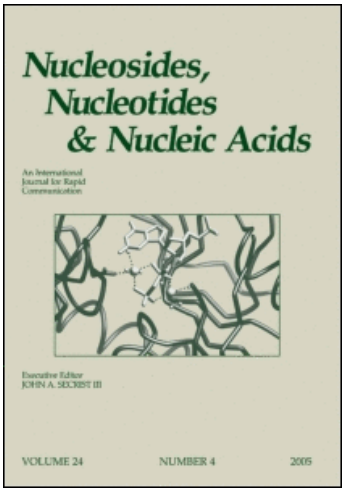

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Synthesis and Anti-Hiv Activity of 4'-Modified Cyclopentenyl Pyrimidine *C*-Nucleosides

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SYNTHESIS AND ANTI-HIV ACTIVITY OF 4′-MODIFIED CYCLOPENTENYL PYRIMIDINE *C*-NUCLEOSIDES

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□ *Novel syntheses of 4′-modified cyclopentenyl pyrimidine* C-*nucleosides were performed via* C-C *bond formation using S_N2 alkylation via the key intermediate mesylates* ***6*** *and* ***16****, which were prepared from acyclic ketone derivatives. When antiviral evaluation of synthesized compound was performed against various viruses such as HIV-1, HSV-1 and HSV-2, isocytidine analogue* ***20*** *showed moderate anti-HIV activity in CEM cell line ($EC_{50} = 13.1\ \mu mol$).*

Keyword Cyclopentenyl *C*-nucleoside; antiviral agents; S_N2 alkylation

INTRODUCTION

Carbanucleosides[1] are derivatives in which the endocyclic oxygen of the nucleoside sugar ring has been replaced by a methylene group. These analogues displace remarkable metabolic stability since they are unaffected by phosphorylases and hydrolases that cleave the glycosidic bond of natural nucleosides.[2] They are also recognized by the same enzymes that recognize normal nucleosides displaying, a wide range of biological properties.[3] For example, the cyclopentanyl cytosine (carbodine, **1**) was previously prepared as a racemic mixture and has been shown to possess significant antitumor (lymphoid leukemia L1210 in mice)[4] and antiviral activities against human influenza type A virus, measles, vescular stomatitis virus, and herpes simplex virus (HSV-1 and HSV-2).[5] Also, the cyclopentene analogue of cytosine (Ce-Cyd, **2**) exhibited antitumor activity in several human tumor xenografts in athymic mice. In vitro it is also active against herpes simplex virus (HSV), cytomegalovirus (CMV), varicella zoster virus (VZV), vaccinia, influenza A, and vesiculae stomatitis virus.[6] Both cyclopentanyl cytosine (**1**, C-Cyd) and

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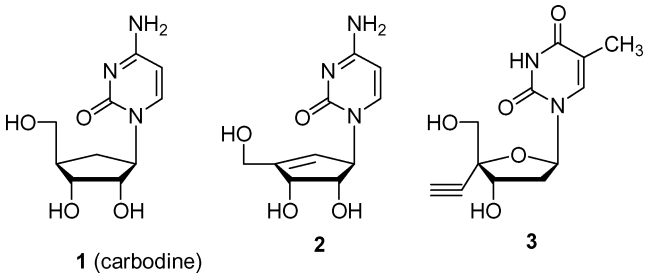


FIGURE 1 Structures of some potent antiviral agents.

cyclopentenyl cytosine (**2**, Ce-Cyd), after being phosphorylated intracellularly to the 5′-triphosphate, are assumed to interact with CTP synthetase, the enzyme that converts UTP to CTP. The depletion of CTP pools is responsible for the antitumor action of Ce-Cyd in vitro and its antitumor activity in vivo.[7] (Figure 1)

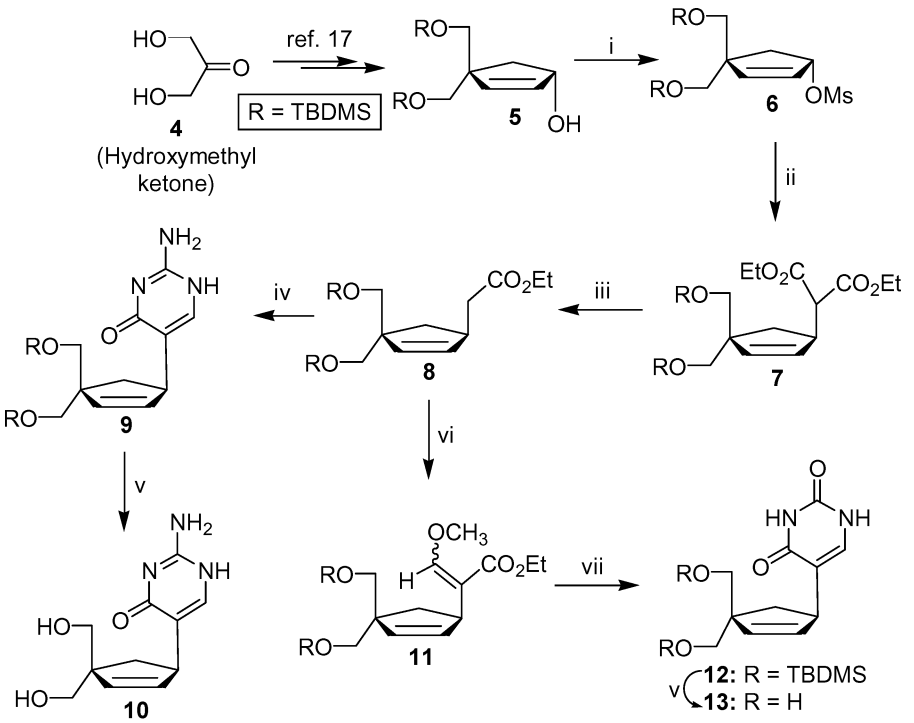
Carbocyclic *C*-nucleosides[8], is unique class of nucleosides in which the heterocycle is connected to a sugar moiety by a *C-C* bond instead of the *C-N* bond of the natural nucleosides. *C*-Nucleosides have received considerable attention due not only to their chemical stability but also to the interesting biological activities of naturally occurring compounds such as pseudoisocytidine,[9] thiazofurin,[10] and 9-deazaadenosine[11] have been reported. Only a few examples of synthetic carbocyclic *C*-nucleosides[12] have been synthesized, probably due to the synthetic difficulties of these nucleosides. In fairly recent studies along this line, carbocyclic 9-deazaadenosine has been showing to be a promising anti-HIV agent.[13]

The introduction of 4′-substitutions onto 2′-deoxynucleosides has provided potent anti-HIV inhibitors accompanied by hypersensitivity to the K65R RT mutant virus.[14] More recently, and of great significant to our aim, the 4′ethynyl substituted d4T analog **3** was reported to have >10-fold improved antiviral activity relative to d4T.[15] Modeling studies demonstrated the presence of a narrow, relatively hydrophobic 4′-pocket that can accommodate these substitutions, contributing to the observed enhancement in potency.[16]

Based on these interesting chemical and biological properties of carbocyclic cytidine analogues and 4′-modified nucleoside, we have determined to synthesize novel 4′-modified carbocyclic *C*-nucleosides.

RESULTS AND DISCUSSION

For the synthesis of target 4′-hydroxymethylated pyrimidine carbocyclic *C*-nucleoside **10**, we utilized the key intermediate **5** as starting material, which was prepared from 1,3-dihydroxy acetone using reported procedure from our group.[17] The allylic hydroxyl group of cyclopentenol was

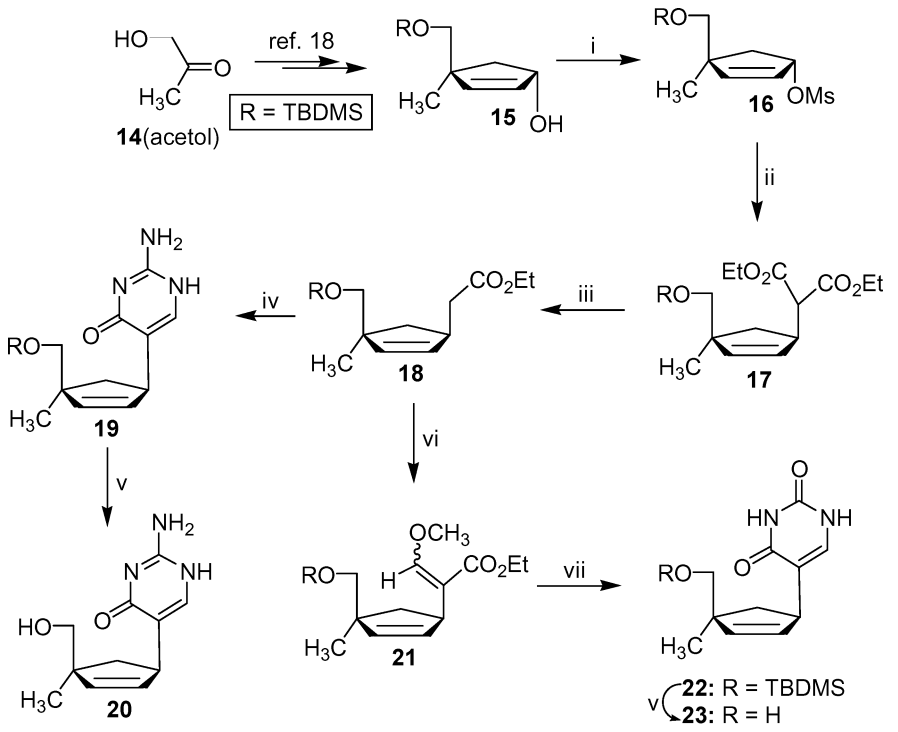


Reagents: i) MsCl, TEA, CH_2Cl_2; ii) NaH, $CH_2(CO_2Et)_2$, THF; iii) LiCl, DMSO; iv) (a) LDA/THF, HCOEt; (b) $H_2NC(=NH)NH_2$.carbonate, NaOEt/EtOH; v) TBAF, THF; vi) (a) LDA, HCOEt; (b) MeI, DMF; vii) NH_2CONH_2, *t*-BuOK, THF.

SCHEME 1 Synthesis of 4′-hydroxymethyl cyclopentene pyrimidine *C*-nucleosides.

methanesulfonylated with MsCl and TEA in anhydrous CH_2Cl_2 to provide key intermediate mesylates **6**, which was alkylated with diethyl malonate by nucleophilic S_N2 substitution conditions to give **7**. Decarboethoxylation of **7** in the presence of lithium chloride in DMSO solvent provided ester derivative **8** in 86% yield. Sequential treatment of **8** with lithium diisopropylamide, ethyl formate and guanidine carbonate in the presence of sodium ethoxide in ethanol gave carbocyclic isocytidine analogue **9**. Desilylation of **9** with tetrabutyl ammonium fluoride in THF provided the desired carbocyclic *C*-isocytidine **10** (Scheme 1).

Synthesis of carbocyclic pseudouridine analogue **13** was prepared from the same intermediate **8** as describe for isocytidine. Generation of enolate with lithium diisopropylamide in THF and formylation with ethyl formate give the corresponding anion, which was methylated with methyl iodide in DMF give the methyl enol ether derivative **11**. Treatment of **11** with urea in the presence of potassium *tert*-butoxide provide pseudouridine analogue **12**. Desilylation with TBAF provided the desired pseudouridine analogue **13**.



Reagents: i) MsCl, TEA, CH_2Cl_2; ii) NaH, $CH_2(CO_2Et)_2$, THF; iii) LiCl, DMSO; iv) (a) LDA/THF, HCOEt; (b) $H_2NC(=NH)NH_2$.carbonate, NaOEt/EtOH; v) TBAF, THF; vi) (a) LDA, HCOEt; (b) MeI, DMF; vii) NH_2CONH_2, *t*-BuOK, THF.

SCHEME 2 Synthesis of 4′-methyl cyclopentene pyrimidine *C*-nucleosides.

For the synthesis of the target 4′-methyl branched pyrimidine *C*-nucleoside analogues from acetol **14**,[18] the mesylate **16** was alkylated with diethyl malonate following the same reaction procedure as described for compound **7**. Decarboethoxylation and construction of pyrimidine bases such as isocytidine and pseudouridine by the similar procedure described for **9** and **12** gave **19** and **22**, which were desilylated using TBAF provided the desired 4′-modified pyrimidine nucleosides **20** and **23**, respectively (Scheme 2).

The antiviral assay against several viruses such as the human immunodeficiency virus 1 (HIV-1), herpes simplex virus-1 and 2 was performed. Synthesized **20** exhibited moderate anti-HIV activity in the CEM cell (EC_{50} = 13.1 μmol) without any cytotoxicity up to 100 μmol (Table 1).

In Vitro Anti-HIV-1 Activity

The assay involved the killing of T4-lymphocytes by HIV-1. T4 lymphocytes (CEM cell line) were exposed to HIV at a virus-to-cell ratio of

TABLE 1 The antiviral activity of the synthesized compounds

	HIV-1 EC_{50} (μM)	HSV-1 EC_{50} (μM)	HSV-2 EC_{50} (μM)	Cytotoxicity CC_{50} (μM)
10	66.2	99	99	99
13	34.8	>100	>100	>100
20	13.1	67.3	>100	>100
23	72.1	>100	>100	>100
AZT	0.01	ND	ND	4.50
GCV	ND	2.2	2.2	>10

AZT: azidothymidine; GCV: ganciclovir.

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%.

approximately 0.05 and treated with the compounds, dissolved in dimethylformamide, at doses ranging from 10^{-8} to 10^{-4}. A complete cycle of virus reproduction is necessary to obtain the required cell killing (incubation at 37°C in a 5% carbon dioxide atmosphere for 6 days). Uninfected cells with the compounds served as a toxicity control, whereas the infected and uninfected cells without the compound served as basic control. After incubation, the tetrazolium salt XTT was added to all wells and cultures were incubated to allow formazan color development by viable cells. Formazan production was measured spectrophotopmetically and possible protective activity was confirmed by microscopical detection of viable cells. The effect of each compound on cell growth of HIV-infected and uninfected cells was compared to that of untreated uninfected cells. All tests were compared with AZT as positive control carried out at the same time under identical conditions.[19]

EXPERIMENTS

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded on a JEOL 300 Fourier transform spectrometer (JEOL, Tokyo, Japan); chemical shifts are reported in parts per million (δ) and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). UV spectra were obtained on a Beckman DU-7 spectrophotometer (Beckman, South Pasadena, CA, USA). The elemental analyses were performed using a Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA). Mass spectra were measured with FAB-MS modified Finningan MAT SSQ 7000 spectrometer (Thermo Electron Corp., Bremen, Germany). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. (7558, Newark, DE, USA). All reactions were carried out under an atmosphere of nitrogen

unless specified. Dry dichloromethane, benzene and pyridine were obtained by distillation from CaH_2. Dry THF was obtained by distillation from Na and benzophenone immediately prior to use.

(±)-Methanesulfonic acid 4,4-bis-(tert-butyldimethylsilanyloxymethyl) cyclopent-2-enyl ester (6): To a solution of the alcohol **5** (3.49 g, 9.36 mmol) in anhydrous CH_2Cl_2 (60 mL), anhydrous triethylamine (3.0 mL) and MsCl (1.18 g, 10.3 mmol) was added at 0°C. The mixture was stirred at the same temperature for 6 hours, and quenched by a cold saturated $NaHCO_3$ solution (1.5 mL). The mixture was extracted with CH_2Cl_2/water. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated in vacuo, and the residue was quickly purified by silica gel column chromatography (EtOAc/hexane, 1:3) to give **6** (2.95 g, 70%) and was subjected to next reaction without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.96 (dd, J = 5.5, 2.0 Hz, 1H), 5.67 (d, J = 5.5 Hz, 1H), 4.67 (t, J = 5.4 Hz, 1H), 3.69 (d, J = 9.6 Hz, 1H), 3.57 (d, J = 9.6 Hz, 1H), 3.48 (d, J = 9.9 Hz, 1H), 3.39 (d, J = 9.9 Hz, 1H), 3.03 (s, 3H), 1.90 (dd, J = 13.6, 6.8 Hz, 1H), 1.57 (d, J = 13.6 Hz, 1H), 0.86 (s, 18H), 0.02 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 136.9, 135.3, 76.0, 67.4, 66.3, 39.0, 25.4, 18.5, −5.6.

(±)-2-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)-cyclopent-2-enyl] malonic acid diethyl ester (7): To a solution of NaH (0.9 g, 37.5 mmol) in THF (100 mL), diethyl malonate (9.01 g, 56.25 mmol) in THF (50 mL) was added under nitrogen atmosphere at room temperature. After 1 hour, mesylate **6** (6.85 g, 15.2 mmol) in THF (200 mL) was slowly added to the reaction mixture. The mixture was stirred overnight at room temperature, the mixture was quenched by the addition of water (100 mL) and extracted with ethyl acetate (100 mL) twice. The combined organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give **7** (5.24 g, 67%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.98 (dd, J = 5.6, 2.0 Hz, 1H), 5.69 (d, J = 5.5 Hz, 1H), 4.19–4.12 (m, 4H), 3.68 (d, J = 9.6 Hz, 1H), 3.59 (d, J = 9.6 Hz, 1H), 3.47–3.40 (m, 2H), 1.89 (m, 1H), 1.58 (dd, J = 13.2, 6.8 Hz, 1H), 1.30–1.25 (m, 6H), 0.88 (s, 18H), 0.02 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 169.1, 169.1, 137.0, 135.6, 67.9, 66.7, 61.3, 61.3, 54.2, 50.2, 25.4, 18.5, 14.1, 14.0, −5.6; Anal. Calcd. for $C_{26}H_{50}O_6Si_2$: C, 60.66; H, 9.79. Found: C, 60.57; H, 9.65; MS (FAB) m/z 515 $[M+H]^+$.

(±)-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)-cyclopent-2-enyl] acetic acid ethyl ester (8). To a solution of **7** (3.81 g, 7.4 mmol) in DMSO (20 mL), LiCl (941 mg, 22.2 mmol) and H_2O (2 drops) were added. The mixture was stirred overnight at 170°C. After cooling to room temperature, H_2O (100 mL) was added to the mixture and extracted with diethyl ether (100 mL) two times. The organic layer was washed with brine and dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated in

vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:12) to give **8** (2.59 g, 79%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.96 (dd, J = 5.4, 2.1 Hz, 1H), 5.63 (dd, J = 5.4, 0.8 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.65 (d, J = 9.8 Hz, 1H), 3.54 (d, J = 9.8 Hz, 1H), 3.39 (d, J = 9.4 Hz, 1H), 3.29 (d, J = 9.4 Hz, 1H), 3.18 (m, 1H), 1.89 (d, J = 13.2 Hz, 1H), 1.58 (dd, J = 13.2, 6.8 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H), 0.88 (s, 18H), 0.02 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 170.9, 137.9, 135.9, 67.4, 66.2, 61.5, 56.4, 43.2, 37.6, 25.4, 18.5, 14.1, −5.6. Anal. Calcd. for $C_{23}H_{46}O_4Si_2$: C, 62.39; H, 10.47. Found: C, 62.46; H, 10.39; MS (FAB) m/z 443 $[M+H]^+$.

(±)-5-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)-cyclopent-2-enyl] isocytosine (9): To a solution of lithium diisopropylamide (4.0 mL, 1 M in hexane) in THF (10 mL), a solution of **8** (1.17 g, 2.65 mmol in THF 15 mL) was slowly added at –78°C under nitrogen atmosphere. The mixture was stirred at the same temperature for 1 hour and ethyl formate (0.845 mL, 10.5 mmol) was added to the mixture. After stirring overnight at room temperature, saturated NH_4Cl solution (100 mL) was added to the mixture and extracted with EtOAc (2 × 100 mL), washed with water and brine solution, dried over $MgSO_4$, and evaporated to dryness to obtain a crude residue. The residue was dissolved in absolute ethanol (5 mL). To a solution of guanidine carbonate (1.35 g, 7.5 mmol) in EtOH (20 mL), EtONa/EtOH (21% solution, 3.23 mL, 10.0 mmol) was added and stirred for 1 hour. To this mixture, the above-obtained residue in ethanol (10 mL) was added and refluxed overnight. The mixture was filtered, concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane/MeOH, 4:1:0.2) to give **9** (740 mg, 60%) as a white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.89 (br s, 1H), 7.31 (s, 1H), 6.50 (br s, 2H), 5.91 (dd, J = 5.4, 2.0 Hz, 1H), 5.67 (d, J = 5.4 Hz, 1H), 3.61 (d, J = 10.0 Hz, 1H), 3.50 (d, J = 9.8 Hz, 1H), 3.35 (d, J = 9.6 Hz, 1H), 3.26 (d, J = 9.6 Hz, 1H), 3.14 (dd, J = 8.6, 4.8 Hz, 1H), 1.81 (dd, J = 13.0, 1.2 Hz, 1H), 1.58 (dd, J = 13.0, 6.6 Hz, 1H), 0.87 (s, 18H), 0.01 (s, 12H); ^{13}C NMR (DMSO-d_6) δ 163.2, 155.8, 138.1, 135.4, 127.1, 115.7, 66.8, 66.0, 57.5, 43.2, 37.5, 25.6, 18.6, −5.5. Anal. Calcd. for $C_{23}H_{43}N_3O_3Si_2$: C, 59.31; H, 9.31; N, 9.02. Found: C, 59.41; H, 9.45; N, 8.91; MS (FAB) m/z 466 $[M+H]^+$.

(±)-5-[4,4-Bis-(hydroxymethyl)-cyclopent-2-enyl] isocytosine (10): To a solution of compound **9** (335 mg, 0.72 mmol) in THF/CH_3CN (1:1) (10 mL), tetrabutylammonium fluoride (TBAF, 2.16 mL, 1.0 M solution in THF) at 0°C was added. The 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 **10** (133 mg, 78%) as a white solid: m.p. 180–182°C: UV (MeOH) λ_{max} 278.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.36 (s, 1H), 5.87 (d, J = 5.6 Hz, 1H), 5.61 (d, J = 5.6 Hz, 1H), 5.01 (t, J = 5.2 Hz, 1H), 4.88 (t, J = 5.2 Hz, 1H), 3.66 (d, J = 9.8 Hz, 1H), 3.56 (d, J = 9.8 Hz, 1H), 3.38 (d, J = 9.8 Hz, 1H), 3.27

(d, J = 9.8 Hz, 1H), 3.09 (m, 1H), 1.77 (d, J = 12.4, 1H), 1.54 (dd, J = 12.4, 6.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 163.3, 156.1, 138.6, 136.2, 128.5, 114.9, 66.2, 65.6, 55.4, 44.3, 35.4. Anal. Calcd. for $C_{11}H_{15}N_3O_3$ (+1.0H_2O): C, 51.75; H, 6.71; N, 16.46. Found: C, 51.68; H, 6.72; N, 16.50; MS (FAB) m/z 260 $[M+Na]^+$.

(±)-2-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)-cyclopent-2-enyl] 3-methoxy-acrylic acid ethyl ester (11): To a solution of lithium diisopropylamide (2M in hexane, 1.97 mL) in THF (10 mL) was added a solution of **8** (1.16 g, 2.63 mmol) in THF (20 mL) at −78°C under nitrogen atmosphere. The mixture was stirred at the same temperature for 1 hour and then ethyl formate (0.85 mL, 10.5 mmol) was added. After stirring at –78°C for an additional hour, the mixture was warmed up to 0°C and allowed to stir overnight at room temperature. The resulting mixture was evaporated to dryness and the residue was dissolved in dry DMF (8 mL) and MeI (0.49 mL, 7.9 mmol) was added slowly under nitrogen atmosphere. After stirring for 5 hours at room temperature, DMF was concentrated under reduced pressure. The residue was dissolved in water (100 mL) and extracted with ethyl acetate (100 mL) twice. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give **11** (810 mg, 66%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (s, 1H), 5.93 (dd, J = 5.5, 2.2 Hz, 1H), 5.60 (d, J = 5.4 Hz, 1H), 4.14 (q, J = 7.0 Hz, 2H), 3.64 (d, J = 10.0 Hz, 1H), 3.52 (d, J = 10.0 Hz, 1H), 3.41 (d, J = 9.2 Hz, 1H), 3.30 (d, J = 9.2 Hz, 1H), 3.84 (s, 3H), 3.15 (m, 1H), 1.86 (d, J = 12.6 Hz, 1H), 1.55 (dd, J = 12.6, 4.8 Hz, 1H), 1.27 (t, J = 7.0 Hz, 3H), 0.87 (s, 18H), 0.01 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 166.4, 157.8, 137.4, 136.1, 111.4, 66.9, 65.3, 59.5, 54.5, 40.2, 33.6, 25.4, 18.5, 14.2, −5.7. Anal. Calcd. for $C_{25}H_{48}O_5Si_2$: C, 61.93; H, 9.98. Found: C, 62.09; H, 10.15; MS (FAB) m/z 485 $[M+H]^+$.

(±)-5-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)cyclopent-2-enyl] uracil (12): A mixture of urea (199 mg, 3.33 mmol) and KO^{t}Bu (369 mg, 3.33 mmol) in THF (8 mL) was stirred for 1 hour at room temperature and then **11** (805 mg, 1.66 mmol) in THF (15 mL) was added to the mixture under anhydrous condition. The mixture was refluxed overnight and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:3) to give **12** (271 mg, 35%) as a white solid: m.p. 171–173°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.09 (br s, 1H), 10.72 (br s, 1H), 6.91 (s, 1H), 5.90 (dd, J = 5.4, 2.0 Hz, 1H), 5.59 (dd, J = 5.4, 1.0 Hz, 1H), 3.66 (d, J = 10.2 Hz, 1H), 3.55 (d, J = 10.0 Hz, 1H), 3.40 (d, J = 9.4 Hz, 1H), 3.31 (d, J = 9.3 Hz, 1H), 3.17 (dd, J = 6.8, 4.4 Hz, 1H), 1.82 (dd, J = 12.2, 1.8 Hz, 1H), 1.59 (dd, J = 12.2, 4.6 Hz, 1H), 0.89 (s, 18H), 0.02 (s, 12H); ^{13}C NMR (DMSO-d_6) δ 164.3, 151.5, 137.9, 135.2, 127.5, 112.4, 67.5, 66.7, 56.6, 48.2, 34.6, 25.3, 18.7, -5.5; Anal. Calcd. for $C_{23}H_{42}N_2O_4Si_2$: C, 59.18; H, 9.07; N, 6.00. Found: C, 59.04; H, 8.95; N, 5.92; MS (FAB) m/z 467 $[M+H]^+$.

(±)-5-[4,4-Bis-(hydroxymethyl)-cyclopent-2-enyl]uracil (13): Pseudouridine derivative **13** was prepared from **12** using the similar procedure described for **10**: yield 76%; m.p. 182–184°C: UV (MeOH) λ_{max} 262.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.12 (br s, 1H), 10.70 (br s, 1H), 6.97 (s, 1H), 5.91–5.83 (m, 1H), 5.68 (dd, J = 5.5, 1.2 Hz, 1H), 4.99 (br d, 2H), 3.69 (d, J = 10.0 Hz, 1H), 3.51–3.43 (m, 2H), 3.30 (d, J = 9.2 Hz, 1H), 1.79 (m, 1H), 1.61 (dd, J = 10.8, 4.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 165.6, 152.5, 137.9, 136.0, 128.3, 113.9, 67.5, 66.2, 57.4, 49.2, 36.3; Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.52; H, 5.99; N, 11.82; MS (FAB) m/z 239 $[M+H]^+$.

Syntheses of compounds **16**∼**23** was performed using the similar procedures as described for the corresponding compounds **6**∼**13**.

Methanesulfonic acid 4-(tert-butyldimethylsilanyloxymethyl)4-methyl-cyclopent-2-enyl ester (16): Yield 72%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.78–5.69 (m, 2H), 4.81 (t, J = 5.6 Hz, 1H), 3.33 (s, 2H), 3.03 (s, 3H), 1.90 (dd, J = 13.5, 7.5 Hz, 1H), 1.57 (dd, J = 13.5, 4.2 Hz, 1H), 1.11 (s, 3H), 0.87 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 141.5, 133.0, 69.7, 56.9, 46.4, 37.8, 25.3, 24.5, 18.4, −5.4.

(±)-2-[4-(tert-Butyldimethylsilanyloxymethyl)-4-methyl-cyclopent-2-enyl] malonic acid diethyl ester (17): Yield 73%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.87–5.79 (m, 2H), 4.20–4.12 (m, 4H), 3.48–3.39 (m, 6H), 1.88 (dd, J = 13.6, 7.4 Hz, 1H), 1.58 (d, J = 13.5 Hz, 1H), 1.29–1.24 (m, 6H), 1.12 (s, 3H), 0.89 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 169.4, 169.0, 140.3, 138.3, 69.9, 61.5, 61.3, 55.3, 51.1, 25.4, 24.2, 18.5, 14.6, 14.2, −5.3; Anal. Calcd. for $C_{20}H_{36}O_5Si$: C, 62.46; H, 9.44. Found: C, 62.31; H, 9.57; MS (FAB) m/z 385 $[M+H]^+$.

(±)-[4-(tert-Butyldimethylsilanyloxymethyl)-4-methyl-cyclopent-2-enyl] acetic acid ethyl ester (18): Yield 75%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.82–5.74 (m, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.40 (dd, J = 12.4, 10.8 Hz, 2H), 3.18 (m, 1H), 1.84 (dd, J = 13.2, 8.8 Hz, 1H), 1.58 (dd, J = 13.2, 4.6 Hz, 1H), 1.24 (t, J = 7.2 Hz, 3H), 1.10 (s, 3H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 170.1, 141.0, 137.9, 69.8, 61.3, 58.3, 47.5, 45.6, 39.8, 25.4, 23.9, 18.5, 14.2, −5.7. Anal. Calcd. for $C_{17}H_{32}O_3Si$: C, 65.33; H, 10.32. Found: C, 65.25; H, 10.27; MS (FAB) m/z 313 $[M+H]^+$.

(±)-5-[4-(tert-Butyldimethylsilanyloxymethyl)-4-methyl-cyclopent-2-enyl] isocytosine (19): Yield 59%; m.p. 176–178°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.79 (br s, 1H), 7.29 (s, 1H), 6.49 (br s, 2H), 5.80–5.71 (m, 2H), 3.38 (dd, J = 13.0, 10.0 Hz, 2H), 3.11 (dd, J = 8.8, 5.6 Hz, 1H), 1.77 (dd, J = 13.0, 2.8 Hz, 1H), 1.58 (dd, J = 13.3, 8.6 Hz, 1H), 1.12 (s, 3H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 164.4, 156.2, 139.1, 137.3, 128.3, 114.8, 68.3, 56.9, 45.3, 38.7, 25.5, 23.3, 18.4, −5.4. Anal. Calcd. for $C_{17}H_{29}N_3O_2Si$: C, 60.86; H, 8.71; N, 12.52. Found: C, 60.98; H, 8.62; N, 12.49; MS (FAB) m/z 336 $[M+H]^+$.

(±)-5-[4-(Hydroxymethyl)-4-methyl-cyclopent-2-enyl]isocytosine (20): Yield 71%; m.p. 184–186°C: UV (MeOH) λ_{max} 277.5 nm; ^{1}H NMR

(DMSO-d_6, 300 MHz) δ 7.34 (s, 1H), 5.84–5.75 (dd, J = 6.6, 4.3 Hz, 2H), 4.93 (t, J = 4.6 Hz, 1H), 3.54 (dd, J = 12.8, 9.6 Hz, 1H), 3.12 (dd, J = 6.4, 5.6 Hz, 1H), 1.68(d, J = 12.8, 1H), 1.52 (dd, J = 12.6, 8.6 Hz, 1H), 1.13 (s, 3H),; ^{13}C NMR (DMSO-d_6) δ 165.0, 158.2, 140.1, 138.2, 129.6, 115.3, 68.0, 57.3, 47.5, 38.4, 23.8; Anal. Calcd. for $C_{11}H_{15}N_3O_2$ (+0.5 MeOH): C, 59.71; H, 7.22; N, 17.71. Found: C, 59.61; H, 7.14; N, 17.80; MS (FAB) m/z 222 $[M+H]^+$.

(±)-2-[4-(tert-Butyldimethylsilanyloxymethyl)-4-methyl-cyclopent-2-enyl]3-methoxy-acrylic acid ethyl ester (21): Yield 70%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (s, 1H), 5.89–5.80 (m, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.57 (dd, J = 13.0, 8.8 Hz, 2H), 3.79 (s, 3H), 3.11 (dd, J = 6.4, 4.8 Hz, 1H), 1.81 (dd, J = 12.8, 8.6 Hz, 1H), 1.52 (d, J = 12.7 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.14 (s, 1H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 167.1, 158.1, 138.4, 137.6, 113.5, 68.4, 57.9, 48.3, 40.8, 35.8, 25.4, 23.8, 18.3, 14.7, −5.4. Anal. Calcd. for $C_{19}H_{34}O_4Si$: C, 64.36; H, 9.67. Found: C, 64.44; H, 9.61; MS (FAB) m/z 377 $[M+Na]^+$.

(±)-5-[4-(tert-Butyldimethylsilanyloxymethyl)-4-methyl-cyclopent-2-enyl]uracil (22): Yield 27%; m.p. 169–172°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.10 (br s, 1H), 10.65 (br s, 1H), 6.94 (s, 1H), 5.78 (d, J = 5.4 Hz, 1H), 5.48 (dd, J = 5.4, 1.0 Hz, 1H), 3.51 (d, J = 12.4 Hz, 1H), 3.40 (d, J = 12.4 Hz, 1H), 3.15 (m, 1H), 1.78 (dd, J = 12.4, 6.8 Hz, 1H), 1.56 (dd, J = 12.4, 2.4 Hz, 1H), 1.12 (s, 3H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 165.0, 153.2, 139.1, 131.2, 125.3, 114.1, 66.4, 58.1, 47.2, 35.3, 25.3, 24.0, 18.8, −5.7; Anal. Calcd. for $C_{17}H_{28}N_2O_3Si$: C, 60.68; H, 8.39; N, 8.32. Found: C, 60.55; H, 8.45; N, 8.41; MS (FAB) m/z 337 $[M+H]^+$.

(±)-5-[4-(Hydroxymethyl)-4-methyl-cyclopent-2-enyl]uracil (23): yield 72%; m.p. 187–189°C: UV (MeOH) λ_{max} 262.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.08 (br s, 1H), 10.73 (br s, 1H), 6.94 (s, 1H), 5.80–5.71 (m, 2H), 4.95 (t, J = 5.4 Hz, 1H), 3.54 (d, J = 12.2 Hz, 1H), 3.42 (d, J = 12.3 Hz, 1H), 3.33 (dd, J = 6.8, 6.0 Hz, 1H), 1.59 (dd, J = 12.8, 6.2 Hz, 1H), 1.45 (d, J = 12.8 Hz, 1H), 1.12 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 164.8, 153.4, 138.9, 137.4, 129.3, 114.7, 67.3, 57.6, 47.6, 37.2, 23.7; Anal. Calcd. for $C_{11}H_{14}N_2O_3$ (+ 1.0 H_2O): C, 54.99; H, 6.71; N, 11.66. Found: C, 55.08; H, 6.68; N, 11.72; MS (FAB) m/z 245 $[M+Na]^+$.

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