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Practical Synthesis of D- and L-2-Cyclopentenone and Their Utility for the Synthesis of Carbocyclic Antiviral Nucleosides against Orthopox Viruses (Smallpox, Monkeypox, and Cowpox Virus)

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Received July 11, 2003

Highly efficient and practical methodology for the syntheses of D- and L-4,5-*O*-isopropylidene-2-cyclopentenone (**9** and **22**), versatile intermediates for the synthesis of carbocyclic nucleosides, have been developed via a ring-closing metathesis reaction from D-ribose in eight steps. The utility of D- and L-4,5-*O*-isopropylidene-2-cyclopentenone is demonstrated by their application for the preparation of D-cyclopentyl-6-azauridine **12** and D-cyclopentenyl-5-halocytosine nucleosides (**33**−**35**) using Mitsunobu reaction to introduce pyrimidine bases as potential antiviral agents. Preliminary antiviral activity against orthopox viruses (smallpox, monkeypox, and cowpox virus) of the synthesized nucleosides are described.

Introduction

Nucleosides have played a major role in the treatment of viral infectious diseases such as human immunodeficiency virus, hepatitis B virus, and various herpes viruses infections. Recently, much attention has been focused on carbocyclic nucleosides, as a synthetic carbocyclic nucleoside such as abacavir[1] has been approved by the Food and Drug Administration as an anti-HIV agent. A carbocyclic nucleoside with an exocyclic double bond, entecavir,[2] is also currently undergoing phase III clinical trials for the treatment of chronic hepatitis B virus infection (Figure 1). Furthermore, carbocyclic nucleosides have recently been reported as antiviral agents against smallpox and monkeypox virus as well as West Nile virus,[3] which are related to bioterrorism-related organisms, and therapeutic agents against these organisms are critically needed as part of national biodefense strategies. In view of these interesting antiviral activities demonstrated by the carbocyclic nucleosides, an efficient preparative synthetic methodology for key intermediates is needed for additional exploration of this important class of compounds.

Previously, the synthesis of enantiomerically pure D- and L-aristeromycin[4] and neplanocin A[5] have been developed in our laboratory.[6] However, the overall availability of optically active carbocyclic nucleosides has been limited due to the lack of a methodology for a preparative-scale preparation of the key intermediate such as D-2-cyclopentenone. D- and L-2-cyclopentenone (**9** and **22**) have been previously prepared from D-ribose,[7] D-lyxose,[8] and D-isoascorbic acid[9] with low and inconsistent yields. Therefore, efficient and practical synthetic methodologies for optically pure D- and L-2-cyclopentenone are highly desirable. Recently, we reported preliminary results of an efficient and practical synthetic methodology of D- and L-2-cyclopentenone[10] as well as antiviral activities of several cyclopentenyl nucleosides as a communication.[3b] Among the synthesized nucleosides, adenine, cytosine, and 5-fluorocytosine analogues were found to be active against HIV, West Nile virus, and orthopox viruses including smallpox virus.[3] Additionally, Morrey et al. reported that 6-azauridine was found to be a potent antiviral agent against West Nile virus.[11] Therefore, herein we report the full accounts of further improved

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10.1021/jo034999v CCC: $25.00
Published on Web 10/23/2003

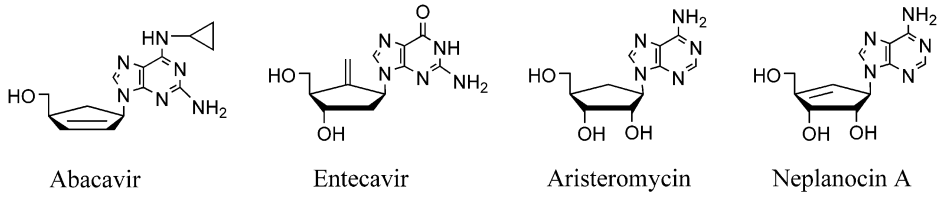
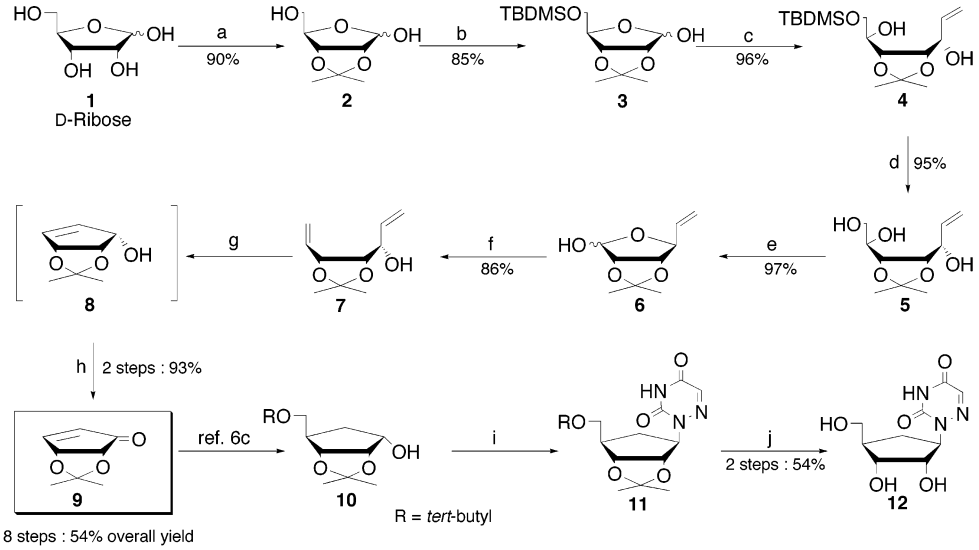


FIGURE 1. Biologically active carbocyclic nucleosides.

SCHEME 1. Synthesis of d-2-Cyclopentenone and D**-Cyclopentyl-6-azauridine**[a]



[a] Reagents and conditions: (a) 2,2-dimethoxypropane, *p*-toluenesulfonic acid, acetone, 0 °C to rt, 1 h; (b) TBDMSCl, imidazole, CH_2Cl_2, rt, 1 h; (c) vinylmagnesium bromide, anhydrous THF, −78 °C to rt, 1 h; (d) TBAF, THF, rt, 1 h; (e) $NaIO_4$, H_2O, rt,1 h; (f) NaH, DMSO, methyltriphenylphosphonium bromide, THF, 0 °C to reflux, 3 h; (g) Grubbs' catalyst, anhydrous CH_2Cl_2, 24 °C, 4 h; (h) pyridinium dichromate, 4 Å molecular sieves, AcOH, CH_2Cl_2, rt, 12 h; (i) 6-azauracil, PPh_3, DIAD, −78 °C to rt, 3 days; (j) 6 N HCl, MeOH, rt, 12 h.

preparative-scale synthesis for the D- and L-2-cyclopentenone (**9** and **22**) over the previously reported method[3b,10] as well as additional exploration of carbocyclic 5-halocyclopentenylpyrimidines and the 6-carbocyclic azauridine derivative as potential antiviral agents.

Results and Discussion

D-Ribose **1** was converted to the isopropylidene-protected derivative **2** with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid in 90% yield, followed by silylation of primarily the hydroxyl group using *tert*-butyldimethylsilyl chloride to give lactol **3** in 85% yield (Scheme 1). Compound **3** was reacted with vinylmagnesium bromide to obtain a ring-opened olefin **4** in quantitative yield as a single stereoisomer. The stereoselectivity is probably due to the steric as well as the electronic effect of the isopropylidene group, which prevents the coordination of vinylmagnesium bromide at the α site. To introduce another olefinic moiety, deprotection of the silyl group was accomplished by using a 1 M solution of TBAF in THF followed by an oxidative cleavage of the vicinal diol with sodium periodate to give a lactol **6** in 92% yield. The lactol **6** was subjected to the Wittig reaction using NaH, DMSO, and methyltriphenylphosphonium bromide to give a diene **7** in 86% yield.[9] The ring-closing metathesis reaction was carried out using Grubbs' catalyst to obtain D-cyclopentenol **8**. It was found that the metathesis reaction was affected by the reaction temperature. Although the diene **7** was converted to ring-closed cyclopentenol **8** at 17 °C with 1 mol % Grubbs' catalyst for 24 h, the reaction was completed within 4 h at 25 °C with the same amounts of catalyst. However, since the ring-closed cyclopentenol **8** was highly volatile, the desired key intermediate D-2-cyclopentenone **9** was directly obtained by oxidation of the secondary alcohol under PDC oxidation conditions without isolation of the cyclopentenol **8** in 54% overall yield from D-ribose. D-2-Cyclopentenone **9** can also be obtained from D-ribonolactone using the intramolecular Horner−Emmons reaction[7] as well as from D-isoascorbic acid using the ring-closing metathesis reaction.[9] However, these synthetic methods are problematic for a large-scale preparation due to extreme sensitivity to the reaction conditions as well as difficulties in controlling stereoselective oxidation and reduction steps, which lower the overall yields. In our synthetic methodology, most reaction conditions are mild and give excellent yields for the D-2-cyclopentenone **9** up to 10 g scale.

An efficient preparative methodology in hand, it was of interest to synthesize cyclopentyl-6-azauridine, in which D-2-cyclopentenone **9** was converted to an additional product **10** by our previously reported method.[6] As observed previously,[12] Mitsunobu reaction of pyrimidines is more difficult and problematic than that of purines, both in terms of protecting group strategies as well as *N*- vs *O*-alkylation. However, upon introduction of the third nitrogen into the pyrimidine ring, the acidity of its adjacent N^1 atom is greatly increased and thus

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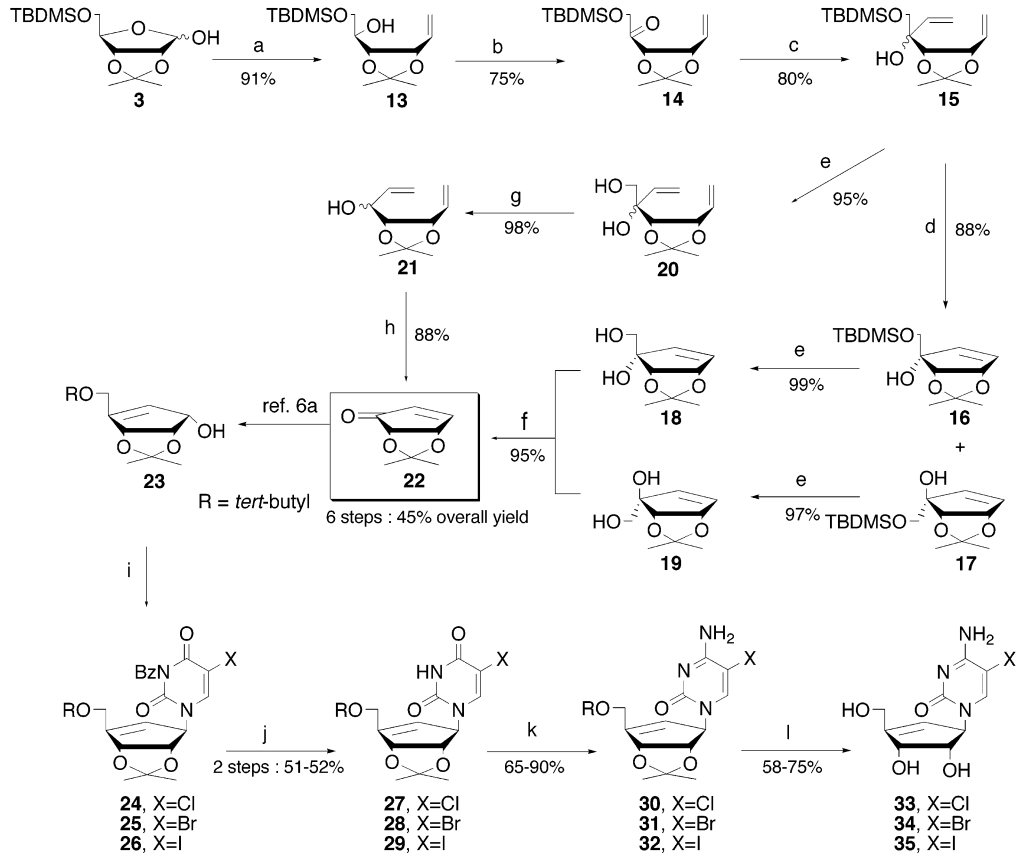
SCHEME 2. Synthesis of L-2-Cyclopentenone and D-Cyclopentenyl Nucleosides[a]



[a] Reagents and conditions: (a) NaH, DMSO, methyltriphenylphosphonium bromide, THF, 0 °C to reflux, 3 h; (b) dicyclohexyl carbodiimide, DMSO, pyridine, trifluoroacetic acid, toluene, rt, 4 h; (c) vinylmagnesium bromide, anhydrous THF, −78 °C to rt, 1 h; (d) 5% Grubbs' catalyst, anhydrous CH_2Cl_2, reflux, 24 h; (e) TBAF, THF, rt, 1 h; (f) $NaIO_4$, H_2O, rt, 0.5 h; (g) (i) $NaIO_4$, H_2O/CH_2Cl_2 (1:2), 0 °C to rt, 0.5 h, (ii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 0.5 h; (h) Grubbs' catalyst, anhydrous CH_2Cl_2, 24 °C, 4 h and then pyridinium dichromate, 4 Å molecular sieves, AcOH, CH_2Cl_2, rt, 12 h; (i) PPh_3, DEAD, N^3-benzoyl-5-chlorouracil (for **28**), N^3-benzoyl-5-bromouracil (for **29**), N^3-benzoyl-5-iodouracil (for **30**), rt, 17 h; (j) saturated NH_3 in MeOH, 0 °C, 4 h; (k) 2,4,6-triisopropylbenzenesulfonyl chloride, DMAP, Et_3N, MeCN, 0 °C to rt, 24 h then 30% NH_4OH, rt, 5 h; (l) CF_3CO_2H/H_2O (2:1), 50 °C, 3 h.

favorable to the regioselective N^1-substitution with respect to the N^3- or *O*-alkylation. This allows us to condense 6-azauracil with **10** to obtain the desired nucleoside **12** under the Mitsunobu conditions. The major problem in direct coupling of the sugar moiety **10** with 6-azauracil would be to discriminate N^1, N^3, and *O*-substituted products. We found that the best method for distinguishing these structures was ^{13}C NMR spectra. In the ^{13}C NMR spectrum of the carbocyclic 6-azauridine derivative **12**, C-1′ appeared at 57.39 (in MeOH-d_4), which was assigned to be the *N*-substituted rather than *O*-substituted product. It is noteworthy to mention that the chemical shift of the C-1′ resonance signal in the ^{13}C NMR spectrum (in DMSO-d_6) of 1-(2,3-dihydroxypropyl)-6-azauracil is at 53.63 ppm,[13] and the chemical shift of C-1′ resonance signal in the ^{13}C NMR (in $CDCl_3$) of *O*- alkylated derivatives of uracil and thymine are >67 ppm.[14] Evidence for the regioselectivity of N^1- instead of N^3-substituted compound was provided by the comparison of ^{13}C NMR data of compound **12** with that of 6-azauridine. The heterocyclic base peaks of **12** (157.4, 149.8, and 135.1 ppm) were similar to those of 6-azauridine (158.5, 149.5, and 137.3 ppm),[15] clearly indicating that it was the N^1-substituted compound. Furthermore, the UV spectrum of **12** (257.5 nm in pH 7) was similar to that of 6-azauridine (253 nm in pH 9).[16] The antiviral activity of synthesized β-D-cyclopentyl-6-azauridine **12** was evaluated against West Nile virus, but it did not show any significant antiviral activity against this virus.

To develop an efficient preparative synthetic method for L-2-cyclopentenone **22**, the protected D-ribose **3** was converted to an olefin **13** by the Wittig reaction using NaH, DMSO, and methyltriphenylphosphonium bromide in refluxing THF in 91% yield (Scheme 2). The oxidation of the secondary hydroxyl group of **13** was highly affected by the oxidation conditions.

Oxidation with pyridinium chlorochromate as an oxidizing agent provided ketone **14** in 53% yield. Although Swern oxidation with DMSO, oxalyl chloride, and triethylamine in dichloromethane gave ketone **14** in 70% yield, the yield was dramatically decreased to 15% in the large scale (10 g scale). However, a milder oxidation condition, Moffatt oxidation with dicyclohexyl carbodiimide, DMSO, pyridine, and trifluoroacetic acid in toluene, was successfully carried out to obtain ketone **14** in

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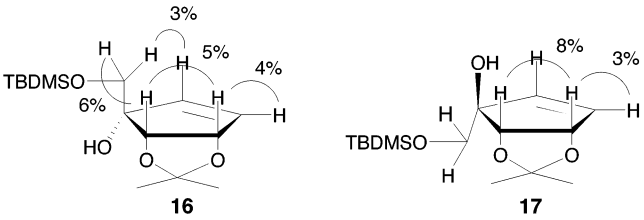


FIGURE 2. NOE relationships of **16** and **17.**

75% yield in a 30 g scale. A Grignard reaction was then performed on **14** to introduce another olefin with vinylmagnesium bromide in anhydrous THF to give an inseparable diastereomeric mixture of dienes **15** in 80% yield. The diene **15** was converted to a cyclopentene moiety by ring-closing metathesis reaction using 5% Grubbs catalyst at refluxing condition in anhydrous CH_2Cl_2 as a separable diastereomeric mixture of α and β cyclopentanol **16** and **17** (**16**/**17** ratio = 1/10) in 88% yield. The α and β isomers were assigned by ^{1}H NMR and NOE spectroscopy (Figure 2). We investigated the reaction with several other protecting groups to improve the ratio (**16**/**17**) without success.

Removal of the primary hydroxyl protecting group using 1 M solution of TBAF in THF gave diols **18** and **19**. Oxidative cleavage with sodium periodate afforded the L-2-cylopentenone **22** in 95% yield which served as the key intermediate for D-cyclopentenyl nucleosides. However, the ring-closing metathesis reaction for the synthesis of L-2-cyclopentenone **22** required harsh conditions in comparison to that of D-2-cycloentenone **9**, which might be due to the steric hindrance of the quaternary carbon adjacent to the vinyl group. An alternative route was developed to generate a diene alcohol **21** which was efficiently converted to the L-2-cycloentenone **22**. Deprotection of the silyl group using TBAF gave diol **20** in 95% yield. Oxidative cleavage of the vicinal diol using sodium periodate followed by reduction of ketone using sodium borohydride and cerium(III) chloride heptahydrate provided alcohol **21** in 98% yield. The L-2-cyclopentenone **22** was obtained from **21** by the same procedure for D-2-cyclopentenone **9**, giving 34% overall yield from D-ribose. D-Cyclopentenyl alcohol **23** was synthesized by the previously reported method from L-2-cycloentenone **22**.[6a] Coupling of **23** with the appropriate protected 5-halouracils was accomplished under the standard Mitsunobu coupling conditions using N^3-benzoyl-5-halouracils, DEAD, and Ph_3P in THF followed by removal of the benzoyl group using saturated methanolic ammonia. The conversion of uracil analogues to cytosine analogues was carried out by the treatment of 2,4,6-triisopropylbenzenesulfonyl chloride, DMAP, and NEt_3 in CH_3CN to give **30**−**32** in 65−90% yield. Deprotection of *tert*-butyl and isopropylidene groups was carried out with CF_3COOH/H_2O (2:1,v/v) solution at 50−60 °C to give β-D-cyclopetenyl-5-halocytosine nucleosides **33**−**35** in 58−75% yield.

The anti-orthopox virus activities of the synthesized β-D-cyclopetenyl-5-halocytosine nucleosides were evaluated, and the results are summarized in Table 1. β-D-Cyclopetenyl cytosine nucleoside **36**, which was previously synthesized in our laboratory, has been shown to have significant anti-orthopox virus activities.[3b]

It was found that β-D-cyclopentenyl-5-iodocytidine **35** showed significant anti-monkeypox virus, anti-cowpox virus, anti-smallpox virus, and anti-vaccinia virus activities. β-D-Cyclopentenyl-5-chlorocytidine **33** exhibited moderate anti-smallpox virus and anti-cowpox virus activities. However, β-D-cyclopentenyl-5-bromocytidine **34** did not display any significant antiviral activity against orthopox viruses.

In summary, we have developed an efficient and practical synthetic method for D- and L-2-cyclopentenone (**9** and **22**) as key intermediates for the synthesis of various carbocyclic nucleosides in a preparative scale (>10 g scale). From these intermediates we synthesized enantimerically pure D-cyclopentyl-6-azauridine and several D-cyclopentenyl-5-halo-cytidine nucleosides, which demonstrated interesting anti-orthopox virus activity.

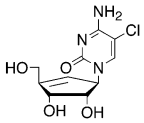
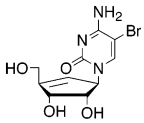
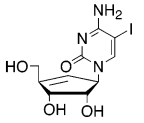
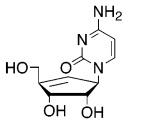
Experimental Section

(4*R*,5*S*)-(+)-1-[4-[2-(*tert*-Butyldimethylsilyloxy)-1-hydroxyethyl]-2,2-dimethyl-1,3-dioxolan-5-yl]-(*S*)-2-propen-1-ol (4). A solution of **3** (91 g 0.30 mol) in dry tetrahydrofuran (1000 mL) was cooled to −78 °C, and vinylmagnesium bromide (1 M solution in tetrahydrofuran, 890 mL, 0.89 mol) was added dropwise at −60 °C. After addition was completed, the reaction mixture was allowed to stir at room temperature for 1 h. Upon recooling the resulting clear brown mixture to −78 °C, saturated NH_4Cl solution (1000 mL) was added dropwise to quench and the resulting solution was extracted with EtOAc (1500 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1:20), giving compound **4** (94 g, 96%) as a colorless oil: $[\alpha]^{23}_D$ +6.86 (C 0.59, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (m, 2H), 5.43 (d, J = 17.2 Hz, 1H), 5.26 (d, J = 10.4 Hz, 1H), 4.35 (bs, OH, D_2O exchangeable, 1H), 4.31 (bs, 1H), 4.07 (m, 2H), 3.86 (m, 2H), 3.65 (dd, J = 6.7 and 9.9 Hz, 1H), 3.36 (bs, OH, D_2O exchangeable, 1H), 1.39 (s, 3H), 1.32 (s, 3H), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 115.9, 108.6, 80.6, 76.5, 69.6, 69.2, 64.1, 27.9, 25.7, 25.3, −5.5. Anal. Calcd for $C_{16}H_{32}O_5Si$: C, 57.79; H, 9.70. Found: C, 58.13; H, 9.80.

(4*R*,5*S*)-(−)-1-[4-(1,2-Dihydroxyethyl)-2,2-dimethyl-1,3-dioxolan-5-yl]-(*S*)-2-propen-1-ol (5). Tetrabutylammonium fluoride (1 M solution in tetrahydrofuran, 333 mL, 333 mmol) was added to a solution of **4 (**107 g, 322 mmol) in tetrahydrofuran (1000 mL) and stirred at room temperature for 1 h. The resulting brown mixture was concentrated in vacuo, and the residue was purified by column chromatography on a silica gel (EtOAc/hexane = 2:1), giving compound **5** (66 g, 95%) as a white crystal: mp 72.4−73.9 °C; $[\alpha]^{23}_D$ −31.33 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (m, 1H), 5.40 (dd, J = 0.8, 17.2 Hz, 1H), 5.31 (dd, J = 0.8, 10.5 Hz, 1H), 4.34 (t, J = 8.1 Hz, 1H), 4.16 (dd, J = 5.4, 9.4 Hz, 1H), 4.06 (dd, J = 5.4, 9.2 Hz, 1H), 3.95−3.87 (m, 1H D_2O exchangeable, 3H), 2.15 (bs, OH, D_2O exchangeable, 1H), 1.40 (s, 3H), 1.34(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 117.1, 80.0, 77.8, 69.3, 64.6, 28.0, 25.4. Anal. Calcd for $C_{10}H_{18}O_5$·0.03 hexane: C, 55.37; H, 8.41. Found: C, 55.60; H, 8.31.

(1*S*,2*S*,3*S*)-2,2-Dimethyl-6-vinyltetrahydrofuro[3,4-*d*]-1,3-dioxol-4-ol (6). A solution of triol **5** (38.9 g, 178.2 mmol) in H_2O (400 mL) was cooled to 0 °C, and $NaIO_4$ (57.2 g, 26.7 mmol) was added portionwise. After being stirred at room temperature for 1 h, the reaction mixture was extracted with EtOAc (500 mL × 3), and the extracts were dried over $MgSO_4$, filtered, and concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1:10), giving compound **6 (**32.4 g, 97%) as a colorless oil: ^{1}H NMR spectral data were identical to the literature;[9] ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 134.4, 117.3, 117.0, 114.3, 112.5, 103.0, 102.9, 96.2, 88.5, 86.6, 84.7, 80.5, 79.0, 26.4, 26.2, 25.0. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05 H, 7.58. Found: C, 58.38; H, 7.74.

TABLE 1. Anti-orthopox Virus Activity of β-D-Cyclopentenyl-5-halocytosine Nucleosides[a]

compd	Anti-orthopox Virus (EC_{50}, μg/mL)				
	VAR-BSH	VAR-7124	MPX	CPX	VAC
 **33**	22.8	>100	ND	21.1	>100
 **34**	100	>100	>100	100	>100
 **35**	10.4	>100	3.7	8.7	10.8
 **36**	0.03[3b]	0.08	0.1	0.06	0.12

[a] VAR-BSH (variola major strain Bangladesh 1975); VAR-7124 (variola major strain 7124); MPX (monkeypox strain Zaire); CPX (cowpox strain Brighton); VAC (vaccinia strain Copenhagen). ND: not determined.

(1*S*,2*S*,3*R*)-(−)-1-(2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-(*S*)-2-propen-1-ol (7). A suspension of NaH (9.9 g, 0.248 mol, 60% dispersion in mineral oil) in tetrahydrofuran (1000 mL) was cooled to 0 °C, and then DMSO (29.3 mL, 0.413 mol) was added. After being stirred at room temperature for 0.5 h, the resulting white suspension mixture was cooled to 0 °C and treated with methyltriphenylphosphonium bromide (88.6 g, 0.248 mol). The reaction mixture was stirred at room temperature for 1 h and then recooled to 0 °C. A solution of lactol **6** (30.8 g, 0.165 mol) in tetrahydrofuran (300 mL) was added to the resulting reaction mixture at 0 °C. After being heated at reflux for 3 h, the reaction mixture was cooled to room temperature. Diethyl ether (1000 mL) was added to the reaction mixture and washed with H_2O (500 mL) and brine (500 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1:10), giving compound **7** (26.2 g, 86%) as a colorless oil. All the spectral data were identical to the literature.[9]

(4*R*,5*R*)-(−)-4,5-*O*-Isopropylidene-2-cyclopentenone (9). To a 500 mL round-bottom flask filled with the Grubbs' catalyst (670 mg, 1 mol %, flushed with N_2 three times) was added a solution of the diene **7** (15.1 g, 81.3 mmol) in anhydrous CH_2Cl_2 (300 mL). After being stirred at 24 °C for 4 h, 4 Å molecular sieve (30 g), pyridinium dichromate (35.3 g, 162.1 mmol), and acetic acid (0.23 mL, 5 mol %) were added to the resulting dark brown mixture. The reaction mixture was stirred at the same temperature for 12 h and filtered over a silica gel pad (∼15 cm) with EtOAc. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on a silica gel (EtOAc/hexane = 1:10), giving compound **9** (11.4 g, 93%) as a white crystal: mp 68.5−70.3 °C; $[\alpha]^{23}_D$ −69.3 (*c* 0.60, $CHCl_3$) [lit.[9] mp 68.6−70.1 °C; $[\alpha]_D$ −70.4 (*c* 0.92, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 2.4, 6.0 Hz, 1H), 6.22 (d, *J* = 6.0 Hz, 1H), 5.28 (dd, *J* = 2.4, 5.6 Hz, 1H), 4.47 (d, *J* = 5.6 Hz, 1H), 1.42 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 134.6, 115.4, 78.6, 76.5, 27.4, 26.1. Anal. Calcd for C_{10} $H_{10}O_3$: C, 62,33; H, 6.54. Found: C, 62.15; H, 6.52.

(1′*R*,2′*S*,3′*R*,4′*R*)-1-[2,3-Dihdroxy-4-(hydroxymethyl)cyclopent-1-yl]-6-azauracil (12). 6-Azauracil (170 mg, 1.5 mmol) and alcohol **10** (245 mg, 1.0 mmol) were dried in vacuo for 3 h at 50 °C. Anhydrous THF (10 mL) was added and the mixture cooled to −78 °C. DIAD (0.5 mL, 2.5 mmol) was added dropwise to a solution of triphenylphosphine (660 mg, 2.5 mmol) in THF (15 mL) at 0 °C. The DIAD and Ph_3P complex was stirred for 10 min before being added to the mixture of 6-azauracil and cyclopentanol **10** at −78 °C. The reaction mixture was stirred at the same temperature for 1 h and allowed to reach room temperature. After being stirred for 3 days at room temperature, the clear amber solution was concentrated in vacuo and the residue was purified by column chromatography on a silica gel (EtOAc/hexane = 1:10), giving compound **11** which was contaminated by reduced DIAD and used in the next reaction without further purification. The crude compound **11** was dissolved in methanol (5 mL) and then added dropwise by 6 N hydrochloric acid (5 mL). After being stirred for 12 h at room temperature, the solvent was evaporated under diminished pressure and the residue was purified by column chromatography on a silica gel (CH_2Cl_2/MeOH = 20:1−10:1), giving carbocyclic 6-azauridine **12** (128 mg, 54%) as a white solid: mp 278−279 °C; $[\alpha]^{23}_D$ −3.26 (*c* 0.61, MeOH); UV (H_2O) λ_{max} 257.5 nm (3,459, pH 2), 257.5 nm (4,548, pH 7), 300 nm (3,110, pH 11); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.34 (s, 1H), 5.14−5.09 (m, 1H), 4.58 (t, *J* = 6.0 Hz, 1H), 4.04 (t, *J* = 6.0 Hz, 1H), 3.74−3.71 (m, 1H), 3.76−3.54 (m,1H), 2.15−2.12 (m,1H), 2.04−1.99 (m,1H), 1.89−1.82 (m, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 157.4, 149.8, 135.1, 72.5, 72.1, 63.6, 57.4, 45.9, 25.6; MS (ESI) *m*/*z* 242 (M^+ − 1), 266 (M^+ + Na), 282 ($M^{\bullet+}$ + K). Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28. Found: C, 44.56; H, 5.54; N, 17.18.

(4*R*,5*S*)-(−)-1-(2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-(*tert*-butyldimethylsilyloxy)-1(*R*)-ethan-1-ol (13). Compound **3** (62.1 g, 204 mmol) was converted to compound **13** (56.1 g, 91%) using the same procedure as for compound **7**: $[\alpha]^{23}_D$ −9.97 (*c* 0.39, MeOH); ^{1}H NMR spectral data were identical to the literature;[17] ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.2, 117.6, 108.7, 78.8, 77.4, 69.6, 64.3, 27.8, 25.4, 18.3, −5.4,

(17) RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7135.

−5.5. Anal. Calcd for $C_{15}H_{29}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.53; H, 10.04.

(4*R*,5*S*)-(−)-1-(2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-(*tert*-butyldimethylsilyloxy)ethan-1-one (14). To a solution of alcohol **13** (31.0 g, 0.10 mol), dicyclohexylcarbodiimide (42.0 g, 0.21 mol), DMSO (18.1 mL, 0.25 mol), and pyridine (17.2 mL, 0.10 mol) in toluene (500 mL) was added trifluoroacetic acid (8.3 mL, 0.10 mol) dropwise at 0 °C for 10 min. After being stirred at room temperature for 10 h, the resulting suspension mixture was filtered through a Celite pad. The filtrate was washed with H_2O, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on a silica gel (EtOAc/hexane = 1:30) to give a crude compound contaminated by reduced DCC which was dissolved in hexane. The precipitate was filtered off, and the filtrate was concentrated in vacuo. The residue was repurified by column chromatography on a silica gel (EtOAc/hexane = 1:30), giving ketone **14** (23.4 g, 75%): $[\alpha]^{23}_D$ −20.34 (*c* 0.70, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74−5.66 (m, 1H), 5.41 (d, J = 16.6 Hz, 1H), 5.24 (d, J = 10.5 Hz, 1H), 4.92−4.87 (m, 2H), 4.47 (d, J = 18.9 Hz, 1H), 4.22 (d, J = 18.9 Hz, 1H), 1.61 (s, 3H), 1.40 (s, 3H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 118.9, 81.9, 78.2, 68.6, 31.4, 27.0, 25.8, 24.9, 22.6, 13.7, −5.5. Anal. Calcd for $C_{15}H_{28}O_4Si$: C, 59.96; H, 9.39. Found: C, 59.92; H, 9.17.

(4*R*,5*S*)-1-(2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-1-(*tert*-butyldimethylsilyloxymethyl)-2-propen-1-ol (15). Compound **14** (20.1 g 67.1 mmol) was converted to inseparable diastereomers **15** (17.0 g, 80%) using the same procedure as for **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14−5.88 (m, 2H), 5.43−5.14 (m, 4H), 4.66 (t, J = 7.1 Hz, 0.9H), 4.54 (t, J = 6.6 Hz, 0.1H), 4.38 (d, J = 6.4 Hz, 0.1H), 4.29 (d, J = 6.9 Hz, 0.9H), 2.77 (s, OH, D_2O exchangeable, 0.9H), 2.51 (s, OH, D_2O exchangeable, 0.1H), 1.53 (s, 0.3H), 1.51 (s, 2.7H), 1.38 (s, 0.3H), 1.36 (s, 2.7H), 0.89 (s, 8.1H), 0.87 (s, 0.9H), 0.05 (s, 5.4H), 0.03 (s, 0.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 138.0, 135.7, 135.3, 117.6, 117.1, 115.8, 115.7, 108.2, 107.9, 79.3, 78.6, 78.3, 75.1, 76.7, 75.1, 74.8, 68.2, 68.0, 27.7, 27.3, 25.8, 25.8, 25.4, 24.9, 18.3, 18.2, −5.4, −5.5. Anal. Calcd for $C_{17}H_{32}O_4Si$: C, 62.15; H, 9.82. Found: C, 62.05; H, 9.76.

(1*R*,4*S*,5*S*)-(+)-4,5-*O*-Isopropylidene-1-(*tert*-butyldimethylsilyloxymethyl)-2-cyclopenten-1-ol (16) and Its Epimer (17). To a 500 mL round-bottom flask filled with Grubbs' catalyst (1.25 g, 5 mol %, flushed with N_2 three times) was added a solution of the diene **15** (10.0 g, 30.4 mmol) in anhydrous CH_2Cl_2 (300 mL). After being heated at reflux for 24 h, the resulting dark brown mixture was concentrated in vacuo and the residue was purified by column chromatography on a silica gel (EtOAc/hexane = 1:10) to give β-cyclopentenol **16** (7.3 g, 80%) and its α-epimer **17** (729 mg, 8%). Compound **16**: $[\alpha]^{23}_D$ +55.97 (*c* 0.37, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (d, J = 5.7 Hz, 1H), 5.74 (d, J = 5.7 Hz, 1H), 5.31 (d, J = 5.3 Hz, 1H), 4.47 (d, J = 5.4 Hz, 1H), 3.92 (d, J = 9.9 Hz, 1H), 3.62 (d, J = 9.9 Hz, 1H), 3.22 (s, OH, D_2O exchangeable, 1H), 1.38 (s, 3H), 1.32 (s, 3H), 0.92 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 135.2, 135.0, 112.1, 84.8, 84.7, 65.0, 27.5, 26.0, 25.9, 18.4, −5.4. Anal. Calcd for $C_{15}H_{29}O_4Si$: C, 59.96; H, 9.39. Found: C, 60.05; H, 9.48. Compound **17**: $[\alpha]^{24}_D$ +72.04 (*c* 0.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (d, J = 5.7 Hz, 1H), 5.66 (d, J = 5.7 Hz, 1H), 5.00 (d, J = 5.3 Hz, 1H), 4.47 (d, J = 5.2 Hz, 1H), 3.69 (ddd, J = 1.5, 9.7, 38.7 Hz, 2H), 3.12 (s, OH, D_2O exchangeable, 1H), 1.43 (s, 3H), 1.39 (s, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 133.2, 112.4, 84.1, 82.5, 80.8, 67.0, 27.9, 26.8, 25.8, −5.5. Anal. Calcd for $C_{15}H_{29}O_4Si$: C, 59.96; H, 9.39. Found: C, 60.10; H, 9.39.

(1*R*,4*S*,5*S*)-(+)-4,5-*O*-Isopropylidene-1-hydroxymethyl-2-cyclopenten-1-ol (18) and Its Epimer (19). α-Cyclopentenol **16** (5.0 g, 17.2 mmol) and β-cyclopentenol **17** (150 mg, 0.49 mmol) were converted to cyclopentenediol **18** (3.9 g, 99%) and **19** (90 mg, 97%), respectively, using the same procedure as for compound **5**. Compound **18**: mp 103−104 °C; $[\alpha]^{23}_D$ +104.12 (*c* 0.28, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (dd, J = 1.6, 5.8 Hz, 1H), 5.64 (d, J = 5.8 Hz, 1H), 5.25 (d, J = 5.8 Hz, 1H), 4.49 (d, J = 5.8 Hz, 1H), 3.84 (dd, J = 4.2, 11.4 Hz, 1H), 3.56 (dd, J = 8.7, 11.2 Hz, 1H), 2.89 (s, OH, D_2O exchangeable, 1H), 2.32 (dd, J = 4.7, 8.6 Hz, OH, D_2O exchangeable, 1H), 1.38 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 135.1, 112.9, 86.3, 84.4, 65.8, 27.1, 25.4. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.06; H, 7.61. Compound **19**: $[\alpha]^{23}_D$ +88.18 (C 0.27, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (dd, J = 1.7, 5.8 Hz, 1H), 5.72 (d, J = 5.8 Hz, 1H), 5.07 (d, J = 5.5 Hz, 1H), 4.61 (d, J = 5.6 Hz, 1H), 3.73 (d, J = 11.5 Hz, 1H), 3.31 (bs, OH, D_2O exchangeable, 1H), 3.26 (d, J = 11.5 Hz, 1H), 2.13 (bs, OH, D_2O exchangeable, 1H), 1.46 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 133.6, 112.8, 83.4, 82.6, 79.1, 66.4, 27.7, 26.5. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.10; H, 7.63.

(4*R*,5*S*)-1-(2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-1-(hydroxymethyl)-2-propen-1-ol (20). Compound **15** (28.5 g, 86.7 mol) was converted to diastereomers **20** (17.6 g, 95%) as a colorless oil using the same procedure as for compound **5**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.17−6.10 (m, 2H), 5.86−5.80 (m, 0.3H), 5.47−5.20 (m, 5.2H), 4.70 (t, J = 6.0 Hz, 1H), 4.62 (t, J = 5.6 Hz, 0.3H), 4.32 (t, J = 5.6 Hz, 1H), 3.76 (d, J = 9.2 Hz, 0.3H), 3.69 (d, J = 8.8 Hz, 1H), 3.45 (d, J = 8.4 Hz, 1H), 2.88 (s, OH, D_2O exchangeable, 0.2H), 2.59 (s, OH, D_2O exchangeable, 1H), 2.25 (s, OH, D_2O exchangeable, 1H), 1.53 (s, 3H), 1.39(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 137.6, 135.5, 135.1, 119.5, 118.5, 117.1, 116.8, 108.8, 108.7, 81.7, 79.6, 79.4, 76.2, 75.3, 69.2, 67.6, 27.6, 27.3, 25.5, 25.0. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.37; H, 8.67.

(4*R*,5*S*)-1-(2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-propen-1-ol (21). To a solution of diol **20** (13.4 g, 63.1 mmol) in CH_2Cl_2 (200 mL) and H_2O (100 mL) was added $NaIO_4$ (16.2 g, 75.8 mmol) at 0 °C and the mixture stirred at room temperature for 35 min. The organic phase was separated, and the water phase was extracted with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. After the residue was dissolved in MeOH (200 mL) and cooled to 0 °C, $CeCl_3{\cdot}7H_2O$ (19.0 g, 51.0 mmol) was added and stirred at 0 °C for 10 min. Sodium borohydride (2.38 g, 63.1 mmol) was then added portionwise. The reaction was stirred at 0 °C for 30 min, and a solution of (EtOAc/hexane = 1:1) was added. After filtering off the precipitate, the filtrate was concentrated in vacuo. The residue was purified by column chromatography on a silica gel (EtOAc/hexane = 10:1) to give alcohol **21** (11.4 g, 98%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04−6.00 (m, 1H), 5.88−5.82 (m, 1H), 5.41−5.23 (m, 4H), 4.63−4.60 (m, 1H), 4.14−4.08 (m, 2H), 2.38−2.36 (m, OH, D_2O exchangeable, 1H), 1.55 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 134.1, 119.7, 117.3, 109.0, 80.8, 79.2, 70.8, 27.6, 25.2. Anal. Calcd for $C_{10}H_{16}O_3{\cdot}0.15CH_2Cl_2$: C, 61.89; H, 8.34. Found: C, 61.83; H, 8.41.

(4*S*,5*S*)-(+)-4,5-*O*-Isopropylidene-2-cyclopentenone (22). Compound **21** (11.4 g, 61.8 mmol) was converted to compound **22** (8.3 g, 88%) using the same procedure as for compound **9**: mp 68.1−69.4 °C; $[\alpha]^{23}_D$ +69.1 (*c* 0.77, $CHCl_3$) [lit.[9] mp 68.7−69.8 °C; $[\alpha]_D$ +69.1 (*c* 1.98, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 2.0, 5.8 Hz, 1H), 6.17 (d, J = 5.9 Hz, 1H), 5.23 (dd, J = 2.3, 5.4 Hz, 1H), 4.42 (d, J = 5.4 Hz, 1H), 1.37 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 134.6, 115.4, 78.6, 76.5, 27.4, 26.1. Anal. Calcd for C_{10} $H_{10}O_3$: C, 62,33; H, 6.54. Found: C, 62.20; H, 6.48.

(1′*S*,2′*R*,3′*S*)-(−)-1-[2,3-(Isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-5-chlorouracil (27). To a solution of N^3-benzoyl-5-chlorouracil (0.75 g, 3.18 mmol), Ph_3P (1.06 g, 4.22 mmol), and **23** (0.51 g, 2.12 mmol) in anhydrous THF was added a solution of diethylazodicarboxylate (0.73 g, 4.22 mmol) in anhydrous THF at 0 °C under N_2 atmosphere. The mixture was stirred for 15 h at room temperature, and solvent was removed in vacuo. The resulting residue was purified by column chromatography on silica gel

(EtOAc/hexane = 1:4) to give **24** (0.92 g) as a crude white solid which was used in the next reaction without further purification. The crude **24** (0.92 g) was dissolved in saturated methanolic ammonia solution (20 mL) at 5 °C and stirred for 3 h at room temperature. The solvent was evaporated under vacuum, and the residue was purified by column chromatography on a silica gel (EtOAc/hexane = 1:1), giving compound **27** (397 mg, 51%) as a white solid: mp 170−172 °C; $[\alpha]^{24}_D$ −55.27 (*c* 0.57, $CHCl_3$); UV (MeOH) λ_{max} 280 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (br s, 1H), 7.44 (s, 1H), 5.78 (s, 1H), 5.62 (s, 1H), 5.38 (d, J = 5.76 Hz, 1H), 4.74 (d, J = 5.81 Hz, 1H), 4.32 (dd, J = 7.48 Hz, J = 15.04 Hz, 2H), 1.57 (s, 3H), 1.50 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 153.0, 149.5, 138.0, 120.9, 112.8, 108.9, 84.4, 83.4, 74.0, 68.0, 58.9, 27.4, 27.2, 25.7; MS *m*/*z* 371 (M + 1), 373 (M + 3). Anal. Calcd for $C_{17}H_{23}ClN_2O_5$: C, 55.06; H, 6.25; N, 7.55. Found: C, 55.06; H, 6.26; N, 7.51.

(1′*S*,2′*R*,3′*S*)-(−)-1-[2,3-(Isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-5-bromouracil (28). Compound **28** was prepared using the same procedure as for compound **27**: yield 52%; mp 196−198 °C; $[\alpha]^{23}_D$ −54.60 (*c* 0.88, $CHCl_3$); UV (MeOH) λ_{max} 282 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (br s, 1H), 7.28 (s, 1H), 5.59 (s, 1H), 5.42 (s, 1H), 5.19 (d, J = 5.78 Hz, 1H), 4.55 (d, J = 5.82 Hz, 1H), 4.14 (dd, J = 16.12 Hz, J = 21.68 Hz, 2H), 1.43 (s, 3H), 1.34 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 153.3, 150.3, 141.0, 121.3, 113.2, 97.0, 84.8, 83.8, 77.1, 74.4, 59.3, 30.7, 27.8, 27.6, 26.2; MS *m*/*z* 415 (M + 1), 417 (M + 3). Anal. Calcd for $C_{17}H_{23}BrN_2O_5$: C, 49.17; H, 5.58; N, 6.75. Found: C, 49.59; H, 5.79; N, 6.52.

(1′*S*,2′*R*,3′*S*)-(−)-1-[2,3-(Isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-5-iodoracil (29). Compound **29** was prepared using the same procedure as for compound **27**: yield 52%; mp 198−200 °C; $[\alpha]^{23}_D$ −86.87 (*c* 0.57, MeOH); UV (MeOH) λ_{max} 289 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (br s, 1H), 7.37 (s, 1H), 5.59 (s, 1H), 5.39 (s, 1H), 5.21 (d, J = 5.74 Hz, 1H), 4.56 (d, J = 5.81 Hz, 1H), 4.14 (dd, J = 15.44 Hz, J = 21.44 Hz, 2H), 1.41 (s, 3H), 1.35 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 153.2, 150.6, 146.1, 121.4, 113.2, 108.8, 84.4, 83.84, 74.4, 68.5, 59.3, 27.8, 27.6, 26.2; MS *m*/*z* 463 (M + 1). Anal. Calcd for $C_{17}H_{23}IN_2O_5$: C, 44.17; H, 5.01; N, 6.06. Found: C, 44.21; H, 5.12; N, 5.97.

(1′*S*,2′*R*,3′*S*)-(−)-1-[2,3-(Isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-5-chlorocytosine (30). A mixture of **27** (0.21 g, 5.61 mmol), 2,2-(dimethylamino)pyridine (0.14 g, 1.12 mmol), triethylamine (0.17 mL, 1.68 mmol), and 2,4,6-triisopropylbenzenesulfonyl chloride (0.51 g, 1.68 mmol) in anhydrous CH_3CN (15 mL) was stirred at room temperature for 36 h. After an addition of 28% NH_4OH (15 mL), the mixture was stirred at room temperature for 5 h. Solvent was coevaporated with ethanol under reduced pressure. The residue was purified by column chromatography on silica gel (MeOH/CH_2Cl_2 = 3:100) to give **30** (0.13 g, 65%) as a white solid: mp 178−180 °C; $[\alpha]^{23}_D$ −38.37 (*c* 0.54, $CHCl_3$); UV (MeOH) λ_{max} 290 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 1H), 5.58 (s, 1H), 5.41 (s, 1H), 5.14 (d, J = 5.69 Hz, 1H), 4.52 (d, J = 5.78 Hz, 1H), 4.12 (dd, J = 15.01 Hz, J = 23.02 Hz, 2H), 1.41 (s, 3H), 1.31 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 154.7, 152.2, 139.9, 121.5, 112.4, 99.8, 84.5, 83.4, 73.8, 68.7, 58.9, 27.4, 25.8; HRMS-ESI calcd for $C_{17}H_{24}ClN_3O_4$ 369.1455, found 370.1538 (M + 1). Anal. Calcd for $C_{17}H_{24}ClN_3O_4 \cdot 0.2H_2O$: C, 54.68; H, 6.59; N, 11.24. Found: C, 54.64; H, 6.55; N, 10.94.

(1′*S*,2′*R*,3′*S*)-(−)-1-[2,3-(Isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-5-bromocytosine (31). Compound **31** was prepared using the same procedure as for compound **30**: yield 90%; mp 194−196 °C; $[\alpha]^{22}_D$ −62.63 (*c* 0.56, MeOH); UV (MeOH) λ_{max} 291 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 5.59 (s, 1H), 5.43 (s, 1H), 5.16 (d, J = 5.70 Hz, 1H), 4.55 (d, J = 5.78 Hz, 1H), 4.14 (dd, J = 15.10 Hz, J = 23.00 Hz, 2H), 1.42 (s, 3H), 1.31 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 155.0, 152.0, 142.3, 121.5, 112.3, 87.1, 84.5, 83.3, 73.8, 68.9, 58.9, 29.6, 27.4, 27.2, 25.8; HRMS-ESI calcd for $C_{17}H_{24}BrN_3O_4$ 413.0950, found 414.1026 (M + 1). Anal. Calcd for $C_{17}H_{24}BrN_3O_4 \cdot 0.4$hexane: C, 51.92; H, 6.65; N, 9.36. Found: C, 52.02; H, 6.45; N, 9.07.

(1′*S*,2′*R*,3′*S*)-(−)-1-[2,3-(Isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-5-iodocytosine (32). Compound **32** was prepared using the same procedure as for compound **30**: yield 65%; mp 200−202 °C; $[\alpha]^{25}_D$ −82.24 (*c* 0.46, MeOH); UV (MeOH) λ_{max} 296 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 5.59 (s, 1H), 5.47 (s, 1H), 5.16 (d, J = 5.71 Hz, 1H), 4.54 (d, J = 5.75 Hz, 1H), 4.13 (dd, J = 15.17 Hz, J = 22.50 Hz, 2H), 1.42 (s, 3H), 1.32 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 152.5, 148.4, 122.0, 112.8, 85.0, 83.8, 74.3, 69.4, 59.9, 28.9, 27.7, 26.2; MS *m*/*z* 462 (M + 1). Anal. Calcd for $C_{17}H_{24}IN_3O_4$: C, 44.26; H, 5.24; N, 9.11. Found: C, 44.35; H, 5.37; N, 8.93.

(1′*S*,2′*R*,3′*S*)-(−)-1-(2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl)-5-chlorocytosine (33). Compound **30** (0.15 g, 0.42 mmol) was dissolved in 30 mL of CF_3COOH/H_2O (2:1, v/v) and heated at 50 °C for 5 h. The solvent was removed under vacuum, and the residue was coevaporated twice with ethanol (20 mL) under vacuum. The resulting residue was purified by column chromatography on silica gel (MeOH/CH_2Cl_2 = 1:5), giving compound **34** (90 mg, 75%) as a white solid (recrytallized from MeOH and diethyl ether): mp 194−196 °C; $[\alpha]^{25}_D$ −96.40 (*c* 0.13, MeOH); UV (H_2O) λ_{max} 299.5 nm (ϵ 12 106, pH 2), 289.0 nm (ϵ 8143, pH 7.4), 290.0 nm (ϵ 7504, pH 11); ^{1}H NMR (400 MHz, MeOH-d_4) δ 5.70 (s, 1H), 5.47 (bs, 1H), 4.53 (d, J = 5.26 Hz, 1H), 4.27 (dd, J = 15.27, 17.72 Hz, 2H), 4.05 (t, J = 5.59 Hz, 1H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 163.7, 152.7, 142.4, 125.9, 102.6, 79.0, 74.6, 69.9, 60.7; MS *m*/*z* 274 (M + 1), 276 (M + 3). Anal. Calcd for $C_{10}H_{12}ClN_3O_4$: C, 43.89; H, 4.42; N, 15.35; Found: C, 43.81; H, 4.51; N, 15.18.

(1′*S*,2′*R*,3′*S*)-(−)-1-(2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl)-5-bromocytosine (34). Compound **34** was prepared using the same procedure as for compound **33**: yield 58%; mp 236−238 °C; $[\alpha]^{28}_D$ −116.27 (*c* 0.49, H_2O); UV (H_2O) λ_{max} 303 nm (ϵ 11 949, pH 2), 291.0 nm (ϵ 9711, pH 7.4), 291.0 nm (ϵ 9658, pH 11); ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.62 (s, 1H), 5.49 (s, 1H), 5.32 (br s, 1H), 4.31 (d, J = 5.64 Hz, 1H), 4.03 (dd, J = 15.20, 17.62 Hz, 2H), 3.89 (t, J = 5.31 Hz, 1H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 162.2, 156.1, 152.1, 143.5, 124.1, 75.3, 72.2, 67.2, 59.0; MS *m*/*z* 318 (M + 1), 320 (M + 3). Anal. Calcd for $C_{10}H_{12}BrN_3O_4$: C, 37.75; H, 3.80; N, 13.21; Found: C, 37.63; H, 3.95; N, 12.97.

(1′*S*,2′*R*,3′*S*)-(−)-1-(2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl)-5-iodocytosine (35). Compound **35** was prepared using the same procedure as for compound **33**: yield 63%; mp 210−212 °C; $[\alpha]^{29}_D$ −127.90 (*c* 0.46, H_2O); UV (H_2O) λ_{max} 312.0 nm (ϵ 14 318, pH 2), 295.5 nm (ϵ 7576, pH 7.4), 297.0 nm (ϵ 8739, pH 11); ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ 7.63 (s, 1H), 5.48 (s, 1H), 5.31 (br s, 1H), 4.30 (d, J = 5.56 Hz, 1H), 4.04 (dd, J = 15.27 Hz, J = 17.72 Hz, 2H), 3.87 (t, J = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6 + D_2O) δ 167.8, 159.5, 155.1, 152.8, 128.3, 81.1, 76.5, 71.1, 62.9, 60.6; HRMS-ESI calcd for $C_{10}H_{11}IN_3O_4$ 364.9873, found 365.9960 (M + 1). Anal. Calcd for $C_{10}H_{12}IN_3O_4$: C, 32.89; H, 3.31; N, 11.51. Found: C, 33.14; H, 3.34; N, 11.27.

Acknowledgment. This research was supported by grants from the National Institute of Allergy and Infectious Diseases (U19 AI 56540, UO1 AI 48495).

Supporting Information Available: Experimental general methods, detailed experimental procedures for compounds **2** and **3**, and spectroscopic data (^{1}H and ^{13}C NMR) for compounds **9**, **12**, **22**, and **33**−**35**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034999V