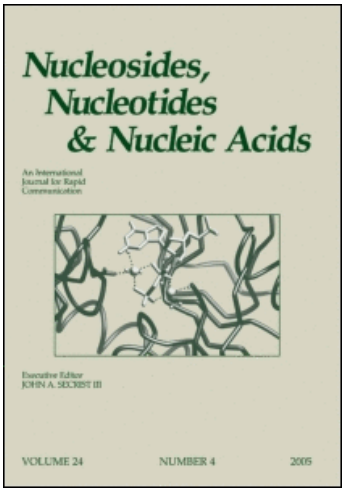

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Selective Synthesis and Application to the Synthesis of (*E*)-Fluorovinyl Nucleosides

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SELECTIVE SYNTHESIS AND APPLICATION TO THE SYNTHESIS OF (*E*)-FLUOROVINYL NUCLEOSIDES

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□ *A selective method for synthesizing* (E)*-fluorovinyl was developed. Novel acyclic* (E)*-fluorovinyl versions of neplanocin A were designed and selectively synthesized as potential antiviral agents. The condensation of the bromide* ***7*** *with the nucleosidic bases (5-FU, C, A, G) and the deprotection afforded the desired acyclic fluorovinyl nucleosides. The synthesized compounds* ***11***, ***12***, ***13***, *and* ***16*** *were evaluated for their antiviral activity. The guanine derivative* ***16*** *showed toxicity-dependent anti-HIV-1 activity in MT-4 cells.*

Keywords Fluorovinyl; neplanocin A; fluoroneplanocin A; antiviral agent

INTRODUCTION

Carbocyclic nucleosides[1] are chemically more stable due to the absence of a true glycosidic bond, and not subject to the action of the enzymes that cleave this linkage in conventional nucleosides.[2] Among these, neplanocin A (**1**)[3] acts as a potent AdoHcy hydrolase inhibitor. Although neplanocin A is a good AdoHcy hydrolase inhibitor, it is believed that the inhibitory activity is so reversible that its action does not last for a long time.[4] The incorporation of halogen atoms into organic molecules often causes profound changes to the biological profiles of the halogenated analogues compared with their hydrocarbon counterparts.[5] Recently, Jeong et al.[6] reported the synthesis and antiviral properties of fluoroneplanocin A derivatives. Among them, fluoroneplanocin A (**2**) exhibited double the inhibitory activity of SAH than the parent neplanocin A (Figure 1). The electronegativity of fluorine (4 versus 3.5 for oxygen) can have pronounced effects on the electron distribution in the molecule,

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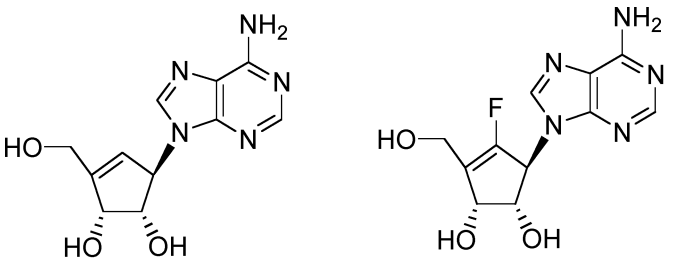


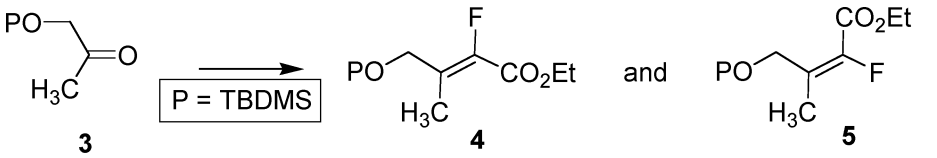
FIGURE 1 Antiviral vinyl nucleosides.

affecting either the basicity or acidity of the neighboring groups, the dipole moments within the molecule and the overall reactivity and stability of the neighboring functional groups.[7] It is supposed that the vinyl hydrogen atom be occupied by fluorine groups, the AdoHcy hydrolase[8] would be bounded to the target nucleosides after a nucleophilic addition and elimination mechanism. Recently, examples of unsaturated acyclic analogues such as 9-[4-hydroxy-3-(hydroxymethyl)-2-butenyl]guanine, 9-[4-hydroxy-3-(hydroxymethyl)-2-butenyl]adenine showing good antiviral activity were discovered. Especially, guanine derivative inhibited AdoHcy hydrolase.[9] Furthermore, it should be noted that fluorine has been used as a good bioisostere because many fluorinated nucleosides such as 2′-F-ddA,[10] 2′-F-ara-ddC,[11] and FLT[12] have significant antiviral activity.

The interesting properties of neplanocin A and fluoroneplanocin A has encouraged extensive research into the synthesis of new acyclic fluorocarbonucleoside analogues that mimic the sugar portion of naturally occurring nucleosides. As part of an ongoing search for less toxic and more effective fluorinated antiviral agents,[13] this study synthesized fluorovinyl nucleosides as acyclic versions of neplanocin A.

RESULTS AND DISCUSSION

The original plan to synthesize the target nucleosides was to use silyl protected acetol **3**[14] as the starting compound. However, the initial attempts to synthesize the target compound **4** from the ketone **3** using a triethyl 2-fluoro-2-phosphonoacetate/*n*-butyllithium in THF solvent system resulted in the production of a fluorovinyl compound **4** with a disappointing low stereoselectivity (1.2:1). It was found that the stereoselectivity of the ester depended on both the base and solvent. The E/Z ratios changed from 3.1/1 to 3.9/1 when the reaction conditions were changed from LDA/THF:DMPU (99:1) to *n*-BuLi/THF:HMPT (99:1). It is possible that the lithium cation is better coordinated by HMPT or DMPU than by THF (Figure 2). Structural assignment on the E/Z olefins was unambiguously determined by NOE comparison which was well studied in our previous synthetic procedure of nucleoside derivatives.[13]



base/cosolvent	ratio of **4/5** (yield(%))
n-BuLi/THF	1/1.2 (30/38)
LDA THF/DMPU (99/1)	1/3.1 (15/47)
n-BuLi/ THF/HMPT (99/1)	1/3.9 (13/51)

FIGURE 2 Reaction conditions for the selective synthesis of *(E)*-fluorovinyl **5**.

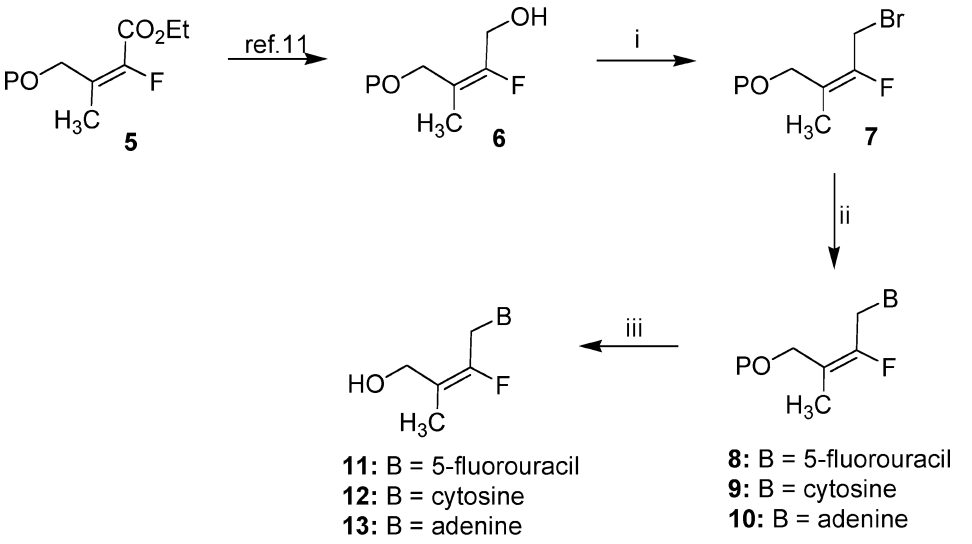
The reduction of the ester **5** with DIBALH gave the alcohol **6** in high yield, which was subjected to a mesylation reaction. The mesylate was found to be unstable during storage or during silica gel column chromatography. Therefore, the allylic bromide **7** was used as a coupling intermediate to solve this problem. The conversion of the allylic alcohol **6** to the bromo derivative **7** was accomplished by the sequential addition of NBS to a solution of the alcohol and triphenylphosphine in high yield.

The condensation of the bromide **7** with the nucleosidic bases (5-FU, C, A) and the deprotection reaction of TBDMS group afforded the desired carbo-acyclic nucleosides, **11–13** (Scheme 1).

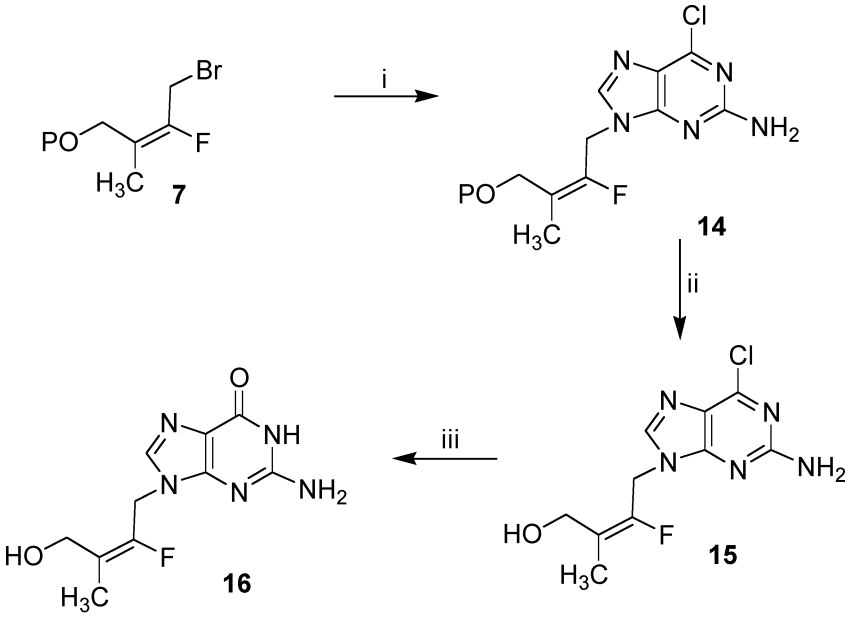
Compound **16** was prepared by condensation reaction of 2-amino-6-chloropurine with the bromide **7** followed by deprotection reaction and conversion of 2-amino-6-chloropurine to guanine. The silyl groups of compound **14** were removed through a similar TBAF treatment to that used for compound **11** to produce guanine carbo-acyclic compound **15**. Treatment of compound **15** with 2-mercaptoethanol and sodium methoxide in methanol, followed by hydrolysis with acetic acid produced the desired guanine acyclic nucleoside **16** (Scheme 2).

The antiviral assays against several viruses such as HIV-1 (MT-4 cells), HSV-1 (CCL81 cells), HSV-2 (CCL-81 cells), and HCMV (AD-169) were performed. As shown in Table 1, first mention all the synthesized fluorovinyl nucleoside analogues did not show any antiviral activity. Interestingly, the guanine nucleoside **16** exhibited toxicity-dependent anti-HIV-1 activity because it showed less than 50% survival at the same concentration exhibit anti-HIV-1 activity in virus-uninfected MT-4 cells.

In conclusion, selective synthetic method for (E)-fluorovinyl was developed, and we have successfully applied to the acyclic nucleosides. The guanine derivative **16** showed toxicity-dependent anti-HIV-1 activity in MT-4



SCHEME 1 Synthesis of *(E)*-fluorovinyl nucleosides.



SCHEME 2 Synthesis of *(E)*-fluorovinyl guanine nucleoside.

TABLE 1 The antiviral activities of the synthesized compounds

	HIV-1 EC_{50} (μM)	HSV-1 EC_{50} (μM)	HSV-2 EC_{50} (μM)	HCMV EC_{50} (μM)	cytotoxicity CC_{50} (μM)
11	>100	>100	>100	99	>100
12	87.4	>100	>100	>100	>100
13	93.9	87.2	>100	>100	>99
16	8.37	98	99	99	>8.37
AZT	0.001	ND	ND	ND	1.2
GCV	ND	ND	ND	0.4	>10
ACV	ND	0.5	ND	ND	>100

ND: not determined.
EC_{50} (μM): Concentration required to inhibit 50% of the virus-induced cytopathicity.
CC_{50} (μM): Concentration required to reduce the cell viability by 50%.

cells. Although we could not find good anti-HIV agents in this study, findings of some anticancer activity in this series will allow this class of nucleosides to be the new template for the development of new anticancer agents. On the basis of this strategy, the synthesis of (Z)-fluorvinyl nucleosides derivatives are in progress.

EXPERIMENTAL SECTION

All the chemicals were of reagent grade and used as purchased. All 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 300 Fourier transform 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 analysis was performed using an Elemental Analyzer System (Profile HV-3). HRMS data were obtained with a Q-Tof2 mass spectrometer (Micromass, Manchester, UK). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. (7558, Newark, DE, USA). Dry THF was obtained by distillation from Na and benzophenone when the solution became purple.

(*E*)-2-Fluoro-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enoic Acid Ethyl Ester (4) and (*Z*)-2-Fluoro-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enoic Acid Ethyl Ester (5)

A solution of commercially available triethyl-2-fluorophosphonoacetate (0.5 g, 2.05 mmol) in THF (6 mL) was cooled to −78°C. n-Butyllithium

(1.28 mL, 2.05 mmol, 1.6 M solution in hexane) was then added dropwise. The mixture was allowed to warm to 0°C, and a solution of compound **2** (386 mg, 2.05 mmol) in a cosolvent system of THF (6 mL)/HMPT (0.45 mL) was slowly added to the mixture at −78°C and stirred for 1 hour at the same temperature. The temperature of the reaction mixture was slowly elevated to 0°C and stirred for a further 4 hours. The reaction was quenched by adding aqueous NH_4Cl and extracted with hexanes. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to dryness. The residue was then separated on a silica gel column eluting with hexanes-EtOAc (50:1) to give compounds **4** (74 mg, 13%) and **5** (289 mg, 51%) as colorless oil: Compound **4**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.35 (d, $J = 3.3$ Hz, 2H), 4.28 (q, $J = 7.2$ Hz, 2H), 2.11 (d, $J = 2.3$ Hz, 3H), 1.30 (t, $J = 7.2$ Hz, 3H), 0.88 (m, 9H), 0.02 (m, 6H); Compound **5**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.65 (d, $J = 2.1$ Hz, 2H), 4.31 (q, $J = 7.2$ Hz, 2H), 1.89 (d, $J = 4.5$ Hz, 3H), 1.33 (t, $J = 7.2$ Hz, 3H), 0.86 (s, 9H), 0.02 (m, 6H).

(*E*)-2-Fluoro-4-(tert-butyldimethylsilanyloxy)-3-methyl-but-2-en-1-ol (6)

DIBALH (12.1 mL, 1.0 M solution in hexanes) was slowly added to a solution of compound **5** (1.52 g, 5.5 mmol) in CH_2Cl_2 (80 mL) at 0°C, and stirred for 2 hours at the same temperature. Methanol (12 mL) was then added. The resulting mixture was stirred at room temperature for 3 hours, and the precipitated solid was filtered through a Celite pad. The filtrate was concentrated under vacuum, and the residue was purified by silica gel column chromatography (EtOAc/hexanes, 1:25) to give compound **7** (1.05 g, 82%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.19 (d, $J = 3.0$ Hz, 2H), 4.17 (d, $J = 21.9$ Hz, 2H), 1.65 (d, $J = 3.0$ Hz, 3H), 0.87 (m, 9H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 153.99, 150.73, 116.00, 115.83, 59.44, 58.24, 57.83, 25.60, 18.29, 12.64, 12.59, −5.41.

(*E*)-2-Fluoro-4-(tert-butyldimethylsilyloxy)-3-methyl-2-but-2-enyl Bromide (7)

To a solution of compound **6** (811 mg, 3.46 mmol) and triphenylphosphine (1.81 g, 6.93 mmol) in CH_2Cl_2 (20 mL), *N*-bromosuccinimide (2.46 g, 6.93 mmol) was added slowly at 0°C. the resulting mixture was warmed to room temperature, stirred for 6 hours, and diluted with CH_2Cl_2. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate and filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by quick flash silica gel column chromatography (EtOAc/hexanes, 1:25) to give the fluorovinyl

bromide **7** (740 mg, 72%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.20 (d, $J = 3.0$ Hz, 2H), 3.95 (s, 1H), 3.87 (s, 1H), 1.60 (d, $J = 3.0$ Hz, 3H), 0.82 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 152.45, 151.99, 115.21, 114.88, 59.21, 41.24, 40.91, 25.56, 18.61, 12.77, −5.57; HRMS (M^+): 297.2845 calcd for $C_{11}H_{22}BrFOSi$, found 297.2839.

1-[(*E*)-2-Fluoro-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enyl] 5-fluorouracil (8)

A solution of the fluorovinyl bromide **7** (395 mg, 1.33 mmol), 5-fluorouracil (261 mg, 2.01 mmol) and cesium carbonate (654 mg, 2.01 mmol) in anhydrous DMF (10 mL) was stirred overnight at 50°C. The reaction was then quenched by adding water and diluted with ethyl acetate. The organic layer was separated and washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexanes/MeOH, 4:1:0.1) to give compound **8** (207 mg, 45%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.72 (br s, 1H), 7.58 (d, $J = 5.8$ Hz, 1H), 4.31 (d, $J = 2.8$ Hz, 2H), 4.19 (s, 1H), 4.13 (s, 1H), 1.72 (d, $J = 3.0$ Hz, 3H) 0.88 (s, 18H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.32, 165.02, 153.45, 152.11, 150.67, 143.88, 139.18, 126.45, 126.03, 114.56, 60.78, 51.65, 51.22, 25.45, 18.71, 12.69, −5.56; Anal calcd for $C_{15}H_{24}F_2N_2O_3Si$: C, 52.00; H, 6.98; N, 8.09. Found: C, 51.79; H, 7.09; N, 7.91.

1-[(*E*-2-Fluoro-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enyl] Cytosine (9)

Compound **9** was prepared from compound **7** using a by the similar procedure to that described for compound **8**: yield 39%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (d, $J = 7.6$ Hz, 1H), 5.76 (d, $J = 7.6$ Hz, 1H), 4.30 (d, $J = 2.8$ Hz, 2H), 4.18 (s, 1H), 4.11 (s, 1H), 1.67 (d, $J = 3.0$ Hz, 3H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.53, 156.43, 152.20, 145.75, 114.71, 114.37, 92.65, 61.43, 51.43, 50.93, 25.76, 18.47, 12.68, −5.65; Anal calcd for $C_{15}H_{26}FN_3O_2Si$: C, 55.02; H, 8.00; N, 12.83. Found: C, 54.90; H, 7.89; N, 12.93.

9-[(*E*)-2-Fluoro-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enyl] Adenine (10)

Compound **10** was prepared from compound **6** using a similar method to that described for compound **7**: yield 48%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.34 (s, 1H), 7.81 (s, 1H), 4.29 (d, $J = 2.8$ Hz, 2H), 4.14 (s, 1H), 4.07 (s, 1H), 1.64 (d, $J = 3.0$ Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ

155.60, 152.67, 151.13, 150.87, 150.12, 141.67, 119.65, 115.62, 115.44, 61.65, 51.74, 51.65, 25.39, 18.72, 12.77, −5.48; Anal calcd for $C_{16}H_{26}FN_5OSi$: C, 54.67; H, 7.46; N, 19.92. Found: C, 54.58; H, 7.38; N, 20.02.

1-[(*E*)-2-Fluoro-4-hydroxy-3-methyl-but-2-enyl] 5-fluorouracil (11)

TBAF (0.6 mL, 1.0 M solution in THF) at 0°C was added to a solution of compound **8** (139 mg, 0.4 mmol) in THF (5 mL). The resulting mixture was stirred overnight at room temperature, and concentrated. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:5) to give compound **11** (72 mg, 78%) as a white solid: mp 158–161°C; UV (H_2 O) λ_{max} 270.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.62 (br s, 1H), 7.49 (d, J = 5.6 Hz, 1H), 5.00 (br s, 1H), 4.33 (d, J = 3.0 Hz, 2H), 4.18 (s, 2H), 1.68 (d, J = 2.8 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 165.78, 165.69, 152.32, 152.56, 152.48, 149.61, 142.12, 138.81, 126.66, 115.21, 115.13, 61.54, 51.60, 12.85; Anal calcd for $C_9H_{10}F_2N_2$ O_3: C, 46.56; H, 4.34; N, 12.07. Found: C, 46.78; H, 4.31; N, 11.90.

1-[(*E*)-2-Fluoro-4-hydroxy-3-methyl-but-2-enyl] Cytosine (12)

Compound **12** was prepared from compound **9** using a similar method to that described for compound **11**: yield 70%; mp 163–165°C; UV (H_2 O) λ_{max} 271.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.47 (d, J = 7.8 Hz, 1H), 5.68 (d, J = 7.8 Hz, 1H), 4.99 (t, J = 5.4 Hz, 1H), 4.42 (d, J = 3.0 Hz, 2H), 4.21 (s, 1H), 4.14 (s, 1H), 1.71 (d, J = 2.8 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 166.12, 157.65, 151.65, 151.48, 146.32, 115.32, 93.71, 60.23, 51.87, 12.70; HRMS (M^+): 213.2181 calcd for $C_9H_{12}FN_3$ O_2, found 213.2189; Anal calcd for $C_9H_{12}FN_3$ O_2+0.5H_2 O: C, 48.64; H, 5.89; N, 18.91. Found: C, 48.61; H, 5.62; N, 18.78.

9-[(*E*)-2-Fluoro-4-hydroxy-3-methyl-but-2-enyl] Adenine (13)

The adenine derivative **13** was prepared from compound **10** using a similar method to that described for compound **11**: yield 77%; mp 183–185°C; UV (H_2O) λ_{max} 260.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.40 (s, 1H), 8.12 (s, 1H), 5.02 (br s, 1H), 4.36 (d, J = 3.0 Hz, 2H), 4.19 (s, 1H), 4.13 (s, 1H), 1.60 (d, J = 3.0 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 154.99, 152.42, 151.12, 149.71, 142.67, 118.65, 114.89, 60.65, 52.45, 52.38, 12.70; Anal calcd for $C_{10}H_{12}FN_5$ O: C, 50.63; H, 5.10; N, 29.52. Found: C, 50.82; H, 5.02; N, 29.39.

9-[(*E*)-2-Fluoro-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enyl] 2-amino-6-chloro-purine (14)

A solution of the 2-amino-6-chloropurine (372 mg, 2.19 mmol) and sodium hydride (61 mg, 2.5 mmol) in anhydrous DMF (12 mL) was stirred for 1 hour at room temperature. A solution of the fluorovinyl bromide **7** (327 mg, 1.1 mmol) in DMF (6 mL) was then added to the mixture and stirred for 5 hours at 80°C. The reaction was quenched by adding a saturated ammonium chloride solution (10 mL), and the mixture was concentrated under reduced pressure. The residue was dissolved in water and extracted three times with CH_2Cl_2. The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 5:1) to give compound **14** (136 mg, 32%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.87 (s, 1H), 5.40 (br s, 2H), 4.20 (d, J = 3.0 Hz, 2H), 4.12 (d, J = 20.8 Hz, 2H), 1.62 (d, J = 3.0 Hz, 3H), 0.89 (m, 9H), 0.01 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 159.23, 154.34, 153.99, 151.21, 150.43, 143.18, 124.67, 115.32, 114.56, 59.21, 58.90, 56.32, 25.55, 18.61, 12.34, 12.20, −5.56; Anal calc for $C_{16}H_{25}ClFN_5OSi$: C, 49.79; H, 6.53; N, 18.15. Found: C, 49.88; H, 6.62; N, 18.30.

9-[(*E*)-2-Fluoro-4-hydroxy-3-methyl-but-2-enyl]2-amino-6-chloropurine (15)

The removal of the silyl groups of compound **15** was performed using a similar procedure described for removing these groups from compound **11**: yield 77%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.94 (s, 1H), 5.36 (br s, 2H), 4.18 (d, J = 3.1 Hz, 2H), 4.04 (d, J = 21.0 Hz, 2H), 1.67 (d, J = 2.8 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 159.54, 154.87, 153.43, 151.01, 149.41, 144.78, 123.21, 116.38, 113.13, 59.01, 57.99, 55.98, 12.54, 12.34; Anal calc for $C_{10}H_{11}ClFN_5$ O: C, 44.21; H, 4.08; N, 25.78. Found: C, 44.43; H, 3.97; N, 25.81.

9-[(*E*)-2-Fluoro-4-hydroxy-3-methyl-but-2-enyl] 2-amino-6-hydroxypurine (16)

2-mercaptoethanol (0.06 mL, 0.86 mmol) and NaOMe (0.78 mL, 0.78 mmol, 1.0 M solution in MeOH) was added to a solution of **15** (47 mg, 0.174 mmol) in MeOH (10 mL), and heated under reflux for 7 hours. After cooling, the reaction mixture was neutralized with glacial AcOH and concentrated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:7) to give compound **16** (29 mg, 67%) as a solid: mp 189–192; UV (H_2 O) λ_{max} 254.5 nm^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.91 (s, 1H), 5.01 (t, J = 4.8 Hz, 1H), 4.22 (d, J = 3.0 Hz, 2H),

4.8 (d, $J = 20.8$ Hz, 2H), 1.65 (d, $J = 3.0$ Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 159.41, 154.32, 153.74, 151.56, 148.98, 145.57, 124.18, 117.36, 112.46, 60.88, 58.24, 56.26, 12.72, 12.41; Anal calc for $C_{10}H_{12}FN_5O_2$: C, 47.43; H, 4.78; N, 27.66. Found: C, 47.59; H, 4.60; N, 27.45.

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