Synthesis and Biological Activity of Novel Acyclic Versions of Neplanocin A

Ying Wu, Joon Hee Hong

College of Pharmacy, Chosun University, Kwangju, Republic of Korea

Novel acyclic Neplanocin A analogues were designed and synthesized. The coupling of the alkyl bromide **6** with nucleosidic bases (T, U, 5-FU, 5-IU, C, A) and desilylation afforded a series of novel acyclic nucleosides. The synthesized compounds **13**–**18** were evaluated for their antiviral and antitumor activity.

Keywords: Neplanocin A; Acyclic nucleoside; Antiviral agents; Antitumor activity

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Introduction

Nucleoside analogues have been the cornerstone of antiviral chemotherapy over the past decades. Although structure-activity relationship studies have not led to a pharmacophore model for the antiviral activities of nucleosides, some structural features have been particularly successful. Since the emergence of the HIV, extensive efforts have been concentrated on various modifications of the sugar moiety of nucleosides, which have resulted in FDA-approved anti-HIV agents such as AZT [1], ddC [2], ddI [3], d4T [4], 3TC [5] and Abacavir [6]. In addition, several nucleosides used as anti-HBV agents including L-F-ddC [7] and L-FMAU [8] have been synthesized. The recent approval of bis-(POC)PMPA [9] by the FDA as anti-HIV agent has strongly warranted a further search of novel nucleosides in this class. However, side effects [10] and the emergence of drug-resistant mutants continue to be a problem with these antiviral agents [11]. It is now clear that judicious combination chemotherapy is the optimum way to improve the quality of life and survival of patients infected with HIV-1. The discovery of the potent and selective antiherpes agents, Acyclovir [12] and Ganciclovir [13] (see Figure 1), has led to an extensive search for more novel nucleoside analogues with improved properties. More recently, the fermentation product Neplanocin A [14] (Figure 1), 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 [15].

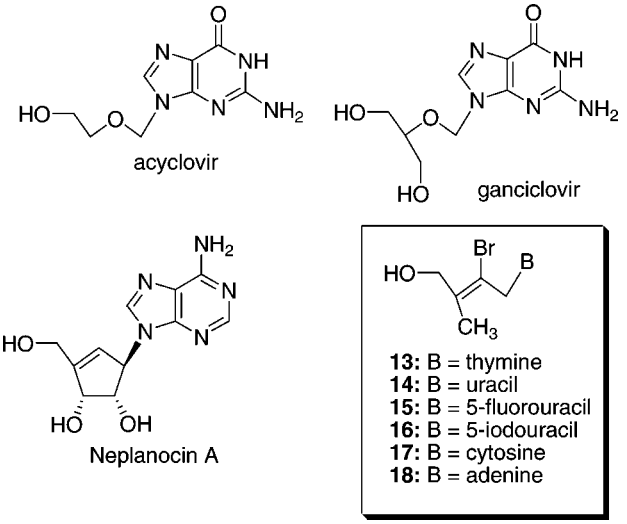

Figure 1. Rational background to the synthesis of target nucleosides.

Because of the unusual presence of a double bond in Neplanocin A and the acyclic nature of Acyclovir, these two compounds have stimulated extensive research in the synthesis of new cyclic and acyclic carba-nucleoside analogues [16] that mimic the sugar portion of naturally occurring nucleosides [17]. 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 [18]. 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 [19].

Correspondence: Joon Hee Hong, College of Pharmacy, Chosun University, Kwangju 501-759, Republic of Korea. Phone: +82 62 2306378, Fax: +82 62 2225414, e-mail: hongjh@chosun.ac.kr

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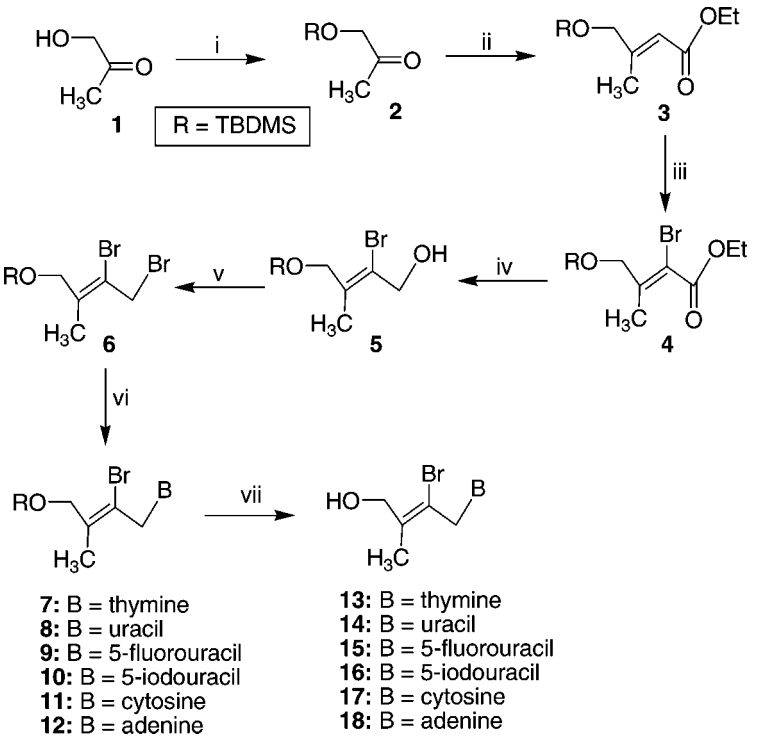

Scheme 1. Synthesis of unsaturated acyclic nucleosides. Reagents: (i) TBDMSCl, imidazole, CH_2Cl_2; (ii) triethyl phosphonoacetate, NaH, THF; (iii) Br_2, pyridine, CCl_4; (iv) Dibal-H, CH_2Cl_2; (v) PPh_3, NBS, CH_2Cl_2; (vi) bases, $CsCO_3$, DMF, rt; (vii) TBAF, THF, rt.

In view of the stimulating results of carboacyclic nucleosides [9, 12, 13] and as part of our ongoing drug discovery efforts to search for less toxic and more effective antiviral agents, this study aimed to synthesize bromovinyl nucleosides as acyclic analogues of Neplanocin A (see Scheme 1).

Results and discussion

Chemistry

In order to couple the allylic alcohol derivative with the adenine base using a nucleophilic substitution type reaction, the alcohol **5** was subjected to a mesylation reaction (MsCl, TEA, CH_2Cl_2). Unexpectedly, the reaction had a low yield (20−30%) and was irreproducible. Therefore, our attention was turned to allylic bromide **6**, which was readily synthesized from hydroxy ketone derivatives such as acetol **1** using a previously reported similar procedure [20]. Conversion of allylic alcohols **5** to the bromo derivatives **6** was accomplished by the sequential addition of NBS to a solution of the alcohol and triphenylphosphine in CH_2Cl_2, in high yield [21]. Direct coupling of the allylic bromide **6** with bases (T, U, 5-FU, 5-IU, C, A) in DMF with cesium carbonate as a basic catalyst provided the desired N^1-alkylated pyrimidine derivatives (**7**−**11**), and the N^9-alkylated purine derivative **12** in the case of adenine [22]. The UV data were in good agreement with those of the appropriate model compounds [23]. Deprotection of the t-butyldimethylsilyl group (TBDMS) using tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) gave the desired nucleosides **13**−**18**.

Biological activity studies

Antiviral activity assays against HIV-1 were performed for all the final nucleosides, and their results are shown in Table 1. Unfortunately, none of them showed any anti-HIV-1 activity in MT-4 cells. Compounds **14** and **15** exhibited potent anti-HIV-1 activities, but these inhibitory effects were associated with a nonspecific cytotoxicity to MT-4 cells.

Because of the outstanding cytotoxic effects of compound **14** and **15** to the MT-4 cell line, we further studied the cytotoxic effects of both compounds on several cancer cell lines. Therefore, based on the cytotoxicity of **14** and **15**, their cytotoxic potentials were evaluated in cultured human lung cells (as shown in Table 2). Relative cell viability compared with untreated cells of lines A 549 (human lung cancer) or Col2 (human colon cancer) was decreased to 60.3 and 51.5%, respectively, after treatment of cells with compound **14** (50 μg/mL). Compound **15** also showed similar cyto-

Table 1. Anti-HIV-1 activities of the synthesized compounds.

	EC_{50}, μg/mL[§]	CC_{50}, μg/mL[#]
13	> 100	> 100
14	3.36	< 3.46
15	1.81	< 1.81
16	> 100	> 100
17	> 100	> 100
18	> 100	> 100
AZT	0.0005	1.0

[§] Indicative of 50% cytostatic concentration in virus-infected MT-4 cells.
[#] Indicative of 50% survival concentration in virus-uninfected MT-4 cells.

Table 2. Cytotoxic potential of **14** and **15** in cultured human cancer cells.

Compounds	A549[§]	Col2[#]
14	60.3[‡]	51.5[‡]
15	58.3[‡]	49.5[‡]

[§] Human lung carcinoma cells.
[#] Human colon carcinoma cells.
[‡] Percentage (%) of survival compared to control cultures at a test concentration of 50 μg/mL.

toxicity to lung cells; 58.3% survival of control in lung cancer cells, and 49.5% in colon cancer cells.

Conclusion

A simple synthetic method for synthesizing novel acyclic Neplanocin A analogues from a ketone derivative was developed in this study. When the synthesized compounds were tested against HIV-1, compound **14** and **15** exhibited toxicity non-related to any anti-HIV-1 activity. 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 a new template for the development of new anticancer agents.

Experimental

General

All the chemicals were of reagent grade and were used as purchased. All the moisture-sensitive reactions were performed in an inert atmosphere with either N_2 or Ar, using distilled dry solvents. The melting points were determined using a Mel-temp II laboratory device and were uncorrected. The NMR spectra were recorded on a JEOL 300 Fourier transform spectrometer; the chemical shifts are reported in parts per million (d) 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). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Dry THF was obtained by distillation from Na and benzophenone when the solution became purple.

Chemistry

*2-(tert-Butyldimethylsilyloxy)-acetone (**2**)*

To a stirred solution of compound acetol (20 g, 0.27 mmol) and imidazole (27 g, 0.405 mmol) in CH_2Cl_2 (300 mL), *t*-butyldimethylsilyl chloride (44 g, 0.297 mmol) was added at 0°C. The mixture was stirred at the same temperature for 5 h and concentrated under reduced pressure. The residue was extracted using EtOAc, dried over $MgSO_4$, filtered and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane, 1:10) to give **2** (39.6 g, 78%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.05 (s, 2H), 2.07 (s, 3H), 0.84 (s, 9H), −0.01 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 208.96, 69.47, 25.67, 18.19, −5.61; Anal calcd. for $C_9H_{20}O_2Si$: C, 57.39; H, 10.70; Found: C, 57.21; H, 10.50.

*(E)-4-(tert-Butyldimethylsilyloxy)-3-methyl-but-2-enoic acid ethyl ester (**3**)*

Sodium hydride (60% in mineral oil, 1.11 g, 27.75 mmol) was suspended in anhydrous THF. To the mixture was slowly added triethyl phosphonoacetate (4.21 g, 27.75 mmol) at 0°C and stirred for 1 h at room temperature. Compound **2** (5.18 g, 27.5 mmol) was added to the reaction mixture at 0°C, stirred for 1 h at room temperature and extracted with EtOAc. 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 silica gel column chromatography (EtOAc/*n*-hexane, 1:15) to give **3** (4.26 g, 60%) as a yellow oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.99 (s, 1H), 4.19 (q, J = 6.9 Hz, 2H), 4.13 (s, 2H), 1.96 (s, 3H), 1.96 (s, 3H), 1.22 (t, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 167.02, 157.06, 113.35, 66.21, 59.51, 25.83, 18.09, −5.36; Anal calcd. for $C_{13}H_{26}O_3Si$: C, 60.42; H, 10.14. Found: C, 60.37; H, 9.97.

*(E)-2-Bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enoic acid ethyl ester (**4**)*

To a stirred solution of compound **3** (300 mg, 1.16 mmol) in CCl_4 under nitrogen was added bromine (203 mg, 1.27 mmol) followed by slow addition of triethylamine (0.242 mL, 1.74 mmol) in an ice bath. The reaction mixture was stirred for 5 h at 0°C, filtered and washed with CCl_4. The filtrate was washed with 2 N HCl and then with sodium bicarbonate solution, dried with anhydrous $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane, 1:20) to give **4** (200 mg, 51%). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.45 (s, 2H), (q, J = 7.2 Hz, 2H), 2.01 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 0.83 (s, 9H), 0.06 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 163.72, 151.55, 109.31, 100.52, 64.01, 62.08, 25.71, 21.09, 18.24, 13.98, −5.55; Anal calcd. for $C_{13}H_{25}BrO_3Si$: C, 46.29; H, 7.47. Found: C, 46.01; H, 7.51.

*(E)-2-bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-en-1-ol (**5**)*

To a solution of compound **4** (5.0 g, 14.82 mmol) in CH_2Cl_2 (200 mL), DIBALH (31.12 mL, 1.0 M solution in hexane) was added slowly at 0°C, and stirred for 1 h at the same temperature. To the mixture, methanol (30 mL) was added. The mixture was then

stirred at room temperature for 3 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/*n*-hexane, 1:20) to give compound **5** (4.07 g, 93%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.42 (s, 2H), 4.24 (s, 2H), 1.94 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 136.45, 112.38, 68.11, 65.21, 25.83, 18.56, 13.56, −5.48; Anal calcd. for $C_{11}H_{23}BrO_2Si$: C, 44.74; H, 7.85. Found: C, 44.50; H, 7.74.

*(E)-Bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-2-but-2-enyl bromide (**6**)*

To a solution of compound **5** (2.04 g, 6.93 mmol) and triphenylphosphine (3.63 g, 13.86 mmol) in CH_2Cl_2 (30 mL), *N*-bromosuccinimide (4.93 g, 13.86 mmol) was added slowly at 0°C, stirred for 5 h at room temperature, 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/*n*-hexane, 1 : 30) to give the allylic bromide **6** (2.16 g, 87%) as a yellow oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.61 (s, 2H), 3.94 (s, 2H), 1.87 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz): d 142.21, 110.38, 67.78, 38.89, 25.67, 18.33, 13.91, −5.48; Anal calcd. for $C_{11}H_{22}Br_2OSi$: C, 36.89; H, 6.19. Found: C, 37.08; H, 5.93.

*1-[(E)-2-Bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enyl] thymine (**7**)*

A solution of the allylic bromide **6** (318 mg, 0.89 mmol), thymine (169 mg, 1.34 mmol) and cesium carbonate (436 mg, 1.34 mmol) in anhydrous DMF (5 mL) was stirred overnight at room temperature. The mixture was quenched by the addition of 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/*n*-hexane/MeOH, 4:1:0.2) to give compound **7** (244 mg, 68%) as a solid. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.42 (br s, 1H), 7.14 (s, 1H), 4.65 (s, 2H), 4.25 (s, 2H), 1.86 (s, 3H), 1.82 (s, 3H), 0.96 (s, 9H), 0.13 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 163.91, 150.67, 141.50, 139.74, 118.29, 110.52, 63.27, 50.99, 25.81, 22.18, 18.33, 12.38, −5.38; Anal calcd. for $C_{16}H_{27}BrN_2O_3Si$: C, 47.64; H, 6.75; N, 6.94. Found: C, 47.87; H, 6.66; N, 6.90.

*1-[(E)-2-Bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enyl] uracil (**8**)*

Compound **8** was prepared from **6** as described for **7**. Yield 64%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.75 (br s, 1H), 7.32 (d, J = 7.8 Hz, 1H), 5.59 (d, J = 7.8 Hz, 1H), 4.72 (s, 2H), 4.30 (s, 2H), 1.90 (s, 3H) 0.88 (s, 18H), 0.15 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 163.46, 150.67, 144.05, 141.98, 117.86, 102.04, 63.29, 51.46, 25.82, 22.20, 18.27, −5.37; Anal calcd. for $C_{15}H_{25}BrN_2O_3Si$: C, 46.27; H, 6.47; N, 7.19. Found: C, 46.49; H, 6.31; N, 7.28.

*1-[(E)-2-Bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enyl] 5-fluorouracil (**9**)*

Compound **9** was prepared from **6** as described for **7**. Yield 60%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 9.00 (br s, 1H), 7.51 (d, J = 5.6 Hz, 1H), 4.77 (s, 2H), 4.41 (s, 2H), 1.92 (s, 3H) 0.89 (s, 18H), 0.23 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 165.23, 153.67, 143.21, 140.98, 127.81, 101.32, 64.26, 52.32, 25.67, 22.32, 18.43, −5.47; Anal calcd. for $C_{15}H_{24}BrFN_2O_3Si$: C, 44.23; H, 5.94; N, 6.88. Found: C, 44.06; H, 6.01; N, 7.08.

*1-[(E)-2-Bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enyl] 5-iodouracil (**10**)*

Compound **10** was prepared from **6** as described for **7**. Yield 68%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 9.21 (br s, 1H), 7.72 (s, 1H), 4.83 (s, 2H), 4.27 (s, 2H), 1.93 (s, 3H) 0.90 (s, 18H), 0.32 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 161.46, 151.10, 146.85, 141.33, 116.37, 68.94, 62.35, 50.89, 25.80, 22.54, 18.57, −5.67; Anal calcd. for $C_{15}H_{24}BrIN_2O_3Si$: C, 34.97; H, 4.69; N, 5.44. Found: C, 34.40; H, 4.58; N, 5.61.

*1-[(E)-2-Bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enyl] cytosine (**11**)*

Compound **11** was prepared from **6** as described for **7**. Yield 68%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.38 (d, J = 7.5 Hz, 1H), 5.78 (d, J = 7.5 Hz, 1H), 4.72 (s, 1H), 4.35 (s, 1H), 4.11 (s, 2H), 1.89 (s, 3H) 0.89 (s, 18H), 0.15 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 166.06, 154.90, 141.30, 118.82, 115.16, 98.97, 64.63, 52.76, 25.80, 21.91, 18.22, −5.47; Anal calcd. for $C_{15}H_{26}BrN_3O_2Si$: C, 46.39; H, 6.75; N, 10.82. Found: C, 46.21; H, 6.67; N, 10.89.

*9-[(E)-2-Bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enyl] adenine (**12**)*

Compound **12** was prepared from **6** as described for **7**. Yield 68%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.26 (s, 1H), 7.75 (s, 1H), 6.09 (br s, 2H), 4.70 (s, 2H), 4.21 (s, 2H), 1.91 (s, 3H) 0.86 (s, 18H), 0.25 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz): d 155.67, 152.78, 150.43, 141,98, 141.02, 119.49, 118.12, 63.72, 51.22, 25.81, 22.04, 18.20, −5.32; Anal calcd. for $C_{16}H_{26}BrN_5OSi$: C, 46.60; H, 6.35; N, 16.98. Found: C, 46.88; H, 6.21; N, 17.19.

*1-[(E)-2-Bromo-4-hydroxy-3-methyl-but-2-enyl] thymine (**13**)*

To a solution of compound **7** (181 mg, 0.45 mmol) in THF (5 mL), TBAF (0.675 mL, 1.0 M solution in THF) at 0°C was added. The mixture was stirred at room temperature for 6 h, and concentrated. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:5) to give compound **13** (105 mg, 81%) as a white solid: mp 174−176°C; UV (H_2O) λ_{max} 268.5 nm. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 11.47 (br s, 1H), 7.33 (s, 1H), 5.10 (t, J = 6.0 Hz, 1H), 4.68 (s, 2H), 3.95 (s, 2H), 1.90 (s, 3H), 1.81 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 163.66, 149.13, 136.09, 116.68, 110.44, 96.60, 65.67, 43.33, 16.38, 12.07; Anal calcd. for $C_{10}H_{13}BrN_2O_3$: C, 41.54; H, 4.53; N, 9.69. Found: C, 41.30; H, 4.62; N, 9.81.

*1-[(E)-2-Bromo-4-hydroxy-3-methyl-but-2-enyl] uracil (**14**)*

Compound **14** was prepared from **8** as described for **13**. Yield 77%; mp 161−163°C; UV (H_2O) λ_{max} 263.5 nm. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 11.57 (br s, 1H), 7.30 (d, J = 7.9 Hz, 1H), 5.48 (d, J = 7.8 Hz, 1H), 5.03 (t, J = 5.4 Hz, 1H), 4.62 (s, 2H), 4.10 (s, 2H), 1.91 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 163.65, 151.21, 145.45, 140.31, 117.34, 103.78, 64.56, 44.34, 16.20; Anal calcd. for $C_9H_{11}BrN_2O_3$: C, 39.29; H, 4.03; N, 10.18. Found: C, 30.37; H, 3.87; N, 10.30.

*1-[(E)-2-Bromo-4-hydroxy-3-methyl-but-2-enyl] 5-fluorouracil (**15**)*

Compound **15** was prepared from **9** as described for **13**. Yield 87%; mp 160−163°C; UV (H_2O) λ_{max} 270.5 nm. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 11.87 (br s, 1H), 7.76 (d, J = 6.0 Hz, 1H), 5.05 (t, J = 5.2 Hz, 1H), 4.80 (s, 2H), 4.32 (s, 2H), 1.90 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 165.76, 154.78, 144.66, 139.26, 126.91, 109.78, 63.92, 43.82, 16.67; Anal calcd. for $C_9H_{10}BrFN_2O_3$: C, 36.88; H, 3.44; N, 9.56. Found: C, 36.68; H, 3.47; N, 9.77.

*1-[(E)-2-Bromo-4-hydroxy-3-methyl-but-2-enyl] 5-iodouracil (**16**)*

Compound **16** was prepared from **10** as described for **13**. Yield 83%; mp 178−180°C; UV (H_2O) λ_{max} 286.0 nm. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 11.70 (br s, 1H), 7.96 (s, 1H), 5.00 (br s, 1H), 4.61 (s, 2H), 4.14 (s, 2H), 1.97 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 161.78, 151.21, 146.71, 140.34, 115.67, 170.78, 63.67, 44.28, 16.75; Anal calcd. for $C_9H_{10}BrIN_2O_3$: C, 26.96; H, 2.51; N, 6.99. Found: C, 27.17; H, 2.36; N, 7.29.

*1-[(E)-2-Bromo-4-hydroxy-3-methyl-but-2-enyl] cytosine (**17**)*

Compound **17** was prepared from **11** as described for **13**. Yield 75%; mp 157−160°C; UV (H_2O) λ_{max} 273.0 nm. ^{1}H-NMR (DMSO-d_6, 300 MHz) d 7.41 (d, J = 7.6 Hz, 1H), 5.80 (d, J = 7.6 Hz, 1H), 4.92 (t, J = 5.6 Hz, 1H), 4.62 (s, 2H), 4.09 (s, 2H), 1.88 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 166.62, 153.31, 140.87, 117.21, 114.87, 99.62, 65.21, 44.76, 16.65; Anal calcd. for $C_9H_{12}BrN_3O_2$: C, 39.43; H, 4.41; N, 15.33. Found: C, 39.65; H, 4.61; N, 15.21.

*9-[(E)-2-hydroxy-4-hydroxy-3-methyl-but-2-enyl] adenine (**18**)*

Compound **18** was prepared from **12** as described for **13**. Yield 80%; mp 181−183°C; UV (H_2O) λ_{max} 261.0 nm. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 8.16 (s, 1H), 8.05 (s, 1H), 7.21 (br s, 2H), 5.07 (t, J = 5.4 Hz, 1H), 4.72 (s, 2H), 4.27 (s, 2H), 1.87 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 155.97, 152.36, 150.04, 141,42, 140.87, 119.25, 117.67, 66.02, 45.28, 17.20; Anal calcd. for $C_{10}H_{12}BrN_5O$: C, 40.29; H, 4.06; N, 23.49. Found: C, 40.05; H, 4.18; N, 23.31.

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