JOC*Note*

An Efficient Synthesis of Novel Carbocyclic Nucleosides with Use of Ring-Closing Metathesis from D-Lactose

Joon Hee Hong,* Myung Jung Shim,† Bong Oh Ro,† and Ok Hyun Ko

College of Pharmacy and College of Education, Chosun University, Kwangju 501-759, South Korea

hongjh@mail.chosun.ac.kr

Received April 10, 2002

Abstract: This paper describes an efficient synthetic route for various types of novel carbocyclic nucleosides. The required stereochemistry of the targeted nucleosides was successfully obtained with use of Grubbs cyclization and Trost allylic alkylation from the carbohydrate chiral template "D-lactose".

The resistance of a glycoside bond to the enzymatic hydrolysis catalyzed by nucleoside phosphorylase[1] is one of the critical points in nucleoside antiviral chemotherapy. To avoid such enzymatic degradation as well as to improve the antiviral activity, a large number of structural modifications on both the sugar and the heterocycle moiety of the nucleosides have been carried out. One strategy has been to replace the oxygen of the furanose ring by a methylene group, which gives rise to carbocyclic nucleosides.[2] Although these two classes of rings are far from identical, the cyclopentene or cyclopentane ring allows carbocyclic nucleosides to be recognized as either substrates or inhibitors of various enzymes.[3] Although some of the synthesized carbocyclic nucleosides display significant antiviral activity, a perpetual structure−activity relationship study should be undertaken to find novel antiviral agents.

Recently, a great deal of attention has been paid to 4′-substituted nucleosides as potent antiviral agents such as 4′-cyanothymidine,[4] 4′-azidothymidine, and 4′-methoxynucleoside.[5] However, only a few examples of 4′-substituted nucleosides of a defined absolute stereochemistry have been reported in the literature. The dearth of 4′-substituted nucleoside examples may be due to the synthetic difficulties in obtaining the necessary tertiary carbon center. Therefore, it is important to develop an efficient methodology for synthesizing a furanosyl or cyclopentane ring containing stereochemically defined tertiary carbons.[6]

On the basis of these interesting observations, and as a part of our ongoing drug discovery programs, novel 4′-hydroxy carbocyclic nucleosides were designed from inexpensive and commercially available D-lactose, which can combine the chemical and biological properties of the 4′-substituted furanose nucleosides and the enzyme-resistant carbocyclic nucleosides.

In this context, a synthetic route for various types of novel 4′-hydroxy-substituted carbocyclic nucleosides with use of a sequential Grubbs' ring closing metathesis (RCM) and an allylic alkylation reaction is described.

As shown in Scheme 1, it is envisaged that a ring-closing metathesis (RCM) of a divinyl derivative **6** could provide a desired key intermediate **8**, which is a direct precursor of the targeted nucleosides. The acid derivative **1** was readily synthesized from D-lactose in five steps by a well-known procedure.[7] Acid **1** was transformed to a Weinreb amide **2** by treating DCC and a DMAP coupling reagent in 88% yield.[8] A direct conversion of the amide **2** to an α,β-unsaturated carbonyl derivative **3** was found to be a low-yielding reaction under the usual conditions (CH_2=CHMgBr, THF, −78 °C) (4−10% yield). The repeated failure of the direct vinylation of **2** resulted in the search for an alternative route for the formation of the desired intermediate **8**, which eventually requires the same number of reaction steps.

Treating **2** with an equimolar amount of $LiAlH_4$ (1.0 M in THF solution) at −78 °C yielded the aldehyde **5** in 82% yield, which was then subjected to carbonyl addition by vinyl-magnesium bromide to furnish product **6** as an inseparable 1:1 diastereomeric mixture in 96% yield. Without separation, a direct cyclization of **6** to cyclopentenol was found to be a high-yielding reaction under the usual Grubbs RCM[9] condition with $Cl_2(Cy_3P)_2RuCHC_6H_5$ as the cyclization catalyst, which was readily separated by silica gel column chromatography to give **7*β*** and **7α** in 48% and 49% yield, respectively. The stereochemistry of **7*β*** and **7α** was unequivocally determined based on 1D and 2D NMR studies.

Cyclopentenol **7*β*** was treated with ethyl chloroformate in pyridine with a catalytic amount of DMAP to furnish the activated key intermediate **8** in a 80% yield, which is ready for condensation with nucleoside bases (adenine, cytosine). To synthesize the adenine and cytosine nucleosides, intermediate **8** was subjected to the Trost coupling conditions.[10]

* Address correspondence to this author at the College of Pharmacy. Phone: 82-62-230-6378. Fax: 82-62-222-5414.

† College of Education.

(1) (a) Razaka, G.; Drouillet, F.; Herdwijn, P.; De Clercq, E. *Nucleic Acid Res*. **1984**, *12*, 2081. (b) Herdewjn. P.; De Clercq, E.; Balzarini, J.; Vanderhaeghe, H. *J. Med. Chem*. **1995**, *28*, 50.

(2) (a) Bricaud, H.; Herdewjn, P.; De Clercq, E. *Biochem. Biopharmacol*. **1983**, 3583. (b) Cookson, R.; Dudfield, P.; Newton, R. *Eur. J. Med. Chim. Ther*. **1985**, *20*, 375.

(3) (a) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571. (b) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611. (c) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229.

(4) O'Yang, C.; Wu, H. Y.; Fraser-Smith, E. B.; Walker, K. A. M. *Tetrahedron Lett*. **1992**, *33*, 37.

(5) Maag, H.; Rydzewski, R. M.; McRoberts, M. J.; Crowford-Ruth, D.; Verheyden, J. P. H.; Prisbe, E. J. *J. Med. Chem*. **1992**, *35*, 1440.

(6) Previously, we have reported synthetic methods of tertiary fluoro- or methyl-substituted nucleosides: (a) Hong, J. H.; Lee, K.; Choi, Y.; Chu, C. K. *Tetrahedron Lett*. **1998**, *39*, 3443. (b) Hong, J. H.; Gao, M. Y.; Chu, C. K. *Tetrahedron Lett*. **1999**, *40*, 231. (c) Hong, J. H.; Gao, M. Y.; Choi, Y.; Cheng, Y.-C.; Schinazi, R. F.; Chu, C. K. *Carbohydr. Res*. **2000**, *328*, 37.

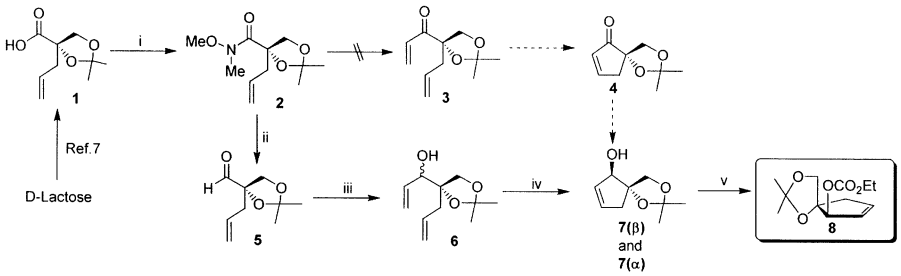
(7) (a) Whistle, R. L.; BeMiller, J. N. *Methods in Carbohydrate Chemistry*; Academic Press: New York, 1963; Vol. II, p 477. (b) Bennani, F.; Florent, J.-C.; Koch, M.; Monneret, C. *Tetrahedron* **1984**, *40*, 4669. (c) Florent, J. C.; Ughetto-Monfrin, J.; Monneret, C. *J. Org. Chem*. **1987**, *52*, 1051. (d) Monneret, C.; Florent, J.-C. *Synlett* **1994**, 305 and references therein.

(8) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett*. **1981**, *22*, 3815.

(9) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Philips, A, J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75. (c) Furstner, A. *Angew. Chem., Int. Ed*. **2000**, *38*, 3012. (d) Seepersaud, M.; Al-Abed, Y. *Tetrahedron Lett*. **2000**, *41*, 7801. (e) Gillaizeau, I.; Charamon, S.; Agrofoglio, L. A. *Tetrahedron Lett*. **2001**, *42*, 8817.

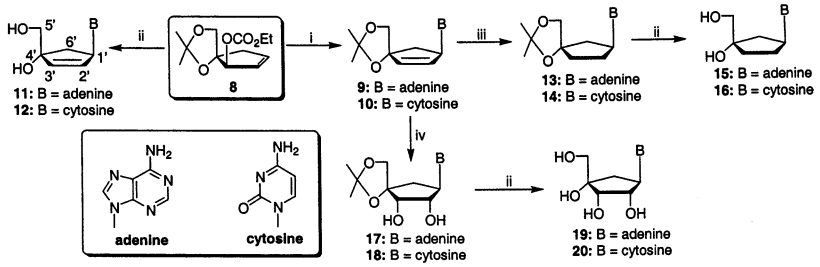
10.1021/jo0202536 CCC: $22.00 © 2002 American Chemical Society
Published on Web 08/20/2002

SCHEME 1[a]



[a] Reagents: (i) *N*,*O*-dihydroxymethylamine hydrochloride, DDC, DMAP, CH_2Cl_2, rt, overnight, 88%; (ii) 1.0 M $LiAlH_4$ in THF, THF, −78 °C, 1 h, 82%; (iii) CH_2=CHMgBr, THF, −78 °C, 1 h, 96%; (iv) $Cl_2(Cy_3P)_2RuCHC_6H_5$, benzene, reflux, 1 h, 97%; (v) $ClCO_2Et$, pyridine, DMAP, rt, overnight, 80%.

SCHEME 2[a]



[a] Reagents: (i) adenine, $Pd_2(dba)_3$·$CHCl_3$, P(*O*-i-Pr)$_3$, NaH, THF/DMSO, reflux, overnight, 55-67%; (ii) 80% AcOH, 80 °C, 8 h, 60−80%; (iii) 10% Pd/C, *n*-butylamine, H_2, EtOH, rt, 20 psi, 3 h, 80−90%; (iv) OsO_4, NMO, acetone/H_2O 5/1, 50 °C, overnight, 76−81%.

[$Pd_2(dba)_3$·$CHCl_3$, P(O-*i*-Pr)$_3$, NaH, THF/DMSO] to give the protected nucleosides **9** and **10** in a high regio- and stereoselective manner with a small amount of its regioisomer (<4%) (Scheme 2). The 2′,3′-dideoxy-4′-hydroxy-carbocyclic nucleosides **11** and **12** were successfully synthesized by an acidic hydrolysis (80% AcOH, 80 °C) of **9** and **10**, respectively, in 60−80% yield. The saturated adenine and cytosine carbocyclic nucleosides **15** and **16** could be readily synthesized from **9** and **10**. On the other hand, the protected nucleosides **9** and **10** were subjected to catalytic hydrogenation conditions (H_2, 10% Pd/C, *n*-butylamine, EtOH) and subsequent acidic hydrolysis to give 2′,3′-dideoxy-2′,3′-didehydro-4′-hydroxy-carbocyclic nucleosides **15** and **16** in 56−64% yield for the two steps, respectively. To synthesize the 2′,3′-dihydroxy nucleosides **19** and **20**, the protected nucleosides **9** and **10** were subjected to a catalytic amount of OsO_4 and 2 M NMO to give the dihydroxylated **17** and **18** as the only reaction products. It is noteworthy that an unexpected higher stereoselectivity was observed in this study than what was reported previously.[11] These stereochemical outcomes suggested that the cyclic isopropylidene groups of **17** and **18** reinforce the steric hindrance of the β-faces. As shown in Figure 1, the stereochemistry of **17** was unambiguously assigned on the basis of the NOE correlations between the proximal hydrogens (H-2′, H-3′ vs H-8) and (H-5′, H-5″ vs H-8), and the structure of **18** was also similarly determined. The isopropylidene protecting groups of **17** and **18** were subsequently hydrolyzed to the

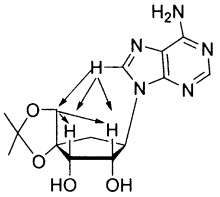


FIGURE 1. NOE correlations between proximal H's of **17**.

2′,3′,4′,5′-tetrahydroxy-carbocyclic nucleosides **19** and **20**, which are, to our best knowledge, the first nucleosides containing four contagious hydroxyl groups. The antiviral activities of the newly synthesized compounds **11**, **12**, **15**, **16**, **19**, and **20** were evaluated against the HBV. However, none showed any significant antiviral activity up to 100 μM.

In summary, a short and concise synthetic route was developed for various types of novel 4′-hydroxy-carbocyclic nucleosides starting from a carboxyl derivative **1**. The required stereochemistry of the desired nucleosides was successfully controlled by Grubbs' cyclization and palladium-catalyzed allylic alkylation. This efficient synthetic method for a stereochemically defined tertiary carbon could be potentially applicable to the synthesis of various types of geminally substituted nucleosides. In addition, it should be noted that all the final nucleosides are novel compounds except **11**.[12]

Experimental Section

All chemicals were reagent grade and used as purchased. All moisture-sensitive reactions were performed under an inert atmosphere of N_2 or Ar with distilled dry solvents. The optical rotations were measured on an Autopol-IV digital polarimeter. The elemental analyses were performed in the Korea Basic Science Institute, Korea. TLC was performed on Uniplates (silica gel) purchased from Analtech Co.

(10) (a) Crimmins, M. T.; King, B. W. *J. Org. Chem*. **1996**, *61*, 4192. (b) Trost, B. M.; Madsen, R.; Guile, S. G.; Elia, A. E. H. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1569. (c) Trost, B. M.; Kuo, G. H.; Benneche, T. *J. Am. Chem. Soc*. **1998**, *110*, 621. (d) Crimmins, M. T.; King, B. W.; Zuerch, W. J.; Choy, A. L. *J. Org. Chem*. **2000**, *65*, 8499.

(11) (a) Brown, B.; Hegedus, L. S. *J. Org. Chem*. **2000**, *65*, 1865. (b) Burlina, F.; Favre, A.; Fourrey, J.-L.; Thomas, M. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 247.

(12) Gurjar, M. K.; Maheswar, K. *J. Org. Chem*. **2001**, *66*, 7552.

(2*S*)-*N*-Methoxy-*N*-methyl-2-hydroxy-2-(hydroxymethyl)-2,2-(*O*-isopropylidene)pentenamide (2). Acid derivative **1** (20 g, 107.4 mmol) was dissolved in anhydrous CH_2Cl_2 (300 mL). *N*,*O*-Dimethylhydroxylamine hydrochloride (12.5 g, 128.9 mmol), DMAP (1.3 g, 10.7 mmol), and triethylamine (17.9 mL, 128.9 mmol) were then added to the reaction mixture. The solution was stirred overnight at room temperature, and both methanol (20 mL) and acetic acid (20 mL) were then added to the reaction mixture. The mixture was stirred for 1 h and neutralized with a saturated aqueous $NaHCO_3$ solution. The resulting solid was filtered off through a short pad of Celite and the filtrate was concentrated in a vacuum. The resulting residue was purified by silica gel column chromatography (EtOAc/hexane, 1:1) to give amide **2** (21.6 g, 88%) as a colorless oil. $[\alpha]^{25}_D$ −18.29° (*c* 3.77, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.82−5.68 (m, 1H), 5.14 (s, 1H), 5.11 (d, J = 6.0 Hz, 1H), 4.50 (d, J = 8.7 Hz, 1H), 3.93 (d, J = 8.7 Hz, 1H), 3. 73 (s, 3H), 3.26 (s, 1H), 2.61 (d, J = 7.2 Hz, 2H), 1.44 (s, 3H), 1.35 (s, 3H);^{13}C NMR ($CDCl_3$, 75 MHz) δ 131.88, 118.93, 110.35, 84.64, 70.49, 60.77, 40.79, 26.57, 25.34; Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.58; H, 8.47; N, 5.99.

(2*S*)-2-Hydroxy-2-(hydroxymethyl)-2,2-(*O*-isopropylidene-)pent-4-enal (5). To a solution of **2** (5.0 g, 21.8 mmol) in dry THF (100 mL) was slowly added $LiAlH_4$ (23.9 mL, 1.0 M solution in THF) at −78 °C. After being stirred for 30 min at the same temperature, the reaction mixture was quenched by adding a saturated aqueous NH_4Cl solution (23 mL). After filtration, the slurry mixture was washed several times with EtOAc. The combined filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (EtOAc/hexane, 1:2) to give aldehyde **5** (3.04 g, 82%) as a colorless oil. $[\alpha]^{25}_D$ −3.1° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.57 (m, 1H), 5.69 (m, 1H), 5.12 (s, 1H), 5.03 (d, J = 10.0, Hz, 1H), 4.11 (d, J = 9.0 Hz, 1H), 3.77 (d, J = 9.0, Hz, 1H), 3.16 (dd, J = 15.0, 7.0 Hz, 1H), 2.60 (dd, J = 15.0, 7.0 Hz, 1H), 1.43 (s, 3H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 130.68, 117.12, 109.38, 82.24, 70.54, 69.21, 41.59, 26.12, 25.12. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.61; H, 8.33.

(3*R*/4*S* or 3*S*/4*S*)-3,4-Dihydroxy-4(*S*)-hydroxymethyl-4,4-(*O*-isopropylidene)hepta-1,6-diene (6). To a cooled (−78 °C) solution of aldehyde **5** (7.5 g, 44.0 mmol) in dry THF (100 mL)-was slowly added vinylmagnesium bromide (41.6 mL, 1.0 M solution in THF) . After 1 h, saturated NH_4Cl solution (42 mL) was added, and the reaction mixture was slowly warmed to room temperature. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:3) to give **6** (8.4 g, 96%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.51−5.71 (m, 2H), 5.16−5.04 (m, 4H), 3.96−3.81 (m, 4H), 3.59−3.43 (m, 4H), 2.47−2.34 (m, 2H), 1.43 (s, 6H), 1.45 (d, J = 1.7 Hz, 6H). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.87; H, 9.23.

(1*R*,5*S*)-5-Hydroxy-5-(hydroxymethyl)-5,5-(*O*-isopropylidene)cyclopentenol (7*β*) and (1*S*,5*S*)-5-Hydroxy-5-(hydroxymethyl)-5,5-(*O*-isopropylidene)cyclopentenol (7α). To a solution of **6** (5.0 g, 25.2 mmol) in anhydrous benzene (50 mL) was added slowly Grubbs catalyst (1.03 g 1,26 mmol) in dry benzene (10 mL) over 10 min under a N_2 atmosphere. The reaction mixture was refluxed for 2 h and cooled to room temperature. The mixture was concentrated in a vacuum, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:3) to give cyclopentenol **7*β*** (2.05 g, 48%) and **7α** (2.44 g, 49%) as colorless oils, respectively. Cyclopentenol **7*β***: $[\alpha]^{25}_D$ −103.5° (*c* 2.24, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.98 (d, J = 6.0 Hz, 1H), 5.84 (dd, J = 6.0, 1.8 Hz, 1H), 4.66 (s, 1H), 4.49 (d, J = 9.3 Hz, 1H), 3.81 (d, J = 8.7 Hz, 1H), 2.62 (dd, J = 3.3, 2.4 Hz, 2H), 1.45 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.43, 131.90, 109.31, 89.55, 81.48, 68.62, 42.31, 26.98, 26.26. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.78; H, 8.21. Cyclopentenol **7α**: $[\alpha]^{25}_D$ +75.8° (*c* 1.27, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.94 (dd, J = 5.1, 2.4 Hz, 1H), 5.83 (m, 1H), 4.35 (d, J = 6.0 Hz, 1H), 4.09 (d, J = 8.7 Hz, 1H), 4.02 (d, J = 9.0 Hz, 1H), 2.77−2.41 (m, 2H), 1.46 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.96, 132.12, 118.66, 110.17, 86.89, 78.12, 72.81, 42.26, 26.53, 26.30. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.55; H, 8.19.

(1*R*,5*S*)-1-Ethoxycarbonyloxy-5-hydroxy-5-(hydroxymethyl)-5,5-(*O*-isopropylidene)cyclopent-2-ene (8). To a solution of **7*β*)**(6.0 g, 35.2 mmol) in anhydrous pyridine (90 mL) was added ethyl chloroformate (6.74 mL, 70.5 mmol) and DMAP (0.86 g, 7.04 mmol). The reaction mixture was stirred overnight at 60 °C and cooled to room temperature. The reaction mixture was quenched with a saturated $NaHCO_3$ solution (5 mL) and concentrated under vacuum. The residue was extracted with EtOAc, dried over $MgSO_4$, filtered, and evaporated to give a yellowish crude product. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:4) to give **8** (6.8 g, 80%) as a colorless oil. $[\alpha]^{25}_D$ −206.5° (*c* 2.6, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.15−6.12 (m, 1H), 5.90−5.86 (m, 1H), 5.46 (s, 1H), 4.35 (d, J = 9.0 Hz, 1H), 4.25 (q, J = 7.5 Hz, 2H), 3.89 (d, J = 9.3 Hz, 1H), 2.64 (m, 2H), 1.44 (s, 3H), 1.40 (s, 3H), 1.34 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.57, 136.58, 128.32, 109.91, 87.89, 85.99, 68.73, 64.18, 43.18, 26.49, 26.42, 14.25. Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.21; H, 7.56.

(1′*R*,4′*R*)-9-[4-Hydroxy-4-(hydroxymethyl)-4,4-(*O*-isopropylidene)cyclopent-2-en-1-yl]adenine (9). To pure NaH (11.7 mg, 0.49 mmol) in anhydrous DMSO (1.7 mL) was added adenine (67 mg, 0.49 mmol). The reaction mixture was stirred for 30 min at 45−55 °C and cooled to room temperature. Simultaneously, P(O-*i*-Pr)$_3$ (0.048 mL, 0.11 mmol) was added to a solution of $Pd_2(dba)_3$·$CHCl_3$ (2.3 mg, 1.25 μmol) in anhydrous THF (1.5 mL), which was stirred for 30 min. To an adenine solution of DMSO was sequentially added a catalyst solution of THF and **8** (108 mg, 0.44 mmol) dissolved in anhydrous THF (1 mL). The reaction mixture was gently refluxed overnight and quenched with water (1 mL). The reaction solvent was removed under vacuum. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:10) to give **9** (69.5 mg, 55%) as a white solid. Mp 186−189 °C; UV (MeOH) λ_{max} 260 nm; $[\alpha]^{25}_D$ +139.5° (*c* 0.3, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.36 (s, 1H), 7.70 (s, 1H), 6.23 (dd, J = 5.4, 1.8 Hz, 1H), 6.12 (dd, J = 9.0, 5.4, 2.1 Hz, 1H), 5.82 (br s, 2H), 4.13 (d, J = 8.7 Hz, 1H), 3.97 (d, J = 9.3 Hz, 1H), 2.91 (dd, J = 14.1, 8.1 Hz, 1H), 2.23 (dd, J = 14.1, 3.9 Hz 1H), 1.44 (s, 3H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.08, 152.88, 151.58, 139.65, 138.21, 137.07, 132.01, 109.76, 90.64, 72.98, 58.72, 44.05, 26.86, 26.24. Anal. Calcd for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.96; N, 24.38. Found: C, 58.29; H, 6.01; N, 24.44.

(1′*R*,4′*R*)-1-[4-Hydroxy-4-(hydroxymethyl)-4,4-(*O*-isopropylidene)cyclopent-2-en]cytosine (10). The reaction procedure for the synthesis of **10** is the same as that of **9**. Yield 67%; mp 168−170 °C; UV (MeOH) λ_{max} 273 nm; $[\alpha]^{25}_D$ +26.38° (*c* 0.5, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.23 (d, J = 7.1 Hz, 1H), 7.05 (br s, 2H), 6.05 (dd, J = 5.5, 2.0 Hz, 1H), 5.89 (dd, J = 5.5, 2.0 Hz, 1H), 5.67 (d, J = 7.1 Hz, 1H), 5.57 (m, 1H), 3.98 (d, J = 8.9 Hz, 1H), 3.88 (d, J = 8.7 Hz, 1H), 2.44 (dd, J = 14.3, 7.7 Hz, 1H), 1.77 (dd, J = 14.5, 5.3 Hz, 1H), 1.30 (s, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.50, 155.67, 141.82, 138.35, 133.90, 108.57, 93.97, 90.37, 72.18, 60.22, 42.97, 26.85, 26.19. Anal. Calcd for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.19; H, 6.66; N, 15.79.

(1′*R*,4′*R*)-9-[4-Hydroxy-4-(hydroxymethyl)cyclopent-2-en-1-yl]adenine (11). The acetonide protected **9** (100 mg, 0.35 mmol) was dissolved in 80% aqueous AcOH solution (5 mL) and stirred for 5 h at 70−80 °C. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure and coevaporated three times with toluene. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:4) to give **11** (69.2 mg, 80%) as a white solid. Mp 145−148 °C; UV (H_2O) λ_{max} 261 nm; $[\alpha]^{25}_D$ +81.35° (*c* 0.5, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.12 (s, 1H), 7.99 (s, 1H), 7.20 (br s, 2H, D_2O exchangeable), 5.99 (dd, J = 8.7, 6.9 Hz, 2H), 5.72 (m, 1H), 5.02 (s, 1H, D_2O exchangeable), 3.45 (d, J = 11.1 Hz, 1H), 3.35 (d, J = 11.1 Hz, 1H), 2.37 (dd, J = 13.8, 8.1 Hz, 1H), 2.09 (dd, J = 18.9, 4.8 Hz, 1H);^{13}C NMR (DMSO-d_6, 75 MHz) δ 156.00, 152.26, 149.09, 141.03, 138.73, 131.24, 122.03, 118.87, 84. 51,

67.05, 58.41, 42.58. Anal. Calcd for $C_{11}H_{13}N_5O_2$: C, 53.43; H, 5.30; N, 28.32. Found: C, 53.39; H, 5.44; N, 28.41.

(1′*R*,4′*R*)-1-[4-Hydroxy-4-(hydroxymethyl)cyclopent-2-en-yl]cytosine (12). To synthesize **12**, the same reaction as that for **11** was used. Yield 60%; mp 140−142 °C; UV (H_2O) λ_{max} 273 nm; $[\alpha]^{25}_D$ +13.7° (*c* 0.6, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.37 (d, J = 6.3 Hz, 1H), 7.27 (br s, 1H, D_2O exchangeable), 7.09 (br s, 1H, D_2O exchangeable), 5.92 (d, J = 3.6 Hz, 1H), 5.71 (m, 3H), 3.41 (d, J = 10.5 Hz, 1H), 3.29 (d, J = 10.5 Hz, 1H), 2.16 (dd, J = 14.4, 8.1 Hz, 1H), 1.73 (dd, J = 14.1, 5.1 Hz, 1H);^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.12, 155.47, 142.12, 132.27, 93.72, 84.22, 66.74, 60.39, 48.58, 42.05. Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.82. Found: C, 53.59; H, 5.70; N, 18.79.

(1′*R*,4′*R*)-9-[4-Hydroxy-4-(hydroxymethyl)-4,4-(*O*-isopropylidene)cyclopentan-1-yl]adenine (13). A mixture of **9** (100 mg, 0.38 mmol), *n*-butylamine, and 10% Pd/C (9 mg) in MeOH (5 mL) was stirred for 2 h at room temperature under hydrogen atmosphere (20 psi). The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:10) to give **13** (98.9 mg, 90%) as a white solid. Mp 182−185 °C; UV (MeOH) λ_{max} 261.5 nm; $[\alpha]^{25}_D$ +68.8° (*c* 0.3, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.33 (s, 1H), 7.80 (s, 1H), 5.90 (br s, 2H, D_2O exchangeable), 5.04 (t, J = 9.3 Hz, 1H), 4.06 (s, 1H), 2.48−2.04 (m, 6H), 1.42 (s, 1H), 1.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.49, 152.56, 149.92, 139.41, 120.32, 109.62, 87.05, 73.23, 55.28, 43.06, 36.42, 30.53, 26.89, 26.73. Anal. Calcd for $C_{14}H_{19}N_5O_2$: C, 58.12; H, 6.62; N, 24.21. Found: C, 58.25; H, 6.78; N, 24.38.

(1′*R*,4′*R*)-1-[4-Hydroxy-4-(hydroxymethyl)-4,4-(*O*-isopropylidene)cyclopentan-1-yl]cytosine (14). The same reaction condition used for **11** was used for the synthesis of **15**. Yield 80%; mp 175−178 °C; UV (MeOH) λ_{max} 273 nm; $[\alpha]^{25}_D$ +3.4° (*c* 0.85, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.61 (d, J = 7.5 Hz, 1H), 7.24 (br s, 2H, D_2O exchangeable), 5.66 (d, J = 7.5 Hz, 1H), 4.83 (m, 1H), 5.02 (s, 1H, D_2O exchangeable), 3.88 (s, 1H), 2.04−1.61 (m, 6H), 1.27 (d, J = 4.5 Hz, 6H);^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.19, 155.52, 143.15, 108.44, 93.57, 86.77, 72.52, 55.88, 41.40, 35.93, 28.90, 26.92, 26.59. Anal. Calcd for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.77; H, 7.40; N, 15.67.

(1′*R*,4′*R*)-9-[4-Hydroxy-4-(hydroxymethyl)cyclopentan-1-yl]adenine (15). Compound **13** (150 mg, 0.52 mmol) was converted to **15** (96.9 mg, 75%) according to the hydrolytic procedure used for preparing **11**. Mp 182−185 °C; UV (H_2O) λ_{max} 260 nm; $[\alpha]^{25}_D$ +16.49° (*c* 1.5, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.22 (s, 1H), 8.12 (s, 1H), 7.18 (br s, 2H, D_2O exchangeable), 5.11 (m, 1H), 4.82 (t, J = 7.5 Hz 1H, D_2O exchangeable), 4.13 (s, 1H, D_2O exchangeable), 3.36 (d, J = 11.1 Hz, 2H), 2.55−2.32 (m, 6H);^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.98,152.17, 149.44, 139.37, 119.19, 80.11, 67.33, 54.11, 42.35, 34.26, 30.73. Anal. Calcd for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07; N, 28.10. Found: C, 52.88; H, 6.21; N, 28.34.

(1′*R*,4′*R*)-1-[4-Hydroxy-4-(hydroxymethyl)-cyclopentan-1-yl] cytosine (16). Compound **14** (90 mg, 0.34 mmol) was converted to **16** (53.6 mg, 70%) according to the hydrolytic procedure used for **11**. Mp 195−198 °C; UV (H_2O) λ_{max} 274 nm; $[\alpha]^{25}_D$ +27.3° (*c* 0.15, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.59 (d, J = 7.2 Hz, 1H), 6.91 (br d, 2H, D_2O exchangeable), 5.68 (d, J = 7.2 Hz, 1H), 5.05 (m, 1H), 4.74 (t, J = 6.0 Hz, 1H, D_2O exchangeable), 4.44 (s, 1H, D_2O exchangeable), 3.33 (s, 2H), 1.97−1.46 (m, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.21, 142.44, 93.74, 79.84, 74.55, 67.39, 55.07, 41.32, 34.45, 31.30, 29.86. Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.66. Found: C, 53.50; H, 6.44; N, 18.49.

(1′*R*,4′*R*)-9-[4-Hydroxy-4-(hydroxymethyl)-4,4-(*O*-isopropylidene)-2,3-dihydroxycyclopentan-1-yl]adenine (17). To a stirred solution of **9** (400 mg, 1.4 mmol) in a cosolvent (5.0 mL, acetone:water/5:1) was added NMO (164 mg, 2.8 mmol) and OsO_4 (0.084 mL, 4% in water). The mixture was stirred overnight at 50 °C and quenched with a saturated Na_2SO_3 solution (5 mL). The resulting solid was removed by filtration through a Celite pad. The filtrate was then concentrated in reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:6) to give **17** (362 mg, 81%) as a white solid. Mp 187−190 °C; UV (MeOH) λ_{max} 260 nm; $[\alpha]^{25}_D$ −1.9° (*c* 0.4, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.16 (s, 1H), 8.11 (s, 1), 7.20 (br d, 2H, D_2O exchangeable), 5.56 (d, J = 6.3 Hz, 1H, D_2O exchangeable), 5.20 (d, J = 4.5 Hz, 1H, D_2O exchangeable), 5.04 (m, 1H), 4.33 (d, J = 9.0 Hz, 1H), 4.12 (m, 1H), 3.93 (m, 1H), 2.49 (dd, J = 9.3, 2.6 Hz, 1H), 2.34 (dd, J = 9.3, 4.5 Hz, 2H), 1.30 (d, J = 5.1 Hz, 6H);^{13}C NMR (DMSO-d_6) δ 155.90, 152.00, 149.68, 140.94, 118.45, 108.27, 86.61, 76.44, 71.33, 69.13, 52.04, 26.68, 26.24. Anal. Calcd for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96; N, 21.79. Found: C, 52.58; H, 5.74; N, 21.44.

(1′*R*,4′*R*)-1-[4-Hydroxy-4-(hydroxymethyl)-4,4-(*O*-isopropylidene)-2,3-dihydroxycyclopentan-1-yl]cytosine (18). Compound **10** (150 mg, 0.57 mmol) was converted to **18** (128.8 mg, 76%) according to the dihydroxylation procedure used for preparing **17**. Mp 161−164 °C; UV (MeOH) λ_{max} 273 nm; $[\alpha]^{25}_D$ +29.9° (*c* 0.9, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.63 (d, J = 7.2 Hz, 1H), 7.05 (br d, 2H, D_2O exchangeable), 5.63 (d, J = 7.1 Hz, 1H), 5.32 (d, J = 6.0 Hz, 1H, D_2O exchangeable), 5.14 (d, J = 4.8 Hz, 1H, D_2O exchangeable), 5.04 (m, 1H), 4.25 (d, J =8.7 Hz, 1H), 3.97 (dd, J = 7.1, 3.5 Hz, 1H), 3.78 (t, J = 5.8 Hz, 1H), 3.75 (dd, J = 8.7 Hz, 1H), 2.04 (m, 2H), 1.29 (d, J = 5.1 Hz, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.05, 156.07, 145.18, 108.20, 92.40, 86.49, 76.27, 70.74, 68.83, 52.98, 26.64, 26.29. Anal. Calcd for $C_{13}H_{19}N_3O_5$: C, 52.52; H, 6.44; N, 14.13. Found: C, 52.67; H, 6.40; N, 14.08.

(1′*R*,4′*R*)-9-[4-Hydroxy-4-(hydroxymethyl)-2,3-dihydroxycyclopentan-1-yl]adenine (19). Compound **17** (431 mg, 1.34 mmol) was converted to **19** (281 mg, 75%) according to the procedure used for preparing **11**. Mp 161−164 °C; UV (H_2O) λ_{max} 260 nm; $[\alpha]^{25}_D$ +6.28° (*c* 0.35, DMF); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.11 (s, 1H), 8.10 (s, 1H), 7.12 (br s, 2H, D_2O exchangeable), 5.27 (d, J = 5.4 Hz, 1H, D_2O exchangeable), 5.04 (m, 1H), 5.00 (d, J = 6.0 Hz, 1H, D_2O exchangeable), 4.74 (s, 1H), 4.61 (br s, 1H, D_2O exchangeable), 4.29 (dd, J = 4.2, 1.8 Hz 1H), 3.83 (t, J = 4.4 Hz, 1H), 3.51 (d, J = 4.8 Hz, 2H), 2.31 (t, J = 13.2 Hz, 1H), 2.05 (dd, J = 8.4, 4.8 Hz, 1H);^{13}C NMR (DMSO-d_6, 75 MHz) δ 162.11, 155.87, 152.03, 149.84, 141.07, 118.38, 79.47, 77.71, 71.35, 64.82, 52.56, 48.61, 35.90, 30.65. Anal. Calcd for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96; N, 21.79. Found: C, 52.11; H, 6.09; N, 21.51.

(1′*R*,4′*R*)-1-[4-Hydroxy-4-(hydroxymethyl)-2,3-dihydroxycyclopentan-1-yl]cytosine (20). Compound **18** (120 mg, 0.40 mmol) was converted to **20** (73 mg, 71%) according to the procedure used for preparing **11**. Mp 215−220 °C; UV (H_2O) λ_{max} 274 nm; $[\alpha]^{25}_D$ +76.5° (*c* 0.4, DMF); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.61 (d, J = 7.8 Hz, 1H), 6.97 (br d, 2H, D_2O exchangeable), 5.62 (d, J = 7.8 Hz, 1H), 5.11 (m, 1H), 5.08 (br s, 1H, D_2O exchangeable), 4.65 (br s, 1H, D_2O exchangeable), 4.12 (t, J = 6.0 Hz, 1H), 3.73 (d, J = 3.9 Hz, 1H), 3.44 (s, 2H), 1.97 (t, J = 12.6 Hz), 1.74 (dd, J = 12.4, 6.9 Hz, 1H);^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.17, 162.33, 156.40, 145.29, 92.32, 79.20, 77.63, 70.86, 64.83, 53.58, 38.66, 35.80, 30.78. Anal. Calcd for $C_{10}H_{15}N_3O_5$: C, 46.69; H, 5.88; N, 16.33. Found: C, 46.81; H, 5.81; N, 16.49.

Acknowledgment. This study was supported by a grant of the Ministry of Health and Welfare, Republic of Korea (01-PJ1-PG3-21500-0013). We also thank the LGCI screening team for the antiviral evaluations.

Supporting Information Available: ^{1}H NMR spectra of **2**, **7α**, **7*β***, **8**, **10**, **11**, **13**, **14**, **16**, **17**, **18**, and **19** and ^{13}C NMR spectra of **8**, **10**, **12**, **13**, **14**, **15**, **17**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0202536