way, the related pyrimidine compounds were prepared (Fig. 2). Direct alkylation of pyrimidines to allylic mesylate **4** in DMF with cesium carbonate as a basic catalyst gave the desired N^1-alkylated products (Bronson *et al.*, 1989). The UV data are in good agreement with those of appropriate model compounds (Cook and Holman, 1980; Ogilvie *et al.*, 1984; Hronowski and Szarek, 1992). Standard deprotection of the silyl protecting groups using tetrabutylammonium

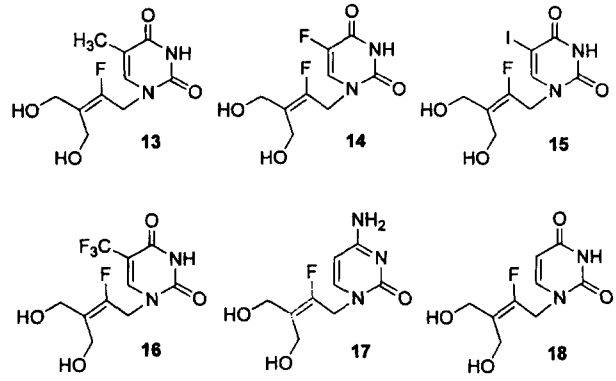


Fig. 2. Structures of open-chain neplanocin analogs.

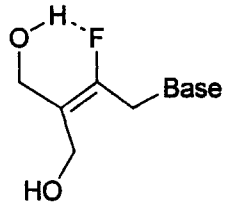


Fig. 3. A Possible conformation of open-chain analogs of neplanocin A.

fluoride (TBAF) in tetrahydrofuran gave fluorobutenylated pyrimidines (**13, 14, 15, 16, 17,** and **18**). The structures of final products were confirmed by UV, high resolution mass, IR, and ^{1}H NMR spectra.

Compounds **12~18** were evaluated for their activity against polio virus, HSV-1, HSV-2 and HIV. However, all compounds were found to be inactive in the assay. The lack of antiviral activity in these examples is presumably due to the intramolecular hydrogen bond formation between fluorine and hydroxyl group (Fig. 3), resulting in the unfavorable conformation for phosphorylation by kinase.

ACKNOWLEDGMENT

We are very grateful to Dr. Chong-Kyo Lee, Korea Research Institute of Chemical Technology, for biological evaluation of the compounds. This work was supported by the Korea Science and Engineering Foundation (KOSEF) through the Research Center for New Drug Development at Seoul National University.

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