Enantiomeric Synthesis of D- and L-Cyclopentenyl Nucleosides and Their Antiviral Activity Against HIV and West Nile Virus

Gyu Y. Song,[†] Vincent Paul,[†] Hyunah Choo,[†] John Morrey,[‡] Robert W. Sidwell,[‡] Raymond F. Schinazi,[§] and Chung K. Chu*[,†]

College of Pharmacy, The University of Georgia, Athens, Georgia 30602, Institute for Antiviral Research, Utah State University, Logan, Utah 84322, and Emory University School of Medicine, and Veterans Affairs Medical Center, Decatur, Georgia 30033

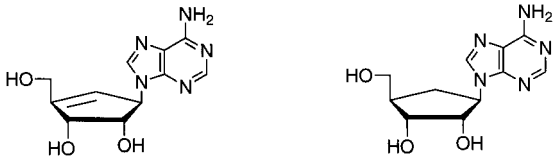
Received June 7, 2001

Enantiomeric synthesis of D- and L-cyclopentenyl nucleosides and their antiviral activity against HIV and West Nile virus are described. The key intermediate (−)- and (+)-cyclopentenyl alcohols (**7** and **15**) were prepared from D-γ-ribonolactone and D-ribose, respectively. Coupling of **7** with appropriately blocked purine and pyrimidine bases via the Mitsunobu reaction followed by deprotection afforded the target L-(+)-cyclopentenyl nucleosides (**24**-**28**, **31**, **33**, and **36**). D-(−)-Cyclopentenyl nucleosides (**1**, **40**, **43**, and **52**−**56**) were also prepared by a similar procedure for L-isomers from **15**. The synthesized compounds were evaluated for their antiviral activity against two RNA viruses: HIV and West Nile virus. Among the synthesized D-(−)-nucleosides, adenine (**1,** neplanocin A), cytosine (**55,** CPE-C), and 5-fluorocytosine (**56**) analogues exhibited moderate to potent anti-HIV activity (EC_{50} 0.1, 0.06, and 5.34 μM, respectively) with significant cytotoxicity in PBM, Vero, and CEM cells. Also, cytosine (**55**) and 5-fluorocytosine (**56**) analogues exhibited the most potent anti-West Nile virus activity (EC_{50} 0.2−3.0 and 15−20 μM, respectively). Among L-(+)-nucleosides, only the cytosine (**27**) analogue exhibited weak anti-HIV activity (EC_{50} 58.9 μM).

Introduction

(−)-Neplanocin A[1] (NPA, **1**, Figure 1), an olefinic analogue of aristeromycin **2**, is a naturally occurring carbocyclic nucleoside in which a methylene group replaces the oxygen atom in the furanose ring. The unusual presence of the double bond in NPA attracted a great deal of interest from synthetic organic chemists, and consequently, several enantiomeric syntheses have been reported.[2,3] NPA is a cyclopentenyl analogue of adenosine, which has been shown to possess both antitumor and antiviral activity.[4,5] Because of the absence of a true glycosidic bond, carbocyclic nucleosides are chemically more stable and, therefore, are not substrates for the enzymes that cleave the glycosidic linkage in conventional nucleosides.[6] Several carbocyclic nucleosides have been reported as potential anti-HIV[7,8] and anti-HBV[9] agents. Among them, carbovir[8] and abacavir[10] are the most interesting compounds because of their potent and selective anti-HIV activity. The FDA recently approved abacavir for the treatment of HIV infection.

The mechanism of the antiviral effect of NPA would be in part due to the inhibition of S-adenosylhomocysteine (AdoHcy) hydrolase.[11] Thus, AdoHcy has become an attractive target for the design of antiviral agents.[12] NPA is of interest as an antiviral agent because of its broad spectrum of antiviral effects.[13] However, the therapeutic utility of NPA as an antiviral agent has been limited because of its significant cytotoxicity. The cytotoxic effect could be attributed mainly to phosphorylation of the primary hydroxyl group at the 6′-position (5′-position of the natural nucleosides) by adenosine kinase, and subsequent phosphorylation to the triphosphate, which may inhibit cellular polymerases and/or be incorporated into the host cells.[11] NPA is also known to be rapidly deaminated by adenosine deaminase to the therapeutically inactive inosine congener,[14] which may reduce the therapeutic potency of the NPA. As indicated, although NPA itself is not useful as an antiviral agent because of its cytotoxicity, it may be a good lead for the development of structurally related therapeutic agents.[15] Therefore, a number of neplanocin analogues have been synthesized and evaluated for their antiviral and anticancer activities.[16] Among them, cyclopentenylcytosine (CPE-C) exhibited significant antiviral activity against both DNA and RNA viruses in vitro as well as antitumor activity.[17] Recently, it was reported that neplanocin A analogues inhibited the Tat-dependent and Tat-independent transactivation of HIV-1.[18,19]



Neplanocin A (NPA, **1**) Aristeromycin **2**

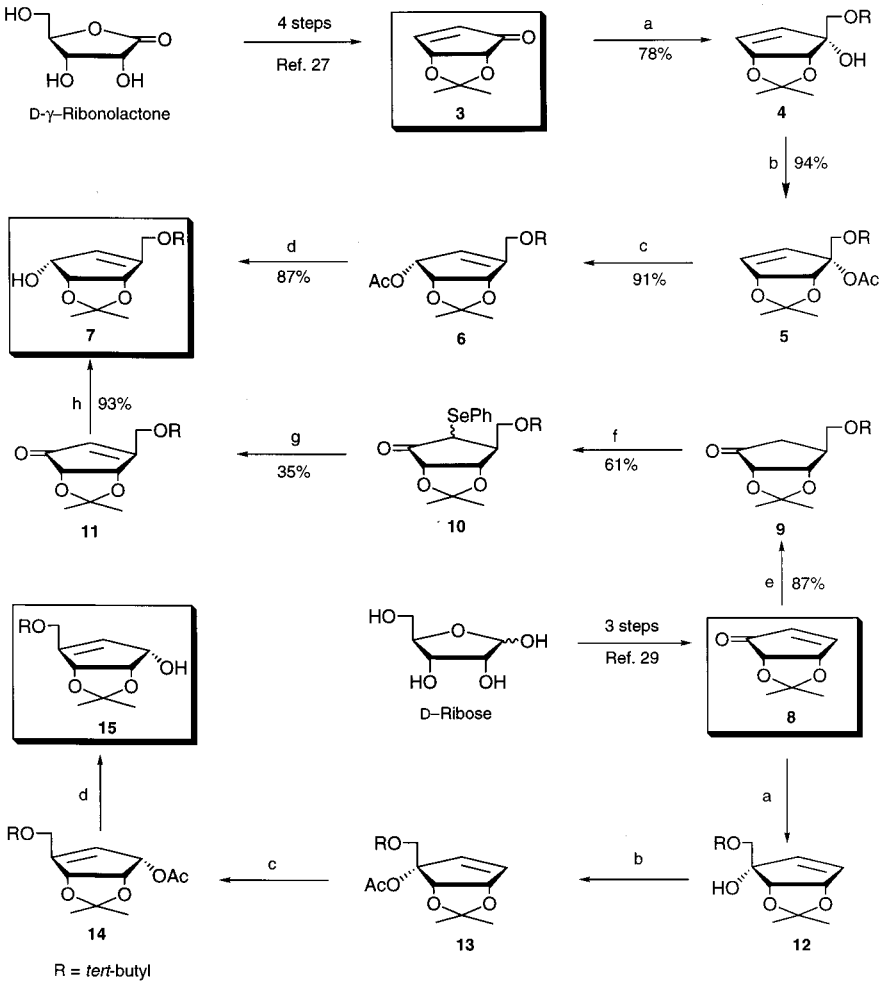
Figure 1. Structures of neplanocin A and aristeromycin.

West Nile virus (WNV) belongs to the family of Flaviviridae, genus *Flavivirus*, which includes hepatitis C, yellow fever, dengue, and Japanese encephalitis viruses.[20] The virus has been found in Africa, Western

* To whom correspondence should be addressed. Tel: (706) 542-5379. Fax: (706) 542- 5381. E-mail: dchu@rx.uga.edu.
[†] The University of Georgia.
[‡] Utah State University.
[§] Emory University School of Medicine, and Veterans Affairs Medical Center.

10.1021/jm010256v CCC: $20.00
Published on Web 10/03/2001

Scheme 1[a]



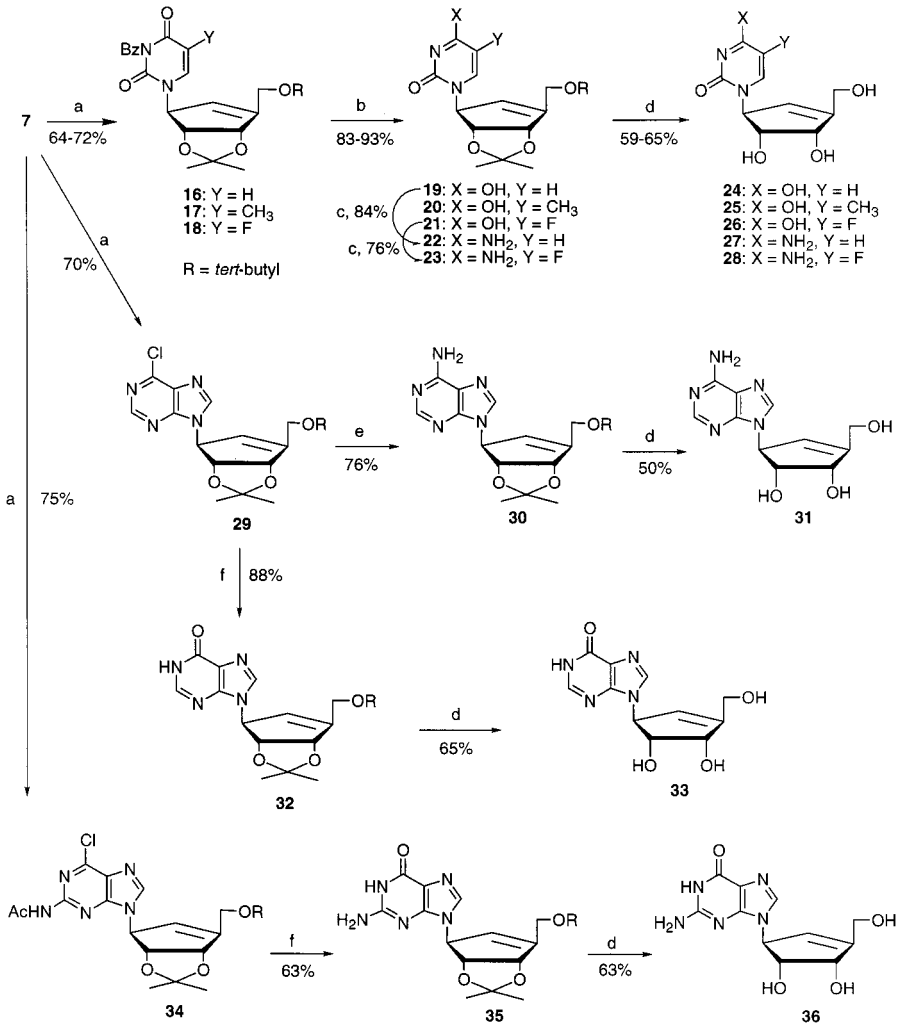
[a] Reagents: (a) $(CH_3)_3COCH_3$, *t*-BuOK, *sec*-BuLi, THF, −78 °C, 3 h; (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 24 h; (c) $PdCl_2(CH_3CN)_2$, *p*-benzoquinone, THF, reflux, 24 h; (d) K_2CO_3, MeOH, rt, 1 h; (e) $(t\text{-}BuOCH_2)_2CuLi$, *t*-BuOMe, THF, −30 °C, 30 min; (f) PhSeBr, LDA, THF, 0 °C, 2 h; (g) H_2O_2/H_2O, CH_2Cl_2, rt, 30 min; (h) $CeCl_3$; $NaBH_4$, CH_3OH, 0 °C, 30 min.

Europe, the Middle East, and the Mediterranean region of Europe.[21] WNV was recognized for the first time in the Americas in August 1999 when an outbreak in New York City resulted in 62 cases of acute encephalitis. Seven patients died, and mortality among horses and birds was substantial. Birds are the natural hosts for this virus, which can be transmitted from infected birds to humans and other animals through the bite of an infected mosquito.[22] Most human infections are mild, and symptoms include fever, headache, and body aches, often with skin rash and swollen lymph glands. More severe infection may be marked by headache, high fever, neck stiffness, coma, tremors, convulsions, muscle weakness, paralysis, and death.[23] There is no specific treatment for WNV nor available vaccine against the virus. Recently, it was reported that ribavirin inhibited WNV replication.[24] As part of our ongoing antiviral drug discovery program, we synthesized the enantiomeric D- and L-cyclopentenyl nucleosides as potential antiviral agents for HIV and WNV.

Chemistry

Although D- and L-neplanocin A have been synthesized by different synthetic methodologies,[25,26] we developed an efficient synthetic procedure, as shown in Scheme 1, which was used for the synthesis of various pyrimidine and purine nucleosides for structure−activity relationship studies. For the synthesis of target compounds, L-(+)-cyclopentenyl nucleosides (**24**−**28**, **31**, **33**, and **36**), we utilized the intermediate, (−)-cyclopentenone **3**,[27] previously prepared in four steps from D-ribonolactone (Scheme 1). Addition of a carbanion of $(CH_3)_3COCH_3$, prepared from $(CH_3)_3COCH_3$, $(CH_3)_3$-COK, and *sec*-BuLi, to compound **3** in THF at −78 °C, proceeded from the least hindered *β*-face to stereoselectively give the α-tertiary cyclopentenyl alcohol **4** in 78% yield. **4** was acetylated by Ac_2O and Et_3N in the presence of DMAP in CH_2Cl_2 to give the cyclopentenyl acetate **5** in 94% yield. The rearrangement of **5** was accomplished by treatment with $PdCl_2(MeCN)_2$ and *p*-benzoquinone in THF at reflux[28] to give **6** in 91% yield, which was then hydrolyzed with K_2CO_3 in MeOH to give the key intermediate, (−)-cyclopentenyl alcohol **7**, for L-nucleosides. In addition, an alternative synthesis of **7** was developed (Scheme 1). We utilized an enantiomer, (+)-cyclopentenone **8**,[29] which was previously prepared in three steps from D-ribose. Treatment of **8** with a solution of lithium bis(*tert*-butoxymethyl)cuprate at −30 °C gave optically pure cyclopentanone **9** as a single isomer in 87% yield. Compound **9** was converted to phenylselenyl ketone **10** as a mixture of two isomers by LDA and phenylselenyl bromide. The selenides **10**

Scheme 2[a]



[a] Reagents: (a) PPh_3, DEAD, N^3-benzoyluracil (for **16**), N^3-benzoylthymine (for **17**), N^3-benzoyl-5-fluorouracil (for **18**), 6-chloropurine (for **29**), N^2-acetylamino-6-chloropurine (for **34**), rt, 17 h; (b) sat. NH_3 in MeOH, 0 °C, 4 h; (c) 2,4,6-triisopropylbenzenesulfonyl chloride, DMAP, Et_3N, MeCN, 0 °C - rt, 24 h then 30% NH_4OH, rt, 5 h; (d) CF_3CO_2H/H_2O (2:1), 50 °C, 3 h; (e) sat. NH_3 in MeOH, steel bomb, 80 °C, 15 h; (f) $HSCH_2CH_2OH$, $NaOCH_3$, reflux, MeOH, 24 h.

was then oxidized by using a bi-phase method (dichloromethane−hydrogen peroxide) buffered with pyridine to give the cyclopentenone intermediate **11** in 35% yield. Selective reduction of the carbonyl group of **11** by sodium borohydride in the presence of cerium(III) chloride exclusively gave the (−)-cyclopentenyl alcohol **7** in 93% yield. The stereoselectivity of the reaction from **11** to **7** is probably due to the electronic effect as well as the steric hindrance of the oxygens of the isopropylidene group, which prevents a nucleophile attack (hydrogen) from the same side of the isopropylidene group.

Coupling of **7** with appropriately blocked purine and pyrimidine bases to L-nucleoside analogues **16**−**18**, **29**, and **34** was carried out with the standard Mitsunobu reaction[30,31] to obtain the desired nucleosides (Scheme 2). Yields varied widely depending on the blocked heterocycles used. To synthesize the pyrimidine analogues, the (−)-cyclopentenyl alcohol **7** was treated with N^3-benzoyluracil,[32,33] N^3-benzoylthymine,[32,33] and N^3-benzoyl-5-fluorouracil,[34] in the presence of diethylazodicarboxylate (DEAD) and Ph_3P in THF at room temperature to give **16**−**18** in 64, 72, and 61% yield, respectively (Scheme 2). Debenzoylation of **16**−**18** with saturated ammonia in MeOH gave **19**−**21**, followed by deprotection of the *tert*-butyl and isopropylidene groups with CF_3COOH/H_2O (2:1, v/v) solution at 50 °C to give the L-(+)-uracil nucleoside **24**, L-(+)-thymine nucleoside **25**, and L-(+)-5-fluorouracil nucleoside **26**, respectively. The uracil **19** and 5-fluorouracil **21** analogues were converted to the corresponding cytosine **22** and 5-fluorocytosine **23** analogues by the reported method,[35] followed by deprotection to obtain the L-(+)-cytosine nucleoside **27** and L-(+)-5-fluorocytosine nucleoside **28**, respectively (Scheme 2). The purine analogues were also prepared using a similar procedure. Treatment of **7** with 6-chloropurine and N^2-acetylamino-6-chloropurine, as described above, gave **29** and **34** in 70 and 75% yield, respectively (Scheme 2).

Treatment of **29** with saturated ammonia in MeOH in a steel bomb at 80 °C gave the adenine analogue **30** in 76% yield, followed by deprotection of *tert*-butyl and isopropylidene groups to obtain the L-(+)-neplanocin A (**31**) in 50% yield, which was further purified by recrystallization from boiling 10% aqueous MeOH. Treatment of **29** with mercaptoethanol and sodium methoxide in refluxing methanol followed by deprotection of *tert*-butyl and isopropylidene groups afforded the L-(+)-hypoxan-

Scheme 3

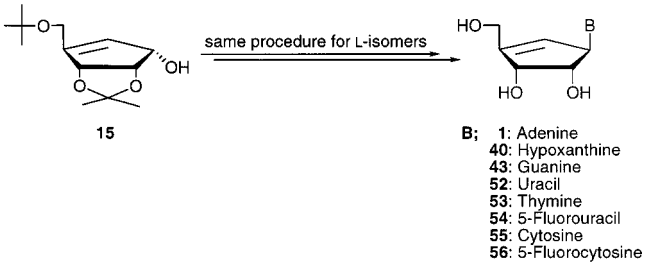


Table 1. Anti-HIV and Anti-West Nile Virus Activities of D- and L-Cyclopentenyl Nucleosides

	EC_{50}, μM		cytotoxicity (IC_{50}, μM)		
compd	HIV-1	West Nile virus	PBM cells	Vero cells	CEM cells
24	>100	>200	>100	>100	>100
25	>100	>200	>100	>100	>100
26	>100	>200	>100	>100	>100
27	58.9	>200	>100	>100	>100
28	>100	>200	>100	>100	>100
31	>100	>200	>100	>100	>100
33	>100	>200	>100	>100	>100
36	>100	>200	>100	>100	>100
1	0.1	>51	44.6	3.5	1.2
40	>100	>200	>100	>100	>100
43	>100	>200	>100	>100	>100
52	>100	>200	>100	>100	>100
53	>100	>200	>100	>100	>100
54	93.1	>200	>100	>100	>100
55	0.06	0.2 (3)[a]	6.5	1.95	0.08
56	5.34	15 (20)	73.7	27.4	51.8
AZT[b]	0.004	ND	>100	29.0	14.3
6-azauridine[b]	ND	1.2	ND	>100	ND

[a] Confirmation result. [b] Positive control; ND, not determined.

thine nucleoside **33**, which was further purified by recrystallization from boiling MeOH. The L-(+)-guanine nucleoside **36** was also prepared using the same procedure for **33** from **34**. For the synthesis of D-(−)-cyclopentenyl nucleosides (**1**, **40**, **43**, and **52**−**56**), we utilized the intermediate (+)-cyclopentenone (**8**),[29] the enantiomer of **3** (Scheme 1). The key intermediate (+)-cyclopentenyl alcohol **15**, the enantiomer of **7**, was prepared in four steps from **8** using the same procedure for **7**. After coupling of **15** with appropriately blocked purine and pyrimidine bases, the final D-(−)-cyclopenetenyl nucleosides (**1**, **40**, **43**, and **52**−**56**) were prepared using the same procedure for L-(−)-cyclopentenyl nucleosides (Scheme 3).

Antiviral Activity. The synthesized nucleosides were tested for their antiviral activities against HIV and West Nile virus, as well as for their cytotoxicity. Anti-HIV-1 activity of the synthesized nucleosides was evaluated in human peripheral blood mononuclear (PBM) cells infected with HIV-1.[36] The results are summarized in Table 1. It was found that among the synthesized D-(−)-nucleosides, adenine (**1**, neplanocin A)[4,5] and cytosine (**55**, CPE-C)[17] analogues exhibited potent antiviral activity (EC_{50} 0.1 and 0.06 μM, respectively) with significant cytotoxicity in PBM, CEM, and Vero cells. 5-Fluorocytosine (**56**) analogue exhibited moderately potent antiviral activity (EC_{50} 5.34 μM) with significant cytotoxicity in PBM, CEM, and Vero cells, and 5-fluorouracil (**54**) analogue exhibited weak antiviral activity (EC_{50} 93.1 μM). In the L-(+)-nucleoside series, only the cytosine (**27**) analogue exhibited weak antiviral activity (EC_{50} 58.9 μM).

The synthesized nucleosides were also evaluated against West Nile virus in vitro (Table 1). D-Cytosine (**55**) and D-5-fluorocytosine (**56**) analogues exhibited the most potent antiviral activity (EC_{50} 0.2−3.0 and 15−20 μM, respectively). However, L-(+)-cyclopentenyl nucleosides did not show any significant antiviral activity.

In summary, we have developed an efficient synthetic methodology for a series of D- and L-cyclopentenyl nucleosides and evaluated their anti-HIV and anti-West Nile virus activities.

Experimental Section

Chemistry. Melting points were determined on a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded on a Brucker 400 AMX spectrometer at 400 (^{1}H) and 100 MHz (^{13}C) in the indicated solvents. UV spectra were obtained on a Beckman DU-650 spectrophotometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Mass spectra were recorded on a Micromass Autospec high-resolution mass spectrometer in FAB mode. Elemental analyses were performed by Atlantic Microlab, Inc. Dry THF was obtained by distillation from Na and benzophenone when the solution became purple.

(1*S*,2*R*,3*R*)-1-(*tert*-Butoxymethyl)-2,3-(isopropylidenedioxy)-4-cyclopenten-1-ol (4). *sec*-Butyllithium solution (1.4 M in hexane, 34.7 mL, 48.6 mmol) was added dropwise to a suspension of potassium *tert*-butoxide (5.94 g, 48.6 mmol) in anhydrous *tert*-butylmethyl ether cooled to −70 °C over 5 min at −70 °C under nitrogen atmosphere. After stirring 3.5 h at this temperature, a solution of **3** (5 g, 32.4 mmol) in THF (100 mL) was added dropwise to the above solution, and the resulting solution was stirred for 3 h at −70 °C. The cooling bath was removed, and the reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution (50 mL) then extracted with $CHCl_3$ (300 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and filtered; and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (5% EtOAc in hexane) to give **4** (6.11 g, 78%) as a syrup. $[\alpha]^{24}_D$ −95.51° (c 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 9H, *tert*-butyl), 1.39 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 3.17 (s, 1H, OH), 3.33 (d, J = 8.75 Hz, 1H, 6a-H), 3.45 (d, J = 8.75 Hz, 1H, 6b-H), 4.47 (d, J = 5.32 Hz, 1H, 2-H), 5.00 (d, J = 5.32 Hz, 1H, 3-H), 5.70 (d, J = 5.75 Hz, 1H, 5-H), 5.89 (dd, J = 5.74, 1.59 Hz, 1H, 4-H). ^{13}C NMR ($CDCl_3$) δ 26.77, 27.37, 27.85, 65.83, 73.05, 80.86, 81.70, 83.99, 112.26, 132.83, 137.02. HR−FAB MS Obsd, *m*/*z* 243.1579; calcd for $C_{13}H_{23}O_4$, *m*/*z* 243.1596 $(M + H)^+$. Anal. ($C_{13}H_{22}O_4$) C, H.

(1*S*,2*R*,3*R*)-1-Acetoxy-2,3-(isopropylidenedioxy)-1-(*tert*-butoxymethyl)-4-cyclopenten (5). A mixture of **4** (4.8 g, 19.8 mmol), acetic anhydride (4.04 g, 39.6 mmol), DMAP (2.41 g, 19.8 mmol), and triethylamine (4.00 g, 39.6 mmol) in CH_2Cl_2 (200 mL) was stirred for 24 h at room temperature. The solvent was evaporated, and the residue was partitioned between CH_2Cl_2 (300 mL) and water (200 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and filtered; and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (5% EtOAc in hexane) to give **5** (5.28 g, 94%) as a syrup. $[\alpha]^{24}_D$ −110.62° (c 1.65, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 9H, *tert*-butyl), 1.37 (s, 6H, $CH_3 \times 2$), 2.07 (s, 3H, acetyl), 3.67 (d, J = 8.81 Hz, 1H, 6a-H), 3.72 (d, J = 8.78 Hz, 1H, 6b-H), 4.79 (d, J = 5.16 Hz, 1H, 2-H), 5.00 (d, J = 4.90 Hz, 1H, 3-H), 5.95 (d, J = 5.85 Hz, 1H, 5-H), 5.89 (dd, J = 5.83, 1.29 Hz, 1H, 4-H). ^{13}C NMR ($CDCl_3$) δ 22.06, 27.51, 27.75, 28.12, 63.55, 73.66, 81.30, 84.36, 89.51, 112.18, 133.96, 134.56, 170.51. HR−FAB MS Obsd, *m*/*z* 285.1683; calcd for $C_{15}H_{25}O_5$, *m*/*z* 285.1701 $(M + H)^+$. Anal. ($C_{15}H_{24}O_5$) C, H.

(1*R*,2*S*,3*S*)-1-Acetoxy-2,3-(isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten (6). A mixture of **5** (2.68 g, 9.42 mmol), $PdCl_2(MeCN)_2$ (122 mg, 0.47 mmol), and *p*-

benzoquinone (407 mg, 3.76 mmol) in dry THF (200 mL) was heated under reflux for 24 h. The reaction mixture was cooled to room temperature, and the solvent was evaporated under vacuum. The residue was purified by silica gel column chromatography (10% EtOAc in hexane) to give **6** (2.44 g, 91%) as a syrup. $[\alpha]^{24}_D$ +56.97° (c 1.28, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H, *tert*-butyl), 1.30 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 2.04 (s, 3H, acetyl), 3.96 (d, J = 13.71 Hz, 1H, 6a-H), 3.72 (d, J = 13.68 Hz, 1H, 6b-H), 4.86 (d, J = 5.56 Hz, 1H, 2-H), 4.89 (d, J = 5.56 Hz, 1H, 3-H), 5.29 (m, 1H, 1-H), 5.69 (br s, 1H, 5-H). ^{13}C NMR ($CDCl_3$) δ 19.85, 25.72, 26.27, 57.51, 72.53, 74.35, 81.85, 111.74, 124.48, 146.11, 169.62. HR−FAB MS Obsd, *m/z* 285.1705; calcd for $C_{15}H_{25}O_5$, *m/z* 285.1701 $(M + H)^+$. Anal. ($C_{15}H_{24}O_5$) C, H.

(1*R*,2*R*,3*S*)-2,3-(Isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-ol (7). Method 1. A mixture of **6** (2.10 g, 7.39 mmol) and K_2CO_3 (2.04 g, 14.7 mmol) in CH_3OH (100 mL) was stirred for 1 h at room temperature. The solvent was evaporated and the residue was partitioned between CH_2Cl_2 (300 mL) and water (200 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and filtered; and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (30% EtOAc in hexane) to give **7** (1.55 g, 87%) as a white solid. **Method 2.** $NaBH_4$ (0.37 g, 9.9 mmol) was added to a solution of **11** (1.6 g, 6.6 mmol) and $CeCl_3 \cdot 7H_2O$ (2.48 g, 6.6 mmol) in MeOH (50 mL) at 0 °C. After 1 h, cold water was added and the mixture was extracted with ether (300 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and filtered; and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (30% EtOAc in hexane) to give **7** (1.5 g, 93%) as a white solid. mp 41−42 °C. $[\alpha]^{25}_D$ −37.60° (c 1.14, $CHCl_3$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 9H, *tert*-butyl), 1.40 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.61 (br s, 1H, OH), 3.99 (d, J = 13.18 Hz, 1H, 6a-H), 4.08 (d, J = 13.18 Hz, 1H, 6b-H), 4.54 (m, 1H, 1-H), 4.75 (t, J = 5.5 Hz, 1H, 2-H), 4.95 (d, J = 5.5 Hz, 1H, 3-H), 5.76 (br s, 1H, 5-H). ^{13}C NMR ($CDCl_3$) δ 26.67, 27.43, 27.64, 58.18, 73.32, 82.98, 112.40, 130.51, 144.01. HR−FAB MS Obsd, *m/z* 243.1603; calcd for $C_{13}H_{23}O_4$, *m/z* 243.1596 $(M + H)^+$. Anal. ($C_{13}H_{22}O_4$) C, H.

(2*S*,3*S*,4*S*)-2,3-(Isopropylidenedioxy)-4-(*tert*-butoxymethyl)-cyclopentan-1-one (9). *sec*-Butyllithium (74.6 mL, 1.3 M in cyclohexane, 0.097 mol) was added dropwise to a suspension of 95% potassium *tert*-butoxide (10.9 g, 0.097 mol) in anhydrous *tert*-butylmethyl ether (400 mL) cooled to −70 °C over 10 min at −70 °C under nitrogen atmosphere. The color became orange. After stirring 3.5 h at −70 °C. a solution of LiBr (16.82 g, 0.19 mol) in dry THF (100 mL) was added dropwise over 10 min at −70 °C then allowed to warm to −15 °C and stirred for 30 min. Upon recooling to −70 °C, a solution of $CuBr \cdot SMe_2$ (9.98 g, 0.048 mol) in diisopropyl sulfide (70 mL) was added dropwise over 10 min. The solution of **8** (5 g, 0.032 mol) in dry THF (50 mL) was added dropwise over 5 min. The reaction mixture was allowed to cool to −30 °C over 15 min, stirred at this temperature for an additional 30 min, then quenched with 50 mL of CH_3OH/CH_3COOH (1:1, v/v) and poured into NH_4Cl/NH_4OH solution. After removal of the aqueous layer, the organic layer was washed with a 1:1 mixture of saturated NH_4Cl and 3% NH_4OH solution, and then with brine. The organic layer was dried over Na_2SO_4 and filtered; and the filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography (15% EtOAc in hexane) to give **9** (6.90 g, 87%) as a white solid. mp 64−66 °C; $[\alpha]^{25}_D$ +178.3° (c 0.59 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (s, 9H, *tert*-butyl), 1.35 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.96 (d, J = 17.8 Hz, 1H, 5a-H), 2.54 (d, J = 8.9 Hz, 1H, 4-H), 2.72 (dd, J = 17.9, 8.9 Hz, 1H, 5b-H), 3.35 (m, 1H, 6a-H), 3.54 (m, 1H, 6b-H), 4.23 (d, J = 5.3 Hz, 1H, 3-H), 4.63 (d, J = 5.4 Hz, 1H, 2-H). HR−FAB MS Obsd, *m/z* 241.1434; calcd for $C_{13}H_{21}O_4$, *m/z* 241.1440 $(M + H)^+$. Anal. ($C_{13}H_{20}O_4 \cdot 0.2H_2O$) C, H.

(2*S*,3*S*,4*S*)-2,3-(Isopropylidenedioxy)-4-(*tert*-butoxymethyl)-5-seleno-phenyl-4-cyclopentan-1-one (10). A solution of LDA (1.5 M in cyclohexane, 1.64 mL, 2.47 mmol) in dry THF (8.0 mL) was stirred under nitrogen at −78 °C and **9** (0.50 g, 2.06 mmol) in dry THF (10 mL) was added dropwise. The solution was stirred for 2 h at 0 °C and benzeneselenyl bromide (0.58 g, 2.47 mmol) in THF (2.5 mL) was added rapidly. The reaction mixture was stirred for 2 h at 0 °C and then warmed to room temperature while monitoring by TLC. After completion of the reaction, the reaction mixture was cooled to 0 °C with an ice bath, then H_2O (1 mL) was slowly added and the reaction mixture was neutralized with HOAc. The solvent was evaporated under vacuum and the resulting yellow oil was dissolved in ether. The organic phase was washed with brine, dried over anhydrous sodium sulfate, and filtered; and the filtrate was evaporated to dryness. The resulting residue was purified by silica gel chromatography (5−10% EtOAc in hexane) to give **10** (0.50 g, 61%) as an orange oil mixture of two anomers. This anomeric mixture was used in the next step without further purification. $[\alpha]^{25}_D$ +137.95° (c 1.21, acetone). Anal. ($C_{19}H_{26}O_4Se \cdot 0.7CH_3COCH_3$) C, H.

(2*S*,3*S*)-2,3-(Isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-one (11). H_2O_2 (24 mL, dissolved in 200 mL of H_2O) was added dropwise to a solution of **10** (11.94 g, 30.04 mmol) in CH_2Cl_2 (600 mL) and pyridine (20 mL), while keeping the temperature at 20−25 °C. The reaction mixture was stirred at room temperature for 30 min and then washed with water (50 mL). The organic phase was washed with 50 mL of saturated sodium chloride, dried over anhydrous sodium sulfate, and filtered; and the filtrate was concentrated under vacuum. The resulting residue was purified by flash chromatography (5% EtOAc in hexane) to give **11** (2.1 g, 30%) as a yellow semisolid. $[\alpha]^{25}_D$ +7.48° (c 0.40, acetone). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 9H, *tert*-butyl), 1.39 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 4.23 (d, J = 17.8 Hz, 1H, 6a-H), 4.42 (d, J = 17.8 Hz, 1H, 6b-H), 4.50 (d, J = 5.5 Hz, 1H, 3-H), 5.11 (d, J = 5.5 Hz, 1H, 2-H), 6.15 (s, 1H, 5-H). Anal. ($C_{13}H_{20}O_4 \cdot 0.2H_2O$) C, H.

(1*R*,2*S*,3*S*)-1-(*tert*-Butoxymethyl)-2,3-(isopropylidenedioxy)-4-cyclopenten-1-ol (12). Compound **12** was prepared from **8** using the same procedure that was used for **4**. ^{1}H NMR and ^{13}C NMR data were identical to that of **4**. $[\alpha]^{24}_D$ +96.40°(c 1.01, $CHCl_3$). HR−FAB MS Obsd, *m/z* 243.1598; calcd for $C_{13}H_{23}O_4$, *m/z* 243.1596 $(M + H)^+$. Anal. ($C_{13}H_{22}O_4$) C, H.

(1*R*,2*S*,3*S*)-1-Acetoxy-2,3-(isopropylidenedioxy)-1-(*tert*-butoxymethyl)-4-cyclopenten (13). Compound **13** was prepared from **12** using the same procedure that was used for **5**. ^{1}H NMR and ^{13}C NMR data were identical to that of **5**. $[\alpha]^{24}_D$ +109.52° (c 1.02, $CHCl_3$). HR−FAB MS Obsd, *m/z* 285.1703; calcd for $C_{15}H_{25}O_5$, *m/z* 285.1701 $(M + H)^+$. Anal. ($C_{15}H_{24}O_5$) C, H.

(1*S*,2*R*,3*R*)-1-Acetoxy-2,3-(isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten (14). Compound **14** was prepared from **13** using the same procedure used for **6**. ^{1}H NMR and ^{13}C NMR data were identical to that of **6**. $[\alpha]^{24}_D$ −56.29° (c 1.41, $CHCl_3$). HR−FAB MS Obsd, *m/z* 285.1711; calcd for $C_{15}H_{25}O_5$, *m/z* 285.1701 $(M + H)^+$. Anal. ($C_{15}H_{24}O_5$) C, H.

(1*S*,2*S*,3*R*)-2,3-(Isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-ol (15). Compound **15** was prepared from **14** using the described procedure for **7**. ^{1}H NMR and ^{13}C NMR data were identical to that of **7**. $[\alpha]^{24}_D$ +36.81° (c 1.14, $CHCl_3$). HR−FAB MS Obsd, *m/z* 243.1598; calcd for $C_{13}H_{23}O_4$, *m/z* 243.1596 $(M + H)^+$. Anal. ($C_{13}H_{22}O_4$) C, H.

General Procedure for the Mitsunobu Condensation. (1′*S*,2′*R*,3′*S*)-N^3-Benzoyl-1-[2,3-(isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]uracil (16). A solution of diethylazodicarboxylate (DEAD, 1.04 g, 5.98 mmol) in dry THF was added dropwise to a solution of **7** (580 mg, 2.39 mmol), triphenylphosphine (1.57 g, 5.98 mmol), and N^3-benzoyluracil (1.03 g, 4.78 mmol) in dry THF at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 16 h, and then the solvent was removed under vacuum. The residue was purified by silica gel column chromatography (50% EtOAc in *n*-hexane) to give **16** (670 mg, 64%) as a white solid. mp 147−149 °C. $[\alpha]^{25}_D$ +17.97°(c 0.74, $CHCl_3$). UV(MeOH) λ_{max} 253 nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 9H, *tert*-butyl), 1.34 (s, 3H, CH_3), 1.41(s, 3H, CH_3), 4.08 (d,

J = 15.13 Hz, 1H, 6′a-H), 4.15 (d, J = 15.07 Hz, 1H, 6′b-H), 4.63 (d, J = 5.71 Hz, 1H, 2′-H), 5.19 (d, J = 5.66 Hz, 1H, 3′-H), 5.38 (s, 1H, 1′-H), 5.63 (s, 1H, 5′-H), 5.80 (d, J = 8.1 Hz, 1H, 5-H), 7.15 (d, J = 8.1 Hz, 1H, 6-H), 7.48−7.95 (m, 5H, phenyl). HR−FAB MS Obsd, *m/z* 441.2026; calcd for $C_{24}H_{29}N_2O_6$, *m/z* 441.2025 $(M + H)^+$. Anal. ($C_{24}H_{28}N_2O_6$) C, H, N.

(1′*S*,2′*R*,3′*S*)-N³-Benzoyl-1-[2,3-(isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]thymine (17). Yield 72%. mp 70−72 °C. $[\alpha]^{24}_D$ +43.68° (c 0.53, $CHCl_3$). UV(MeOH) λ_{max} 251.5 nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 9H, *tert*-butyl), 1.34 (s, 3H, CH_3), 1.41(s, 3H, CH_3), 1.94 (s, 3H, $COCH_3$), 4.10 (d, J = 15.13 Hz, 1H, 6′a-H), 4.16 (d, J = 15.07 Hz, 1H, 6′b-H), 4.64 (d, J = 5.71 Hz, 1H, 2′-H), 5.20 (d, J = 5.66 Hz, 1H, 3′-H), 5.38 (s, 1H, 1′-H), 5.62 (s, 1H, 5′-H), 6.93 (s, 1H, 6-H), 7.47−7.93 (m, 5H, phenyl). HR−FAB MS Obsd, *m/z* 455.2132. Calcd for $C_{25}H_{31}N_2O_6$, *m/z* 455.2182 $(M + H)^+$.

(1′*S*,2′*R*,3′*S*)-N³-Benzoyl-1-[2,3-(isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-5-fluorouracil (18). Yield 61%. mp 72−73 °C. $[\alpha]^{24}_D$ +13.81°(c 0.70, $CHCl_3$). UV(MeOH) λ_{max} 250 nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 9H, *tert*-butyl), 1.34 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 4.11 (d, J = 14.94 Hz, 1H, 6′a-H), 4.16 (d, J = 15.17 Hz, 1H, 6′b-H), 4.61 (d, J = 4.79 Hz, 1H, 2′-H), 5.20 (d, J = 5.24 Hz, 1H, 3′-H), 5.41 (s, 1H, 1′-H), 5.63 (s, 1H, 5′-H), 7.24 (d, J = 6.03 Hz, 1H, 6-H), 7.50−7.94 (m, 5H, phenyl). HR−FAB MS Obsd, *m/z* 459.1935; calcd for $C_{24}H_{28}FN_2O_6$, *m/z* 459.1944 $(M + H)^+$.

General Procedure for Debenzoylation. (1′*S*,2′*R*,3′*S*)-1-[2,3-(Isopropylene- dioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]uracil (19). Compound **16** (380 mg, 0.85 mmol) was dissolved in saturated MeOH (30 mL) with NH_3 and stirred for 4 h at room temperature. The solvent was evaporated under vacuum, and the residue was purified by silica gel column chromatography (5% MeOH in $CHCl_3$) to give **19** (267 mg, 93%) as a white solid. mp 147−149 °C. $[\alpha]^{25}_D$ +39.28°(c 0.70, MeOH). UV(MeOH) λ_{max} 266 nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 9H, *tert*-butyl), 1.35 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 4.08 (d, J = 14.94 Hz, 1H, 6′a-H), 4.15 (d, J = 15.07 Hz, 1H, 6′b-H), 4.55 (d, J = 5.81 Hz, 1H, 2′-H), 5.17 (d, J = 5.66 Hz, 1H, 3′-H), 5.41 (s, 1H, 1′-H), 5.59 (s, 1H, 5′-H), 5.68 (d, J = 8.0 Hz, 1H, 5-H), 7.04 (d, J = 8.0 Hz, 1H, 6-H). HR−FAB MS Obsd, *m/z* 337.1762; calcd for $C_{17}H_{25}N_2O_5$, *m/z* 337.1763 $(M + H)^+$.

(1′*S*,2′*R*,3′*S*)-1-[2,3-(Isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]thymine (20). Yield 87%. mp 173−174 °C. $[\alpha]^{25}_D$ +111.15°(c 0.5, $CHCl_3$). UV(MeOH) λ_{max} 266 nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 9H, *tert*-butyl), 1.35 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.99 (s, 3H, $COCH_3$), 4.10 (d, J = 15.13 Hz, 1H, 6′a-H), 4.16 (d, J = 15.07 Hz, 1H, 6′b-H), 4.55 (d, J = 5.71 Hz, 1H, 2′-H), 5.20 (d, J = 5.66 Hz, 1H, 3′-H), 5.41 (s, 1H, 1′-H), 5.59 (s, 1H, 5′-H), 6.82 (s, 1H, 6-H). HR−FAB MS Obsd, *m/z* 351.1913; calcd for $C_{18}H_{27}N_2O_5$, *m/z* 351.1919 $(M + H)^+$. Anal. ($C_{18}H_{26}N_2O_5 \cdot 0.2H_2O$) C, H, N.

(1′*S*,2′*R*,3′*S*)-1-[2,3-(Isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-5-fluorouracil (21). Yield 83%. mp 198−200 °C. $[\alpha]^{24}_D$ +17.85° (c 0.50, $CHCl_3$). UV(MeOH) λ_{max} 273.5 nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 9H, *tert*-butyl), 1.35 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 4.09 (d, J = 14.93 Hz, 1H, 6′a-H), 4.16 (d, J = 15.07 Hz, 1H, 6′b-H), 4.55 (d, J = 5.79 Hz, 1H, 2′-H), 5.18 (d, J = 5.66 Hz, 1H, 3′-H), 5.43 (s, 1H, 1′-H), 5.59 (s, 1H, 5′-H), 7 (d, J = 5.90 Hz, 1H, 6-H). HR−FAB MS Obsd, *m/z* 355.1650; calcd for $C_{17}H_{24}FN_2O_5$, *m/z* 355.1669 $(M + H)^+$. Anal. ($C_{17}H_{23}FN_2O_5 \cdot 0.3H_2O$) C, H, N.

(1′*S*,2′*R*,3′*S*)-1-[2,3-(Isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]cytosine (22). A mixture of **19** (500 mg, 1.47 mmol), 4-dimethylamino pyridine (359 mg, 2.94 mmol), triethylamine (297 mg, 2.94 mmol), and 2,4,6-triisopropylbenzene sulfonyl chloride (890 mg, 2.94 mmol) in dry acetonitrile (50 mL) was stirred at room temperature for 24 h. After addition of 30% NH_4OH (10 mL), the mixture was further stirred for 5 h, then $CHCl_3$ (200 mL) and water (100 mL) were added, and the resulting mixture was partitioned. The organic phase was washed with saturated aqueous NH_4Cl solution, dried over anhydrous Na_2SO_4, filtered, and then concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (5% MeOH in $CHCl_3$) to give **22** (409 mg, 84%) as a white solid. mp 228−230 °C. $[\alpha]^{26}_D$ +34.38°(c 0.30, MeOH). UV(MeOH) λ_{max} 275 nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 9H, *tert*-butyl), 1.33 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 4.08 (d, J = 14.76 Hz, 1H, 6′a-H), 4.15 (d, J = 15.07 Hz, 1H, 6′b-H), 4.55 (d, J = 5.72 Hz, 1H, 2′-H), 5.16 (d, J = 5.64 Hz, 1H, 3′-H), 5.44 (s, 1H, 1′-H), 5.58 (s, 1H, 5′-H), 5.80 (d, J = 7.36 Hz, 1H, 5-H), 7.16 (d, J = 7.36 Hz, 1H, 6-H). HR−FAB MS Obsd, *m/z* 336.1918; calcd for $C_{17}H_{26}N_3O_4$, *m/z* 336.1923 $(M + H)^+$. Anal. ($C_{17}H_{25}N_3O_4 \cdot 0.1H_2O$) C, H, N.

(1′*S*,2′*R*,3′*S*)-1-[2,3-(Isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-5-fluorocytosine (23). Compound **23** was prepared from **21** using the same procedure as for **22**. Yield 76%. mp 194−196 °C. $[\alpha]^{26}_D$ +24.63° (c 1.30, MeOH). UV (MeOH) λ_{max} 285.5 nm.^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 9H, *tert*-butyl), 1.33 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 4.09 (d, J = 14.34 Hz, 1H, 6′a-H), 4.16 (d, J = 15.01 Hz, 1H, 6′b-H), 4.55 (d, J = 5.67 Hz, 1H, 2′-H), 5.15 (d, J = 5.11 Hz, 1H, 3′-H), 5.44 (s, 1H, 1′-H), 5.59 (s, 1H, 5′-H), 7.16 (d, J = 5.98 Hz, 1H, 6-H). HR−FAB MS Obsd, *m/z* 354.1810; calcd for $C_{17}H_{25}FN_3O_4$, *m/z* 354.1829 $(M + H)^+$. Anal. ($C_{17}H_{24}FN_3O_4 \cdot 0.21CHCl_3$) C, H, N.

General Procedure for Deprotection of *tert*-Butyl and Isopropylidene Groups. (1′*S*,2′*R*,3′*S*)-1-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]uracil (24). Compound **19** (200 mg, 0.59 mmol) was dissolved in 50 mL of CF_3COOH/H_2O (2:1, v/v) and heated to 50 °C for 3 h. The solvent was removed under vacuum, and the residue was coevaporated with ethanol (3 × 10 mL) under vacuum. The residue obtained was purified by silica gel column chromatography (20% MeOH in $CHCl_3$) to give **24** (87 mg, 61%) as a white foam. $[\alpha]^{25}_D$ +79.87° (c 0.20, MeOH) [lit[16a] for D-isomer, $[\alpha]^{20}_D$ −84° (c 1.19, MeOH)]. UV (H_2O) λ_{max} 268.0 (ϵ 9 866) (pH 2), 268.0 (ϵ 8 526) (pH 7), 267.0 nm (ϵ 6 640) (pH 11). ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ 3.84 (t, J = 5.27 Hz, 1H, 2′-H), 4.04 (br s, 2H, 6′a,b-H), 4.29 (d, J = 5.29 Hz, 1H), 5.31 (br s, 1H, 1′-H), 5.48 (s, 1H, 5′-H), 5.58 (d, J = 7.74 Hz, 1H, 5-H), 7.31 (d, J = 7.74 Hz, 1H, 6-H). HR−FAB MS Obsd, *m/z* 241.0826; calcd for $C_{10}H_{13}N_2O_5$, *m/z* 241.0824 $(M + H)^+$. Anal. ($C_{10}H_{12}N_2O_5 \cdot 0.36CHCl_3$) C, H, N.

(1′*S*,2′*R*,3′*S*)-1-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]thymine (25). Yield 59% (recrystallized from EtOH). mp 211 °C (dec) [lit[16a] for D-isomer, 210−211.5 °C (dec)]. $[\alpha]^{27}_D$ +94.53° (c 0.70, MeOH) [lit[16a] for D-isomer, $[\alpha]^{24}_D$ −108° (c 0.65, MeOH)]. UV (H_2O) λ_{max} 273.0 (ϵ 8 906) (pH 2), 272.0 (ϵ 7 449) (pH 7), 273.5 nm (ϵ 8 169) (pH 11). ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ 1.75 (s, 3H, CH_3), 3.87 (t, J = 5.68 Hz, 1H, 2′-H), 4.05 (br s, 2H, 6′a,b−H), 4.29 (d, J = 5.72 Hz, 1H, 3′-H), 5.34 (br s, 1H, 1′-H), 5.47 (s, 1H, 5′-H), 7.17 (s, 1H, 6-H). HR−FAB MS Obsd, *m/z* 255.0984; calcd for $C_{11}H_{15}N_2O_5$, *m/z* 255.0980 $(M + H)^+$. Anal. ($C_{11}H_{14}N_2O_5 \cdot 0.9EtOH$) C, H, N.

(1′*S*,2′*R*,3′*S*)-1-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-5-fluorouracil (26). Yield 64%. $[\alpha]^{27}_D$ +76.82° (c 0.34, MeOH). UV (H_2O) λ_{max} 274.5 (ϵ 5 955) (pH 2), 275.5 (ϵ 5 434) (pH 7), 273.5 nm (ϵ 5 362) (pH 11). ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ 3.87 (t, J = 5.39 Hz, 1H, 2′-H), 4.04 (br s, 2H, 6′a,b-H), 4.29 (d, J = 5.57 Hz, 1H, 3′-H), 5.29 (br s, 1H, 1′-H), 5.48 (s, 1H, 5′-H), 7.64 (d, J = 6.95 Hz, 1H, 6-H). HR−FAB MS *m/z* 259.0743; calcd for $C_{10}H_{12}FN_2O_5$, *m/z* 259.0730 $(M + H)^+$. Anal. ($C_{10}H_{11}FN_2O_5 \cdot 0.5CH_2Cl_2$) C, H, N.

(1′*S*,2′*R*,3′*S*)-1-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]cytosine (26). Yield 62% (recrystallized from MeOH). mp 138−140 °C [lit[17a] for D-form, 138−141 °C]. $[\alpha]^{26}_D$ 103.42° (c 0.44, H_2O) [lit[16a] for D-isomer, $[\alpha]^{20}_D$ −67.5° (c 1.84, MeOH), lit[17a] for D-isomer, $[\alpha]^{23}_D$ −104.5° (c 0.13, H_2O)]. UV (H_2O) λ_{max} 284.5 (ϵ 14 353) (pH 2), 275.0 (ϵ 9 724) (pH 7), 275.5 nm (ϵ 9 525) (pH 11). ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ 3.81 (t, J = 5.20 Hz, 1H, 2′-H), 4.04 (br s, 2H, 6′a,b-H), 4.31 (d, J = 5.64 Hz, 1H, 3′-H), 5.33 (br s, 1H, 1′-H), 5.46 (s, 1H, 5′-H), 5.71 (d, J = 7.32 Hz, 1H, 5-H), 7.29 (d, J = 7.32 Hz, 1H,

6-H)- HR−FAB MS Obsd, *m/z* 240.0990; calcd for $C_{10}H_{14}N_3O_4$, *m/z* 240.0984 $(M + H)^+$. Anal. ($C_{10}H_{13}N_3O_4 \cdot 0.2MeOH$) C, H, N.

(1′*S*,2′*R*,3′*S*)-1-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-5-fluorocytosine (28). Yield 65%. $[\alpha]^{25}_D$ +63.8° (c 0.48, MeOH). UV (H_2O) λ_{max} 293.5 (ϵ 6 906) (pH 2), 285.0 (ϵ 4 798) (pH 7), 285.0 nm (ϵ 6 851) (pH 11). ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ 3.81 (t, J = 5.20 Hz, 1H, 2′-H), 4.04 (br s, 2H, 6′a,b-H), 4.31 (d, J = 5.64 Hz, 1H, 3′-H), 5.33 (br s, 1H, 1′-H), 5.46 (s, 1H, 5′-H), 5.71 (d, J = 7.32 Hz, 1H, 5-H), 7.29 (d, J = 7.32 Hz, 1H, 6-H). HR−FAB MS Obsd,; *m/z* 258.0898; calcd for $C_{10}H_{13}FN_3O_4$, *m/z* 258.0890 $(M + H)^+$. Anal. ($C_{10}H_{12}FN_3O_4 \cdot 0.85CH_2Cl_2$) C, H, N.

(1′*S*,2′*R*,3′*S*)-9-[2,3-(Isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-6-chloropurine (29). Compound **29** was prepared from **7** using the same procedure as for **16**. Yield 70%. mp 134 °C. $[\alpha]^{25}_D$ +49.53° (c 0.39, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 9H, *tert*-butyl), 1.36 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 4.21 (d, J = 15.4 Hz, 1H, 6′a-H), 4.29 (d, J = 15.4 Hz, 1H, 6′b-H), 4.72 (d, J = 5.61 Hz, 1H, 2′-H), 5.37 (d, J = 6.00 Hz, 1H, 3′-H), 5.66 (br s, 1H, 1′-H), 5.82 (s, 1H, 5′-H), 8.04 (s, 1H, 8-H), 8.79 (s, 1H, 2-H). HR−FAB MS Obsd, *m/z* 379.1526; calcd for $C_{18}H_{24}ClN_4O_3$, *m/z* 379.1536 $(M + H)^+$. Anal. ($C_{18}H_{23}ClN_4O_3 \cdot 0.4CH_3COCH_3$) C, H, N.

(1′*S*,2′*R*,3′*S*)-9-[2,3-(Isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]adenine (30). A solution of **29** (900 mg, 2.4 mmol) in saturated methanol (100 mL) with NH_3 was heated at 80 °C in a steel bomb for 10 h. After the solution was cooled, the solvent was removed under vacuum and the residue was purified by silica gel column chromatography (0−1% MeOH in $CHCl_3$) to give **30** (660 mg, 76%) as a white solid. mp 74 °C. $[\alpha]^{25}_D$ +46.71° (c 0.34, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H, *tert*-butyl), 1.36 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 4.14 (d, J = 13.96 Hz, 1H, 6′a-H), 4.21 (d, J = 14.43 Hz, 1H, 6′b-H), 4.69 (d, J = 5.13 Hz, 2H, 2′-H), 5.32 (d, J = 5.52 Hz, 1H, 3′-H), 5.58 (s, 1H, 1′-H), 5.81 (s, 1H, 5′-H), 7.69 (s, 1H, 8-H), 8.40 (s, 1H, 2-H). HR−FAB MS Obsd, *m/z* 360.2032; calcd for $C_{18}H_{26}N_5O_3$, *m/z* 360.2035 $(M + H)^+$. Anal. ($C_{18}H_{26}N_5O_3 \cdot 0.3MeOH$) C, H, N.

(1′*S*,2′*R*,3′*S*)-9-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]adenine [L-(+)-Neplanocin A, 31]. Compound **31** was prepared from **30** using the same procedure that was used for **24**. Yield 50% [(recrystallized from MeOH−H_2O (9:1)]. mp 220 °C [lit[1] for D-isomer, 220 °C]. $[\alpha]^{25}_D$ +155° (c 0.3, H_2O) [lit[1] for D-isomer, $[\alpha]^{23}_D$ −157° (c 0.5, H_2O)]. UV (H_2O) λ_{max} 259.0 (ϵ 17 456) (pH 2), 260.5 (ϵ 17 170) (pH 7), 261.0 nm (ϵ 16 821) (pH 11). ^{1}H NMR (400 MHz, Me_2SO-d_6+D_2O) δ 4.10 (br s, 2H, 6′a,b-H), 4.27 (t, J = 5.61 Hz, 1H, 2′-H), 4.40 (d, J = 5.56 Hz, 1H, 3′-H), 5.33 (br s, 1H, 1′-H), 5.69 (br s, 1H, 5′-H), 8.07 (s, 1H, 2-H), 8.11 (s, 1 H, 8-H). HR−FAB MS Obsd, *m/z* 264.1070; calcd for $C_{11}H_{14}N_5O_3$, *m/z* 264.1096 $(M + H)^+$. Anal. ($C_{11}H_{13}N_5O_3 \cdot 0.1H_2O$) C, H, N.

(1′*S*,2′*R*,3′*S*)-9-[2,3-(Isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]hypoxanthine (32). A mixture of **29** (240 mg, 0.63 mmol), 2-mercaptoethanol (197 mg, 2.53 mmol), and sodium methoxide (136 mg, 2.53 mmol) was refluxed for 24 h. After the mixture cooled, it was neutralized with acetic acid, and the solvent was concentrated under vacuum. The residue was purified by silica gel column chromatography (3% MeOH in $CHCl_3$) to give **32** (190 mg, 88%) as a white solid. mp 238−240 °C. $[\alpha]^{27}_D$ +50.32° (c 0.50, MeOH). UV(MeOH) λ_{max} 249.5 nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 9H, *tert*-butyl), 1.37 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 4.13 (d, J = 15.4 Hz, 1H, 6′a-H), 4.20 (d, J = 15.4 Hz, 1H, 6′b-H), 4.68 (d, J = 5.61 Hz, 1H, 2′-H), 5.31 (d, J = 5.51 Hz, 1H, 3′-H), 5.59 (br s, 1H, 1′-H), 5.75 (s, 1H, 5′-H), 7.71 (s, 1H, 8-H), 8.10 (s, 1H, 2-H). HR−FAB MS Obsd, *m/z* 361.1878; calcd for $C_{18}H_{25}N_4O_4$, *m/z* 361.1875 $(M + H)^+$. Anal. ($C_{18}H_{24}N_4O_4 \cdot$ 0.15 MeOH) C, H, N.

(1′*S*,2′*R*,3′*S*)-9-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl] hypoxanthine (33). Compound **33** was prepared from **32** using the same procedure as for **24**. Yield 65% (recrystallized from MeOH). mp 230−232 °C (dec) [lit[16c] for D-isomer, 229−231 °C (dec)]. $[\alpha]^{26}_D$ +141.24° (c 0.55, H_2O) [lit[16c] for D-isomer, $[\alpha]^{23}_D$ −143° (c 0.57, H_2O)]. UV (H_2O) λ_{max} 249.5 (ϵ 12 546) (pH 2), 249.5 (ϵ 11 475) (pH 7), 254.5 nm (ϵ 12 834) (pH 11). ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ 4.09 (br s, 2H, 6′a,b-H), 4.21 (t, J = 5.22 Hz, 1H, 2′-H), 4.39 (d, J = 5.31 Hz, 1H, 3′-H), 5.33 (br s, 1H, 1′-H), 5.67 (s, 1H, 5′-H), 8.00 (s, 1H, 8-H), 8.01 (s, 1H, 2-H). HR−FAB MS Obsd, *m/z* 265.0972; calcd for $C_{11}H_{13}N_4O_4$, *m/z* 265.0936 $(M + H)^+$. Anal. ($C_{11}H_{12}N_4O_4 \cdot 0.3H_2O$) C, H, N.

(1′*S*,2′*R*,3′*S*)-N²-Acetylamino-9-[2,3-(isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-6-chloropurine (34). Compound **34** was prepared from **7** using the same procedure used for **16**. Yield 75%. mp 182−184 °C. $[\alpha]^{24}_D$ +7.46° (c 0.18, MeOH). UV(MeOH) λ_{max} 249.5 nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 9H, *tert*-butyl), 1.36 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.55 (s, 3H, acetyl), 4.23 (d, J = 6.8 Hz, 1H, 6′a-H), 4.26 (d, J = 6.8 Hz, 1H, 6′b-H), 4.74 (d, J = 5.74 Hz, 1H, 2′-H), 5.41 (d, J = 5.44 Hz, 1H, 3′-H), 5.42 (br s, 1H, 1′-H), 5.77 (s, 1H, 5′-H), 6.44 (br s, 1H, NH), 7.90 (s, 1H, 8-H). HR−FAB MS Obsd, *m/z* 436.1737; calcd for $C_{20}H_{27}ClN_5O_4$, *m/z* 436.1751 $(M + H)^+$. Anal. ($C_{20}H_{26}ClN_5O_4$) C, H, N.

(1′*S*,2′*R*,3′*S*)-9-[2,3-(Isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]guanine (35). Compound **35** was prepared from **34** using the same procedure used for **32**. Yield 63%. mp > 300 °C (dec). $[\alpha]^{24}_D$ +33.88° (c 0.30, MeOH). UV(MeOH) λ_{max} 254 nm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.17 (s, 9H, *tert*-butyl), 1.27 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 4.03 (d, J = 15.08 Hz, 1H, 6′a-H), 4.26 (d, J = 15.33 Hz, 1H, 6′b-H), 4.59 (d, J = 5.5 Hz, 1H, 1′-H), 5.24 (s, 1H, 2′-H), 5.36 (d, J = 5.60 Hz, 1H, 3′-H), 5.62 (s, 1H, 5′-H), 6.49 (br s, 1H, NH), 7.42 (s, 1H, 8-H). HR−FAB MS Obsd, *m/z* 376.1974; calcd for $C_{18}H_{26}N_5O_4$, *m/z* 376.1984 $(M + H)^+$. Anal. ($C_{18}H_{25}N_5O_4$) C, H, N.

(1′*S*,2′*R*,3′*S*)-9-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]guanine (36). Compound **36** was prepared from **35** using the same procedure as for **16**. Yield 63% [recrystallized from MeOH/H_2O (2:1)]. mp > 220 °C (dec) [lit[16a] for D-isomer, > 220 °C (dec)]. $[\alpha]^{27}_D$ +54.51° (c 0.15, H_2O) [lit[16a] for D-isomer, $[\alpha]^{20}_D$ −87° (c 0.15, *N*,*N*-dimethylformamide)]. UV (H_2O) λ_{max} 254.5 (ϵ 8 641) (pH 2), 252.5 (ϵ 11 324) (pH 7), 256.5 nm (ϵ 8 317) (pH 11). ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ 4.08 (br s, 2H, 6′a,b-H), 4.16 (t, J = 5.11 Hz, 1H, 2′-H), 4.41 (d, J = 5.5 Hz, 1H, 3′-H), 5.15 (s, 1H, 1′-H), 5.62 (s, 1H, 5′-H), 7.59 (s, 1H, 8-H). HR−FAB MS Obsd, *m/z* 280.1039; calcd for $C_{11}H_{14}N_5O_4$, *m/z* 280.1045 $(M + H)^+$. Anal. ($C_{11}H_{13}N_5O_4 \cdot$ 1.2H_2O) C, H, N.

General Procedure for the D-Cyclopentenyl Nucleosides. The final D-cyclopentenyl nucleosides were prepared from **15** using same procedure that was used for the L-cyclopentenyl nucleosides. ^{1}H NMR data were identical to that of the L-isomer.

(1′*R*,2′*S*,3′*R*)-9-[2,3-(Isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-6-chloropurine (37). $[\alpha]^{24}_D$ −48.99° (c 0.35, $CHCl_3$). HR−FAB MS Obsd, *m/z* 379.1516; calcd for $C_{18}H_{24}ClN_4O_3$, *m/z* 379.1536 $(M + H)^+$. Anal.($C_{18}H_{23}ClN_4O_3 \cdot 0.22MeOH$) C, H, N.

(1′*R*,2′*S*,3′*R*)-9-[2,3-(Isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]adenine (38). $[\alpha]^{24}_D$ −45.08° (c 0.48, $CHCl_3$). HR−FAB MS Obsd, *m/z* 360.2032; calcd for $C_{18}H_{26}N_5O_3$, *m/z* 360.2035 $(M + H)^+$. Anal. ($C_{18}H_{26}N_5O_3$) C, H, N.

(1′*R*,2′*S*,3′*R*)-9-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]adenine [D-(−)-Neplanocin A, 1]. $[\alpha]^{24}_D$ −155° (c 0.3, H_2O) [lit.[1] $[\alpha]^{23}_D$ = −157° (c 0.5, H_2O)]. HR−FAB MS Obsd, *m/z* 264.1092; calcd for $C_{11}H_{14}N_5O_3$, *m/z* 264.1096 $(M + H)^+$. Anal. ($C_{11}H_{13}N_5O_3 \cdot 0.2H_2O$) C, H, N.

(1′*R*,2′*S*,3′*R*)-9-[2,3-(Isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]hypoxanthine (39). $[\alpha]^{27}_D$ −52.48° (c 0.39, MeOH). HR−FAB MS Obsd, *m/z* 361.1897; calcd for $C_{18}H_{25}N_4O_4$, *m/z* 361.1875 $(M + H)^+$. Anal. ($C_{18}H_{24}N_4O_4$) C, H, N.

(1′*R*,2′*S*,3′*R*)-9-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl] hypoxanthine (40). $[\alpha]^{24}_D$ −143.8° (c 0.59, H_2O). HR−FAB MS Obsd, *m/z* 265.0972; calcd for $C_{11}H_{13}N_4O_4$, *m/z* 265.0936 $(M + H)^+$. Anal. ($C_{11}H_{12}N_4O_4 \cdot 0.54H_2O$) C, H, N.

(1′*R*,2′*S*,3′*R*)-N²-Acetylamino-9-[2,3-(isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-6-chloropurine (41). $[\alpha]^{24}_D$ −8.02° (c 0.23, MeOH). HR−FAB MS Obsd, *m/z* 436.1737; calcd for $C_{20}H_{27}ClN_5O_4$, *m/z* 436.1751 $(M + H)^+$.

(1′*R*,2′*S*,3′*R*)-9-[2,3-(Isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]guanine (42). $[\alpha]^{24}_D$ −33.15° (c 0.35, MeOH). HR−FAB MS Obsd, *m/z* 376.1974; calcd for $C_{18}H_{26}N_5O_4$, *m/z* 376.1984 $(M + H)^+$.

(1′*R*,2′*S*,3′*R*)-9-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]guanine (43). $[\alpha]^{27}_D$ −53.96° (c 0.15, H_2O). HR−FAB MS Obsd, *m/z* 280.1039; calcd for $C_{11}H_{14}N_5O_4$, *m/z* 280.1045 $(M + H)^+$. Anal. ($C_{11}H_{13}N_5O_4 \cdot 1.2H_2O$) C, H, N.

(1′*R*,2′*S*,3′*R*)-N³-Benzoyl-1-[2,3-(isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]uracil (44). $[\alpha]^{25}_D$ −16.74° (c 0.31, $CHCl_3$). HR−FAB MS Obsd, *m/z* 441.2025; calcd for $C_{24}H_{29}N_2O_6$, *m/z* 441.2025 $(M + H)^+$.

(1′*R*,2′*S*,3′*R*)-N³-Benzoyl-1-[2,3-(isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]thymine (45). $[\alpha]^{24}_D$ −42.83° (c 0.59, $CHCl_3$). HR−FAB MS Obsd, *m/z* 455.2132; calcd for $C_{25}H_{31}N_2O_6$, *m/z* 455.2182 $(M + H)^+$.

(1′*R*,2′*S*,3′*R*)-N³-Benzoyl-1-[2,3-(isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-5-fluorouracil (46). $[\alpha]^{24}_D$ −12.89° (c 0.40, $CHCl_3$). HR−FAB MS Obsd, *m/z* 459.2035; calcd for $C_{24}H_{28}FN_2O_6$, *m/z* 459.1944 $(M + H)^+$. Anal. ($C_{24}H_{27}FN_2O_6 \cdot 0.4H_2O$) C, H, N.

(1′*R*,2′*S*,3′*R*)-1-[2,3-(Isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]uracil (47). $[\alpha]^{25}_D$ −41.15° (c 0.75, MeOH). HR−FAB MS Obsd, *m/z* 337.1762; calcd for $C_{17}H_{25}N_2O_5$, *m/z* 337.1763 $(M + H)^+$. Anal. ($C_{17}H_{24}N_2O_5$) C, H, N.

(1′*R*,2′*S*,3′*R*)-1-[2,3-(Isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]thymine (48). $[\alpha]^{25}_D$ −110.16° (c 0.54, $CHCl_3$). HR−FAB MS Obsd, *m/z* 351.1913; calcd for $C_{18}H_{27}N_2O_5$, *m/z* 351.1919 $(M + H)^+$.

(1′*R*,2′*S*,3′*R*)-1-[2,3-(isopropylenedioxy)-4-(*tert*-butoxymethyl)-4′-cyclopenten-1-yl]-5-fluorouracil (49). $[\alpha]^{24}_D$ −19.88° (c 0.42, $CHCl_3$). HR−FAB MS Obsd, *m/z* 355.1650; calcd for $C_{17}H_{24}FN_2O_5$, *m/z* 355.1669 $(M + H)^+$.

(1′*R*,2′*S*,3′*R*)-1-[2,3-(Isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]cytosine (50). $[\alpha]^{26}_D$ −34.46° (c 0.35, MeOH). HR−FAB MS Obsd, *m/z* 336.1920; calcd for $C_{17}H_{26}N_3O_4$, *m/z* 336.1923 $(M + H)^+$.

(1′*R*,2′*S*,3′*R*)-1-[2,3-(Isopropylidenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-5-fluorocytosine (51). $[\alpha]^{26}_D$ −23.70° (c 1.30, MeOH). HR−FAB MS Obsd, *m/z* 354.1810; calcd for $C_{17}H_{25}FN_3O_4$, *m/z* 354.1815 $(M + H)^+$.

(1′*S*,2′*R*,3′*S*)-1-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]uracil (52). $[\alpha]^{25}_D$ −80.53° (c 0.25, MeOH). HR−FAB MS Obsd, *m/z* 241.0826; calcd for $C_{10}H_{13}N_2O_5$, *m/z* 241.0824 $(M + H)^+$. Anal. ($C_{10}H_{12}N_2O_5$) C, H, N.

(1′*R*,2′*S*,3′*R*)-1-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]thymine (53). $[\alpha]^{27}_D$ −98.98° (c 0.75, MeOH). HR−FAB MS Obsd, *m/z* 255.0984; calcd for $C_{11}H_{15}N_2O_5$, *m/z* 255.0980 $(M + H)^+$. Anal. ($C_{11}H_{14}N_2O_5$) C, H, N.

(1′*R*,2′*S*,3′*R*)-1-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-5-fluorouracil (54). $[\alpha]^{27}_D$ −78.21° (c 0.39, MeOH); HR−FAB MS Obsd, *m/z* 259.0743; Calcd for $C_{10}H_{12}FN_2O_5$, *m/z* 259.0730 $(M + H)^+$. Anal. ($C_{10}H_{11}FN_2O_5 \cdot 0.3H_2O$) C, H, N.

(1′*R*,2′*S*,3′*R*)-1-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]cytosine (55). $[\alpha]^{23}_D$ −105.10° (c 0.34, H_2O). HR−FAB MS Obsd, *m/z* 240.0990; calcd for $C_{10}H_{14}N_3O_4$, *m/z* 240.0984 $(M + H)^+$. Anal. ($C_{10}H_{13}N_3O_4 \cdot 0.12MeOH$) C, H, N.

(1′*R*,2′*S*,3′*R*)-1-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-5-fluorocytosine (56). $[\alpha]^{25}_D$ −60.93° (c 0.50, MeOH). HR−FAB MS Obsd, *m/z* 258.0898; calcd for $C_{10}H_{13}FN_3O_4$, *m/z* 258.0890 $(M + H)^+$. Anal. ($C_{10}H_{12}FN_3O_4 \cdot 0.2MeOH$) C, H, N.

Antiviral Assays for West Nile Virus. A New York isolate of West Nile virus from homogenized crow brain dated 8/20/00 (Robert Lacniotti, Division of Vector-Borne Infectious Diseases, Centers for Disease Control and Prevention, Ft. Collins, CO) was used. African green monkey kidney (Vero 76, ATCC CCL1587) were maintained during the antiviral experiments in MEM with 1% FBS, 0.1% $NaHCO_3$, and 50 μg/mL gentamycin (Sigma, St. Louis, MO). The cytopathic effect (CPE) inhibitory assay was described elsewhere[37] with the following modifications. Serial dilutions of test compounds were added to lightly confluent Vero cells in 96-well microplates, after which 5 cell culture 50% infectious doses ($CCID_{50}$) of WNV New York isolate were added to the cells. Uninfected cells, infected cells with no drug, and uninfected drug-treated cells were used as controls. Duplicates of toxicity controls at each drug concentration and triplicates of test samples were performed. After 6 days post-virus exposure, cells were visually scored for CPE. The 50% effective concentration (EC_{50}) and the 50% inhibitory cytotoxic concentration (IC_{50}) were calculated by regression analysis using the means of the CPE ratings at each concentration of the compound. Neutral red vital stain was used to verify the visual CPE assay and to provide a more quantitative result.[38] After visually reading the CPE, cells were incubated with neutral red for 2−3 h at 37 °C. Free dye was washed from the wells, and the uptake dye was quantified using a microplate reader (Bio-Tek EL 1309, BioTek, Burlington, VT) at absorbance 540 and 405 nm. Absorbance values were expressed as percentages of controls, and EC_{50} and IC_{50} values were calculated by regression analysis.

Acknowledgment. This research was supported in part by U.S. Public Health Service Research Grants (AI 32351, UO1 AI 48495, Veterans Affairs) from the National Institutes of Health and Korea Science and Engineering Foundation (KOSEF). We thank Dr. Christopher Tseng of the National Institute of Allergy and Infectious Diseases, NIH, for encouraging us to evaluate the synthesized nucleosides against West Nile virus.

References

(1) Yaginuma, A.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. Studies on neplanocin A, New antitumor antibiotic. I. Producing organism, isolation and characterization. *J. Antibiot.* **1981**, *34*, 359−366.

(2) Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. Enantioselective synthesis of the carbocyclic nucleoside, (−)-aristeromycin and (−)-neplanocin A by a chemoenzymatic approach. *J. Am. Chem. Soc.* **1983**, *105*, 4049−4055.

(3) Lim, M. I.; Marquez, V. E. Total synthesis of (−)-neplanocin A1. *Tetrahedron Lett.* **1983**, *24*, 5559−5562.

(4) Marquez, V. E.; Lim, M. I. Carbocyclic nucleosides. *Med. Res. Rev.* **1986**, *6*, 1−40.

(5) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. Synthesis of carbocyclic nucleosides. *Tetrahedron* **1994**, *50*, 10611−10670.

(6) Montgomery, J. A. Studies on the biologic activity of purine and pyrimidine analogs. *Med. Res. Rev.* **1982**, *2*, 271−308.

(7) Hayashi, S.; Norbeck, D. W.; Rosenbrook, W.; Fine, R. L.; Matsukura, M.; Plattner, J. J.; Broder, S.; Mitsuya, H. Cyclobut-A and cyclobut-G, carbocyclic oxetanocin analogs that inhibit the replication of human immunodeficiency virus in T cells and monocytes and macrophage in vitro. *Antimicrob. Agents Chemother.* **1990**, *34*, 287−294.

(8) Vince, R.; Hua, M. Synthesis and anti-HIV activity of carbocyclic 2′,3′-didehydro-2′,3′-dideoxy 2,6-disubstituted purine nucleosides. *J. Med. Chem.* **1990**, *33*, 17−21.

(9) Price, P. M.; Banerjee, R.; Jeffrey, A. M.; Acs, G. The mechanism of inhibition of hepatitis B virus replication by the carbocyclic analog of 2′-deoxyguanosine. *Hepatology* **1992**, *16*, 8−12.

(10) Daluge, S. M.; Good, S. S.; Martin, M. T.; Tibbels, S. R.; Miller, W. H.; Averett, D. R.; St. Clair, M. H.; Ayers, K. M. The 34th Interscience Conference on Antimicrobial Agents and Chemotherapy, Orlando, FL, Oct, 1994; Abstract 16.

(11) Turner, M. A.; Yang, X.; Yin, D.; Kuczera, K.; Borchardt, R. T.; Howell, P. L. Structure and function of S-Adenosylhomocysteine Hydrolase. *Cell Biochem. Biophys.* **2000**, *33*, 101−125.

(12) De Clercq, E.; Cools, M. Antiviral potency of adenosine analogs: correlation with inhibition of S-adenosylhomocysteine hydrolase. *Biochem. Biophys. Res. Commun.* **1985**, *129*, 306−311.

(13) De Clercq, E. Antiviral and antimetabolic activities of neplanocins. *Antimicrob. Agents Chemother.* **1985**, *28*, 84−89.
(14) Keller, B. T.; Borchardt, R. T. In *Biological Methylation and Drug Design*; Borchardt, R. T., Creveling, C. R., Ueland, P. M., Eds.; Hummana: Clifton, NJ, 1987; pp 385−396.
(15) Shuto, S.; Obara, T.; Saito, Y.; Andrei, G.; Snoeck, R.; De Clercq, E.; Matsuda, A. New neplanocin analogues. 6. Synthesis and potent antiviral activity of 6′-homoneplanocin A. *J. Med. Chem.* **1996**, *39*, 2392−2399.
(16) (a) Arita, M.; Okumoto, T.; Saito, T.; Hoshino, Y. Enantioselective synthesis of new analogs of neplanocin A and their biological activity. *Carbohydr. Res.* **1987**, *171*, 233−258. (b) Tseng, C. K. H.; Marquez, V. E.; Fuller, R. W.; Goldstein, B. M.; Haines, D. R.; McPherson, H.; Parsons, J. L.; Shannon, W. M.; Arnett, G.; Hollingshead, M.; Driscoll, J. S. Synthesis of 3-deazaneplanocin A, a powerful inhibitor of S-adenosylhomocycteine hydrolase with potent and selective in vitro and in vivo antiviral activities. *J. Med. Chem.* **1989**, *32*, 1442−1446. (c) Nokami, J.; Matsuura, H.; Takahashi, H.; Yamashita, M. Synthesis of carbocyclic nucleosides, (−)-neplanocin A and its analogues. *Synlett* **1994**, 491−493.
(17) (a) Marquez, V. E.; Lim, M. I.; Treanor, S. P.; Polwman, J.; Priest, M. A.; Markovac, A.; Khan, S.; Kaskar, B.; Driscoll, J. S. Cyclopentenylcytosine. A carbocyclic nucleoside with antitumor and antiviral properties. *J. Med. Chem.* **1988**, *31*, 1687−1694. (b) Lim, M. I.; Moyer, J. D.; Cysyk, R. L.; Marquez, V. E. Cyclopentenyluridine and cyclopentenylcytidine analogues as inhibitor of uridine-cytidine kinase. *J. Med. Chem.* **1984**, *27*, 1536−1538.
(18) Daelemans, D.; Vandamme, A. M.; Shuto, S.; Matsuda, A.; De Clercq, E. Stereospecificity of 6′-*C*-neplanocin A analogues as inhibitors of S-adenosylhomocysteine hydrolase activity and human immunodeficiency virus replication. *Nucleosides Nucleotides* **1998**, *17*, 479−486.
(19) Mayers, D. L.; Mikovits, J. A.; Joshi, B.; Hewlett, I. K.; Estrada, J. S.; Wolfe, A. D.; Garcia, G. E.; Doctor, B. P.; Burke, D. S.; Gordon, R. K.; Lane, J. R.; Chiang, P. K. Anti-human immunodeficiency virus 1 (HIV-1) activities of 3-deazaadenosine analogs: Increased potency against 3′-azido-3′-deoxythymine-resistant HIV-1 strains. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 215−219.
(20) Gubler, D. J.; Roehring, J. J. In *Topley and Wilson's Microbiology and Microbial Infections*; Mahy, B. W., Collier, L., Eds.; Arnold: London, 1998; Vol. 1, pp 579−600.
(21) Hubalek, Z.; Halouzka, J. West Nile fever − a reemerging mosquito-borne viral disease in Europe. *Emerging Infect. Dis.* **1999**, *5*, 643−650.
(22) Anderson, J. F.; Andreadis, T. G.; Vossbrinck, C. R.; Tirrell, S.; Wakem, E. M.; French, R. A.; Garmendia, A. E.; Van Kruiningen, H, J. Isolation of West Nile virus from mosquitoes, crows, and a Cooper's hawk in Connecticut. *Science* **1999**, *286*, 2331−2333.
(23) National Atlas of the United States of America. http://nationalatlas.gov/virusintro.html. Accessed Nov. 15, 2000.
(24) Jordan, I.; Briese, T.; Fischer, N.; Lau, J. Y−N.; Limpkin, W. I. Ribavirin inhibits West Nile virus replication and cytopathic effects in neural cells. *J. Infect. Dis.* **2000**, *182* (4), 1214−1217.
(25) Marquez, V. E.; Lim, M. I.; Tseng, C. K.-H. Total synthesis of (−)-neplanocin A. *J. Org. Chem.* **1988**, *53*, 5709−5714.
(26) (a) Hegedus, L. S.; Geisler, L. Synthesis of (+)-neplanocin a from a chromium−carbene complex-derived optically active butenolide. *J. Org. Chem.* **2000**, *65*, 4200−4203. (b) Shin, D. H.; Lee, H. W.; Park, S. S.; Kim, J. H.; Jeong, L. S. Synthesis of (−)-neplanocin A analogues as potential antiviral agents. *Arch. Pharm. Res.* **2000**, *23*, 302−309.
(27) (a) Chun, B. K.; Chu, C. K. Asymmetric synthesis of carbocyclic C-nucleoside, (−)-9-deazaaristeromycin. *Tetrahedron Lett.* **1999**, *40*, 3309−3312. (b) Borcherding, D. R.; Scholtz, S. A.; Borchardt, R. T. Synthesis of analogues of neplanocin A: Utilization of optically active dihydroxycyclopentenones derived from carbohydrates. *J. Org. Chem.* **1987**, *52*, 5457−5461.
(28) Medich, J. R.; Kunnen, K. B.; Johnson, C. R. Synthesis of the carbocyclic nucleoside (−)-neplanocin A. *Tetrahedron Lett.* **1987**, *28*, 4131−4134.
(29) (a) Wang, P.; Agrofoglio, L. A.; Newton, M. G.; Chu, C. K. Chiral synthesis of carbocyclic analogues of L-ribofuranosides. *J. Org. Chem.* **1999**, *64*, 4173−4178. (b) Ali, S. M.; Ramesh, K.; Borchardt, R. T. Efficient enantioselective synthesis of carbocyclic nucleosides and prostaglandin synthons. *Tetrahedron Lett.* **1990**, *31*, 1509−1512.
(30) Cadet, G.; Chan, C. S.; Daniel, R. Y.; Davis, C. P.; Guiadeen, D.; Rodriguez, G.; Thomas, T.; Walcott, S.; Scheiner, P. Ring-expanded nucleoside analogues. 1,3-Dioxan-5-yl pyrimidines. *J. Org. Chem.* **1998**, *63*, 4574−4580.
(31) Jenny, T. F.; Previsani, N.; Benner, S. A. Carbocyclic analogs of nucleosides via modified Mitsunobu reactions. *Tetrahedron Lett.* **1991**, *32*, 7029−7032.
(32) Cruickshank, K. A.; Jiricny, J.; Reese, C. B. The benzoylation of uracil and thymine. *Tertahedron Lett.* **1984**, *25*, 681−684.
(33) Frieden, M.; Giraud, M.; Reese, C. B.; Song, Q. L. Synthesis of 1-[*cis*-3-(hydroxymethyl)cyclobutyl]-uracil, -thymine and -cytosine. *J. Chem. Soc., Perkin. Trans. 1* **1998**, 2827−2832.
(34) Lucey, N. M.; McCormick, J. E.; McElhinney, R. S. Nucleoside analogues. Part 10. Synthesis of three unusual 5-fluorouracil seco-nucleosides incorporating *N*-(2-chloroethyl)-*N*-nitrosourea residues. *J. Chem. Soc. Perkin Trans. 1* **1990**, 795−802.
(35) Shuto, S.; Obara, T.; Saito, Y.; Andrei, G.; Snoeck, R.; De Clercq, E.; Matsuda, A. New neplanocin analogues. 6. Synthesis and potent antiviral activity of 6′-homoneplanocin A. *J. Med. Chem.* **1996**, *39*, 2392−2399.
(36) Lee, K.; Choi, Y. S.; Gullen, E.; Schlueter-Wirtz, S.; Schinazi, R. F.; Cheng, Y. C.; Chu, C. K. Synthesis and anti-HIV and anti-HBV activities of 2′-fluoro-2′,3′-unsaturated L-nucleosides. *J. Med. Chem.* **1999**, *42*, 1320−1328.
(37) Smee, D. F.; Alaghamandan, H. A.; Kini, G. D.; Robins, R. K. Antiviral activity and mode of action of ribavirin 5′-sulfamate against Semliki Forest virus. *Antiviral Res.* **1988**, *10*, 253−262.
(38) Player, M. R.; Barnard, D. L.; Torrence, P. F. Potent inhibition of respiratory syncytial virus replication using a 2−5 A-antisence chimera targeted to signals within the virus genomic RNA. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 8874−8879.

JM010256V