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First synthesis of 2′-oxabicyclo[3.1.0]hexyl nucleosides with a *north* conformation

Won Hee Kim [a], Ah-Young Park [a], Jin-Ah Kang [a], Jungsu Kim [a], Jin-Ah Kim [a], Hyung-Rock Lee [a], Pusoon Chun [a], Jungwon Choi [b], Chong-Kyo Lee [c], Lak Shin Jeong [d], Hyung Ryong Moon [a,*]

[a] *Laboratory of Medicinal Chemistry, College of Pharmacy and Research Institute for Drug Development, Pusan National University, 30 Jangjeon-dong, Geumjeong-gu, Busan 609-735, Republic of Korea*
[b] *Department of Chemistry, The University of Suwon, Kyunggi 445-743, Republic of Korea*
[c] *Pharmacology Research Center, Korea Research Institute of Chemical Technology, Daejon 305-600, Republic of Korea*
[d] *Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul 120-750, Republic of Korea*

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ABSTRACT

The first synthesis of 2′-oxabicyclo[3.1.0]hexyl nucleosides, a novel class of bicyclonucleosides, with a *north* conformation was successfully accomplished starting from (*S*)-epichlorohydrin via a tandem alkylation–lactonization, a less steric hindrance-dependent silylation in equilibrium and a coupling reaction with nucleobases under Vorbruggen conditions. Addition of acetic acid prevented a benzoyl group from migrating during desilylation with TBAF. ^{1}H NMR and X-ray crystallographic analysis indicated that the anomeric effect worked on the β-2′-oxabicyclo[3.1.0]hexyl nucleosides.

1. Introduction

Herpes simplex virus (HSV) is one of the most widespread viruses all over the world. There are two types (HSV-1 and HSV-2), two species of the herpes virus family, *Herpesviridae*, which cause infection in humans. Herpes simplex viruses cause symptoms including watery blister in the skin or mucous membranes of the mouth, lips, and genitals. Although antiviral drugs such as acyclovir (ACV),[1,2] penciclovir,[3] and their prodrugs (valaciclovir[4] and famciclovir[5,6]) have been used for the treatment of HSV-1 and -2 infections to reduce the physical symptoms (Fig. 1), the efficacy is known to be very low and many people infected with HSV experience sporadic episodes of reactivation of HSV shed in neural ganglia. Nucleoside derivatives including ganciclovir (GCV),[7] 5-iodo-2′-

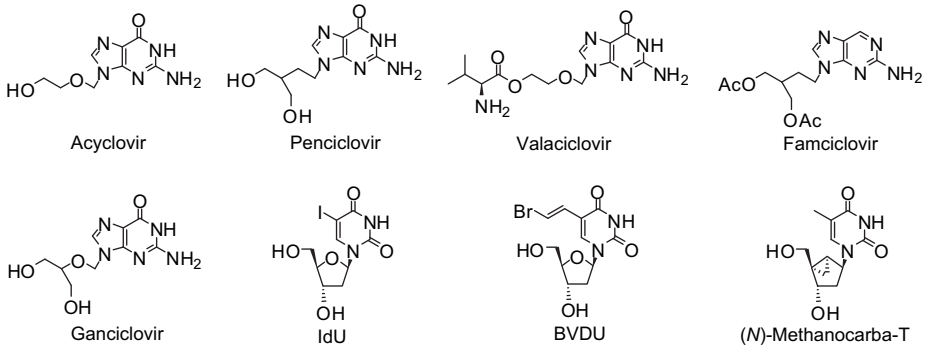

Figure 1. Nucleoside analogues showing *anti*-herpetic activity.

* Corresponding author. Tel.: +82 51 510 2815; fax: +82 51 513 6754.
E-mail address: mhr108@pusan.ac.kr (H.R. Moon).

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deoxyuridine (IdU),[8] 5-bromovinyl-2′-deoxyuridine (BVDU),[9–12] and (*N*)-methanocarba-T[13] (Fig. 1) have been found to exhibit significant activity against HSV, cytomegalovirus (CMV), and other herpesviruses. Especially, (*N*)-methanocarba-T, which adopted a locked *north* conformation in the pseudorotational cycle[14] (Fig. 2) showed superior *anti*-HSV activity to ACV.[13] (*N*)-Methanocarba-T is known to be phosphorylated into the corresponding diphosphate via its monophosphate by the HSV thymidine kinase (HSV-TK).[15,16] Similarly, it is known that ACV and GCV are also phosphorylated into the corresponding monophosphates, respectively, by the HSV-TK.[15,16] (*N*)-Methanocarba-T, ACV, and GCV are very poor substrates for phosphorylation by cellular thymidine kinase. Therefore, they are extremely selective and low in cytotoxicity.

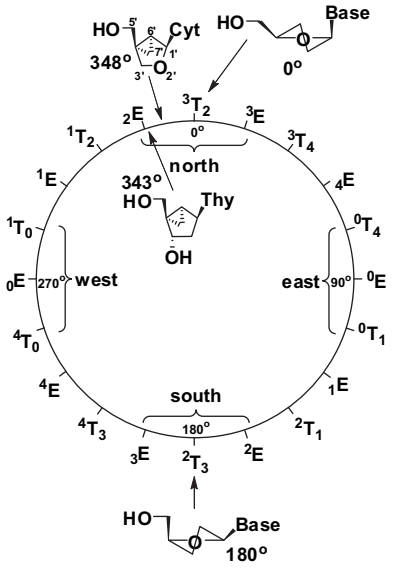


Figure 2. Pseudorotational cycle.

3′-Deoxynucleoside derivatives including 2′,3′-dideoxynucleosides (ddNs), 2′,3′-didehydro-2′,3′-dideoxynucleosides (d4Ns), and AZT (azidothymidine, 3′-azido-3′-deoxythymidine, zidovudine) showed antiretroviral activity by terminating the growing viral DNA chains as well as by inhibiting the action of reverse transcriptase, the enzyme that retroviruses use to make their DNA copies from their RNA (Fig. 3).[17–22] The termination of DNA chains resulted from the absence of 3′-hydroxy group of 3′-deoxynucleosides.

While the structure-activity relationships (SARs) have been well explored within nucleosides with bicyclo[3.1.0]hexanes and bicyclo[3.1.0]hexene,[13,23–26] the SAR of bicyclo[3.1.0]hexyl nucleosides having a heteroatom on their pseudosugar template is not yet developed.

On the basis of these findings, novel 3′-deoxy-2′-oxabicyclo[3.1.0]hexyl nucleosides were designed and synthesized in order to search for more efficient therapeutic agents against HSV and to provide nucleosides used in probing the conformational preferences of enzymes associated with the metabolism of nucleosides and nucleotides, and their antiviral activities were evaluated against several viruses.

2. Results and discussion

Synthesis of a glycosyl donor **18** bearing an oxabicyclo[3.1.0]-hexane template is shown in Scheme 1. Compound **7** was synthesized according to the procedure reported by our laboratory,[25] starting from (*S*)-epichlorohydrin via a tandem alkylation–lactonization and a chemoselective reduction of ester in the presence of lactone. The lactone moiety of **5** is more susceptible to hydrolysis than the ethyl ester, may be due to the structural constraint caused by a fused cyclopropane ring. Treatment of **5** with 1 equiv of sodium hydroxide in EtOH afforded monocarboxylate sodium salt **6**, the ester functional group of which was chemoselectively reduced by sodium borohydride under reflux. Under acidic conditions, the bis-hydroxymethyl compound **6a** cyclized back to the lactone **7**. Protection of the hydroxyl group of **7** by treatment with 4-methoxybenzyltrichloroacetimidate, prepared from 4-methoxybenzyl alcohol and trichloroacetonitrile in the presence of sodium hydride,[27,28] provided the corresponding 4-methoxybenzyl (PMB) ether **8** in 85% yield.

The PMB ether **8** was reduced with Dibal-H at −78 °C to give the corresponding lactol **9** in 95% yield. Treatment of lactol **9** with *tert*-butyldiphenylsilylchloride produced ring-opened silyl ether **10** in 97% yield, indicating that the reaction proceeded much faster at the primary hydroxyl group exposed in the ring-opened form, **9a**, of **9** than at the secondary one of the lactol form **9**. Compound **10** was reduced with sodium borohydride at 0 °C to give alcohol **11** in 95% yield. Benzoylation with benzoyl chloride, DMAP, and pyridine in methylene chloride converted compound **11** to the corresponding benzoate **12** in 95% yield. Now, three hydroxymethyl groups were protected with three different protecting groups. Reaction sequence composed of a removal of TBDPS, an oxidation to the corresponding aldehyde and a lactonization after debenzoylation was chosen to obtain the desired lactol **16**. Deprotection of TBDPS group with 1 M TBAF gave the corresponding alcohol **13** and a benzoyl-migrating

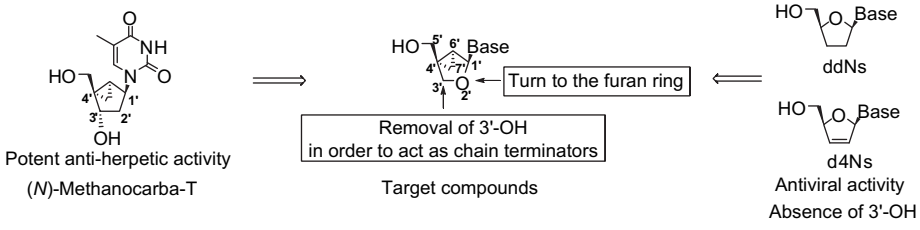
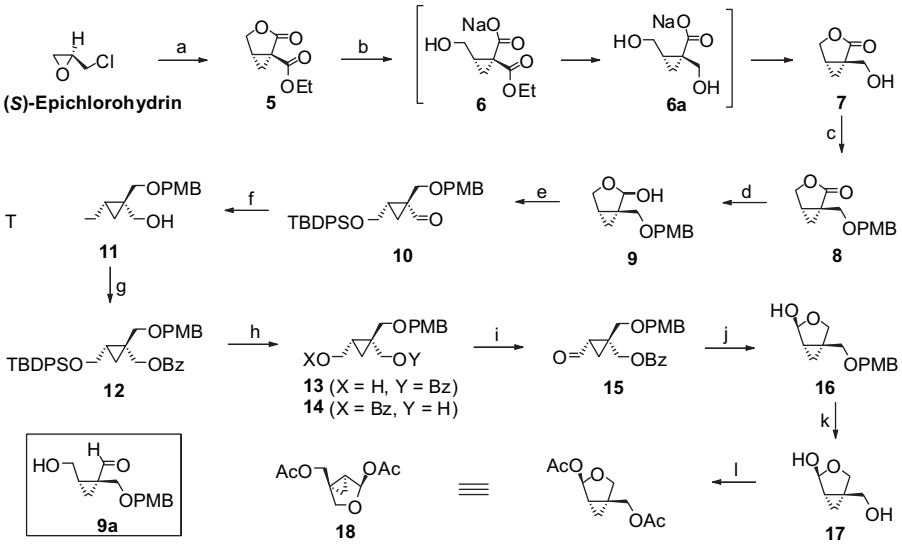


Figure 3. Rationale for the targeted 2′-oxabicyclo[3.1.0]hexyl nucleosides.

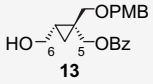
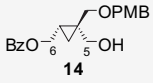
Making more similar sugar ring size to that of natural nucleosides might induce more potent antiviral activity. Replacement of the 2′-methylene group of bicyclo[3.1.0]hexane template in (*N*)-methanocarba-T by an oxygen atom affords a tetrahydrofuran ring, which natural nucleosides bear (Fig. 3).

compound **14** (**13**:**14**=7:1). In ^{1}H NMR of **13** (Table 1), the peaks of 5-H_2 should appear more down field than those of 6-H_2 due to an electron-withdrawing effect by the adjacent benzoyl group and each proton of 5-H_2 can not appear as peaks to be more complex than a doublet. Contrarily, the peaks of 5-H_2 of **14** should be located



Scheme 1. Reagents and conditions: (a) $CH_2(CO_2Et)_2$, Na, EtOH, reflux, 20 h, 67%; (b) (i) 1 equiv NaOH, EtOH, rt, 16 h; (ii) $NaBH_4$, reflux, 3 h, then 2 M HCl, rt, 18 h, 62%; (c) PMBOC(=NH)CCl_3, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 16 h, 85%; (d) (i) Dibal-H, CH_2Cl_2, −78 °C, 30 min, 95%; (e) TBDPSCl, imidazole, CH_2Cl_2, rt, 3 h, 97%; (f) $NaBH_4$, MeOH, 0 °C, 10 min, 95%; (g) BzCl, DMAP, pyridine, CH_2Cl_2, rt, 8 h, 95%; (h) 1 M TBAF, 1 equiv AcOH, THF, rt, 7 h, 100%; (i) oxalyl chloride, DMSO, CH_2Cl_2, −78 °C, 1 h, then Et_3N, rt, 1 h, 94%; (j) 1 M NaOMe, MeOH, rt, 4 h, 99%; (k) 3 M HCl, 1,4-dioxane, rt, two days, 66%; (l) Ac_2O, pyridine, rt, overnight, 70%.

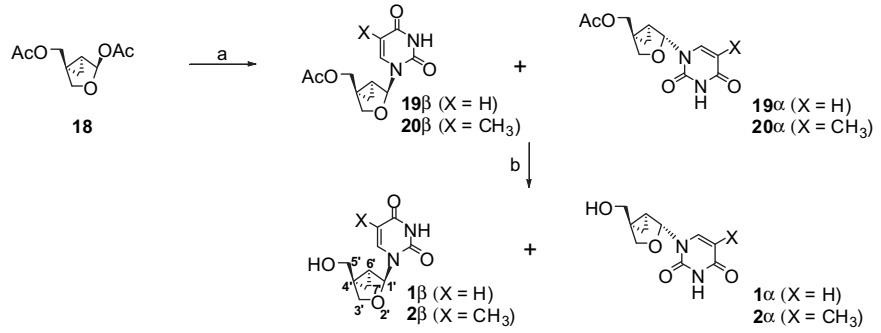
Table 1
Comparison of ^{1}H NMR peaks of 5-H_2 and 6-H_2 in **13** and **14**

	5-H_2, δ_H (m, *J* in Hz)	6-H_2, δ_H (m, *J* in Hz)	OH, δ_H (m, *J* in Hz)
 **13**	4.17 (d, 11.6) 4.78 (d, 11.6)	3.51 (dd, 9.2, 11.6) 3.85 (dd, 5,6, 12.0)	2.08 (s)
 **14**	3.63 (dd, 5.0, 11.5) 3.98 (dd, 6.0, 12.0)	4.28 (dd, 8.5, 12.0) 4.61 (dd, 6.5, 11.5)	2.70 (t, 6.0)

upfield from those of 6-H_2 and each peak of 5-H_2 can appear as a doublet of doublets when being coupled with the proton bonded to the adjacent OH. Therefore, the two products obtained could be easily differentiated by ^{1}H NMR. The migration would result from the basic reaction conditions. Therefore, upon desilylation with 1 M TBAF, 1 equiv acetic acid was added in order to prevent the migration of the benzoyl group. As expected, the benzoyl-migrating product was not observed in the presence of acetic acid and the desired product **13** was obtained in quantitative yield. Swern oxidation of **13** with oxalyl chloride and DMSO at −78 °C gave the corresponding aldehyde **15**. Removal of benzoyl group of **15** using NaOMe in MeOH produced lactol **16**, which was equipped with oxabicyclo[3.1.0]hexanol template for a proper glycosyl donor.

Before coupling of **16** with nucleobases, the PMB group was changed into an acetyl group, which was more stable under acidic conditions and easily deprotectable under basic conditions. Removal of the PMB group of **16** with 3 M HCl in 1,4-dioxane gave the corresponding diol **17**. Acetylation of **17** with acetic anhydride and pyridine produced the glycosyl donor **18**, which was ready to couple with natural nucleobases. In **17** and **18**, each compound was obtained as a single anomer and each anomeric proton was not coupled with a neighboring methinyl proton in ^{1}H NMR, implying that the anomeric OH and OAc groups were disposed at the β face due to the anomeric effect.[29,30] In case of **16**, although the appearance of the anomeric proton in ^{1}H NMR spectrum was a doublet, the proton was coupled with the proton of OH, not the neighboring methinyl proton, thus implying that the anomeric effect caused the anomeric OH to be disposed at the β face.

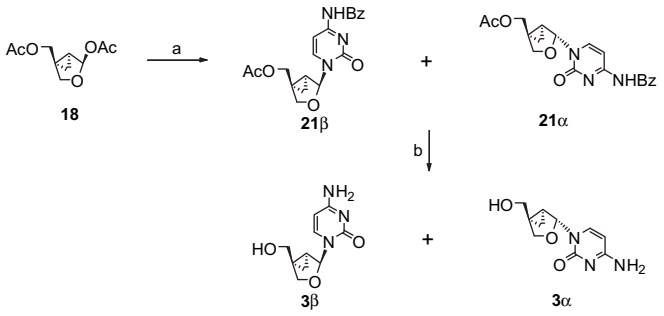
Synthesis of uracil and thymine nucleosides is shown in Scheme 2. The glycosyl donor, diacetate **18** was condensed with persilylated uracil and thymine in the presence of TMSOTf used as an acid catalyst to give an inseparable mixture of the protected uracil and thymine nucleosides of α- and β-anomers, respectively (**19α** and **19β**: 84%; **20α** and **20β**: 87%).[31] Finally, deprotection of the



Scheme 2. Reagents and conditions: (a) (i) uracil or thymine, HMDS, $(NH_4)_2SO_4$, reflux, overnight; (ii) TMSOTf, CH_3CN, rt, 2 h, 84% for **19α/β**, and 87% for **20α/β**; (b) 1 M NaOMe, MeOH, rt, overnight, 72% for **1β**, 23% for **1α**, 54% for **2β**, and 36% for **2α**.

acetyl groups in **19α/β** and **20α/β** with 1 M NaOMe afforded the final uracil nucleosides, **1β** (72%) and **1α** (23%), and thymine nucleosides, **2β** (54%) and **2α** (36%), respectively. In both nucleosides, β-anomers were produced as major products, suggesting that the methylene group of the fused cyclopropane ring might act as an important steric factor upon coupling reaction with nucleobases. This trend was also observed in reactions with other nucleobases such as N^4-benzoylcytosine and N^6-benzoyladenine.

Synthesis of cytosine nucleosides is depicted in Scheme 3. Diacetate **18** was condensed with silylated N^4-benzoylcytosine in the presence of TMSOTf to give an inseparable mixture of the N^4-benzoylcytosine nucleosides of β-anomer **21β** and α-anomer **21α** in 64% yield. Removal of the benzoyl and acetyl groups of **21α/β** with NaOMe in MeOH produced the final cytosine nucleosides, β-anomer **3β** (83%) as a major product and α-anomer **3α** (13%) as a minor product, respectively.



Scheme 3. Reagents and conditions: (a) (i) N^4-benzoylcytosine, HMDS, $(NH_4)_2SO_4$, reflux, overnight; (ii) TMSOTf, CH_3CN, rt, 2 h, 64% for **21α/β**; (b) 1 M NaOMe, MeOH, rt, overnight, 83% for **3β**, and 13% for **3α**.

Synthesis of adenine nucleoside derivatives is shown in Scheme 4. In a similar method used for the coupling reaction with pyrimidine bases, the acetate **18** was condensed with persilylated N^6-benzoyladenine to give an inseparable mixture of the protected adenine nucleosides of β-anomer **22β** and α-anomer **22α** in 89% yield. By treatment with 1 M NaOMe, the final adenine nucleosides, **4β** and **4α** were obtained in 87% and 11% yields, respectively. Comparison of literature UV data[32,33] confirmed us that they were N-9 regioisomers. To the best of our knowledge, all the final nucleosides are the first example of oxabicyclo[3.1.0]hexyl nucleoside derivatives with the fixed *north* conformation.

neighboring methine carbon (dihedral angle≈0), while that of its α-nucleoside was coupled. Therefore, nucleosides in which the appearance of the anomeric proton was a singlet were assigned to β-nucleosides and nucleosides in which that was a doublet (J=2.4–3.0 Hz) were assigned to α-nucleosides. Later, X-ray crystal structure (Fig. 4) proved the assignments made by the splitting pattern of the anomeric proton peak in ^{1}H NMR to be correct. It is notable that in the ^{1}H NMR spectra of all the final nucleosides, each proton peak of 7′-H_2 in β-nucleosides appeared far away from each other while the proton peaks of 7′-H_2 in α-nucleosides appeared as an overlapped appearance or very close two peaks. It is also notable that the protons of 5′- H_2 of α-nucleosides appeared almost as a singlet whereas those of β-nucleosides appeared as a pair of doublets. Interestingly, a 'W (^4J)' coupling, one of the long-range couplings, between the $H_{7'\text{-exo}}$ and the $H_{3'\text{-exo}}$ was found in only β-nucleosides.

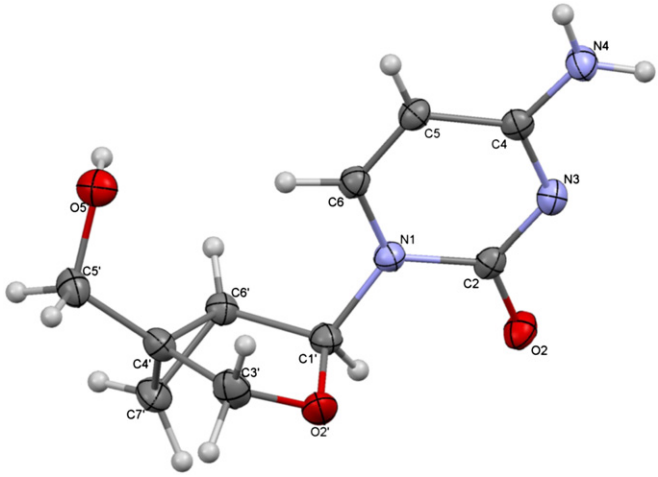
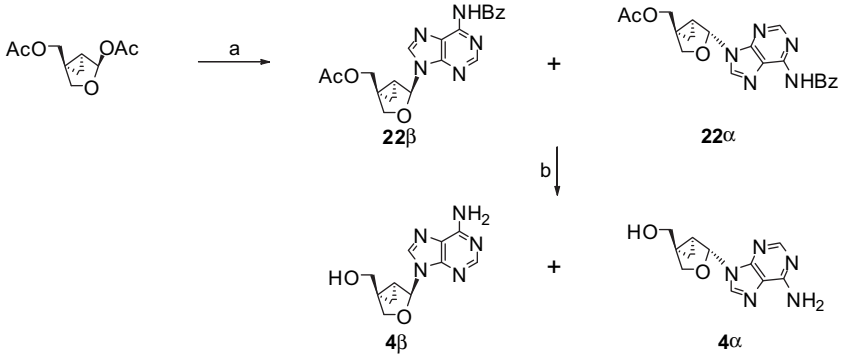


Figure 4. X-ray structure of 2′-oxabicyclo[3.1.0]hexyl cytosine nucleoside **3β**.

The crystal structure of the 2′-oxabicyclo[3.1.0]hexyl cytosine **3β** allowed us to confirm all the spectral assignments made by ^{1}H NMR. The crystal structure in Figure 4 showed that as expected, **3β** took the *north* conformation even though the nucleoside bore an oxygen atom on its pseudosugar ring, unlike bicyclo[3.1.0]hexyl nucleosides very well known to have a *north* conformation. X-ray crystallographic analysis in detail showed that the $C_{1'}$–$O_{2'}$ bond



Scheme 4. Reagents and conditions: (a) (i) N^6-benzoyladenine, HMDS, $(NH_4)_2SO_4$, reflux, overnight; (ii) TMSOTf, CH_3CN, rt, 2 h, 89% for **22α/β**; (b) 1 M NaOMe, MeOH, rt, overnight, 87% for **4β**, and 11% for **4α**.

Initially, the stereochemistry of the anomeric carbon was determined by a ^{1}H NMR coupling pattern on the basis of the fact that the anomeric proton of β-bicyclo[3.1.0]hexyl nucleoside with a *north* conformation was not coupled with the proton bonded to the

length (1.42 Å) was shorter than that (1.44 Å) of $O_{2'}$–$C_{3'}$, indicating that the anomeric effect ($n_{O2'} \rightarrow \sigma^*_{C1'\text{-}N1}$) worked on the β-nucleoside.[29,30] The crystal structure also showed that the conformation was restricted toward a $_2E$ conformation (the pseudorotation phase

angle P=348.0°, the maximum torsion angle υ_{max}=29.4°), one of the *north*-type puckered conformations.

3. Antiviral activity

To gain preliminary insight into the biological potential thymine and uracil nucleosides, **1α**, **1β**, **2α**, and **2β** were first subjected to antiviral screening versus herpes simplex virus types 1 and 2, coxsackie B virus types 1 and 3, poliovirus type 3 and human immunodeficiency virus types 1 and 2. Except thymine nucleoside **2β** exhibited toxicity-dependent *anti*-HIV types 1 and 2 activity (EC_{50}=45.44 μg/mL), its α anomer **2α** and uracil nucleosides **1α** and **1β** did not show antiviral activity. Also, no cytotoxicity arose up to 100 μg/mL in the cell lines used in the antiviral assays: Vero, HeLa and HTLV-1-infected human T-lymphocyte.

4. Conclusion

2′-Oxabicyclo[3.1.0]hexyl nucleoside derivatives **1α**/**β**, **2α**/**β**, **3α**/**β**, and **4α**/**β** with a *north* conformation have been designed and successfully synthesized to search for new antiviral agents including *anti*-HSV agents. These nucleosides are the first example of oxabicyclohexyl nucleosides having a fixed *north* conformation and a heteroatom on their pseudosugar ring template. It was observed that the addition of acetic acid prevented the migration of benzoyl group during desilylation with TBAF. The lack of antiviral activity with all the nucleosides tested may be very closely related to the absence of 3′-hydroxy group, which looks like a requisite substituent for antiviral activity. The crystal structure confirmed all the spectral assignments made by ^{1}H NMR and proved that 2′-oxabicyclo[3.1.0]hexyl nucleosides took a fixed *north* conformation. Also, X-ray crystallographic analysis provided that the anomeric effect worked on β-2′-oxabicyclo[3.1.0]hexyl nucleosides. These 2′-oxabicyclo[3.1.0]hexyl nucleoside derivatives will give great help for the preference studies between the conformation and enzymes related with the metabolism of nucleosides and nucleotides.

5. Experimental

5.1. General

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Varian Unity INOVA 400 and Varian Unity AS 500 instruments. Chemical shifts are reported with reference to the respective residual solvent or deuteriated peaks (δ_H 3.30 and δ_C 49.0 for CD_3OD, δ_H 7.27 and δ_C 77.0 for $CDCl_3$). Coupling constants are reported in hertz. The abbreviations used are as follows: s (singlet), d (doublet), m (multiplet), t (triplet), dd (doublet of doublets), br s (broad singlet). All the reactions described below were performed under argon or nitrogen atmosphere and monitored by TLC. All anhydrous solvents were distilled over CaH_2 or Na /benzophenone prior to use.

*5.1.1. (+)-(1R,5S)-Ethyl 2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylate (**5**).* Sodium (2.42 g, 105 mmol) was dissolved in EtOH (195 mL), and diethyl malonate (16.7 mL, 110 mmol) was added at 0 °C over 5 min to the solution. (*S*)-(+)-Epichlorohydrin (7.8 mL, 100 mmol) in EtOH (5 mL) was added dropwise to the solution at room temperature over 1 h, and the mixture was stirred under reflux for 20 h. The mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in methylene chloride and washed with H_2O. The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using hexane and ethyl acetate (3:1) to give cyclopropane-fused lactone **5** (11.40 g, 67%) as a colorless oil: $[\alpha]_D^{25}$ +121.44 (*c* 1.32, $CHCl_3$); IR (neat): ν 1766, 1743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (dd, 1H, *J*=4.8, 9.2 Hz, 4-*H*H), 4.22 (qd, 2H, *J*=2.4, 6.8 Hz, C*H*$_2$), 4.15 (d, 1H, *J*=9.2 Hz, 4-H*H*), 2.70 (m, 1H, 5-H), 2.04 (dd, 1H, *J*=4.8, 8.4 Hz, 6-*H*H), 1.34 (t, 1H, *J*=4.8 Hz, 6-H*H*), 1.27 (t, 3H, *J*=6.8 Hz, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 166.9, 67.2, 62.2, 29.6, 28.1, 20.9, 14.3; LRMS(FAB+) *m*/*z* 170 (M^+); HRMS(FAB+) *m*/*z* $C_8H_{10}O_4$ (M^+) calcd 170.0579, obsd 170.0576.

*5.1.2. (+)-(1R,5S)-1-(Hydroxymethyl)-3-oxabicyclo[3.1.0]hexan-2-one (**7**).* A solution of **5** (10.56 g, 62.04 mmol) in EtOH (204 mL) was treated with sodium hydroxide (2.48 g, 62.04 mmol) in EtOH (204 mL). After being stirred for 16 h at room temperature, sodium borohydride (11.74 g, 310.21 mmol) was added and the mixture was refluxed for 3 h. After cooling to room temperature, 2 M HCl (186 mL) was added slowly at 0 °C. The reaction mixture was evaporated under reduced pressure to remove EtOH, and to the resulting solution was added 2 M HCl (408 mL). After being stirred for 18 h at room temperature, the aqueous layer was extracted with methylene chloride several times. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography using methylene chloride and MeOH (20:1) to give lactone **7** (4.97 g, 62%) as a colorless oil: $[\alpha]_D^{25}$ +71.81 (*c* 2.07, $CHCl_3$); IR (neat): ν 3331, 1765 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (dd, 1H, *J*=4.8, 9.2 Hz, 4-*H*H), 4.13 (d, 1H, *J*=9.6 Hz, 4-H*H*), 4.06 (d, 1H, *J*=12.0 Hz, C*H*HOH), 3.57 (d, 1H, *J*=12.4 Hz, CH*H*OH), 3.41 (br s, 1H, O*H*), 2.28 (m, 1H, 5-H), 1.28 (dd, 1H, *J*=4.8, 7.6 Hz, 6-*H*H), 0.94 (t, 1H, *J*=5.2 Hz, 6-H*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 69.1, 60.7, 30.8, 22.0, 16.5; LRMS(FAB+) *m*/*z* 129 $(M+H)^+$; HRMS(FAB+) *m*/*z* $C_6H_9O_3$ $(M+H)^+$ calcd 129.0552, obsd 129.0546.

*5.1.3. (+)-(1R,5S)-1-((4-Methoxybenzyloxy)methyl)-3-oxabicyclo[3.1.0]hexan-2-one (**8**).* To a stirred suspension of NaH (300 mg, 7.6 mmol, 60% w/w in mineral oil) in Et_2O (80 mL) was added a solution of *p*-methoxybenzyl alcohol (9.34 mL, 75.24 mmol) in Et_2O (70 mL). After the resultant cloudy orange mixture was stirred for 30 min at room temperature and cooled to 0 °C, trichloroacetonitrile (7.6 mL, 75.79 mmol) was added. The reaction mixture was allowed to warm to room temperature for 4 h, and concentrated under reduced pressure before petroleum ether (100 mL) and MeOH (0.32 mL, 8.0 mmol) were added. The suspension was filtered through Celite and concentrated under reduced pressure to give the crude imidate (20.79 g, 100%) as a yellowish oil. To a stirred solution of the crude imidate (20.79 g, 67.71 mmol) and lactone **7** in methylene chloride (100 mL), was added $BF_3\cdot OEt_2$ (0.12 mL, 1.00 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. To the reaction mixture was added hexane (300 mL), and the precipitates were filtered through a pad of Celite and washed with CH_2Cl_2/hexane (10 mL, 1:2). The organic layers were washed with a saturated $NaHCO_3$ solution, dried with $MgSO_4$, concentrated under reduced pressure and purified by silica gel column chromatography using hexane and ethyl acetate (2:1) to give PMB ether **8** (9.51 g, 85%) as a colorless oil: $[\alpha]_D^{25}$ +4.69 (*c* 1.07, $CHCl_3$); IR (neat): ν 3084, 1767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, 2H, *J*=8.8 Hz, Ar), 6.85 (d, 2H, *J*=8.8 Hz, Ar), 4.50 (d, 1H, *J*=12.0 Hz, PMPC*H*H), 4.43 (d, 1H, *J*=11.6 Hz, PMPCH*H*), 4.27 (dd, 1H, *J*=4.8, 9.2 Hz, 4-*H*H), 4.12 (d, 1H, *J*=9.2 Hz, 4-H*H*), 4.07 (d, 1H, *J*=10.8 Hz, C*H*HOPMB), 3.38 (s, 3H, OCH_3), 3.39 (d, 1H, *J*=10.8 Hz, CH*H*OPMB), 2.23 (td, 1H, *J*=4.8, 7.6 Hz, 5-H), 1.28 (dd, 1H, *J*=4.4, 7.2 Hz, 6-*H*H), 0.93 (t, 1H, *J*=4.4 Hz, 6-H*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 159.5, 130.1, 129.6, 114.0, 73.1, 68.7, 67.2, 55.2, 28.9, 21.9, 16.5; LRMS(FAB+) *m*/*z* 249 $(M+H)^+$; HRMS(FAB+) *m*/*z* $C_{14}H_{17}O_4$ $(M+H)^+$ calcd 249.1127, obsd 249.1135.

*5.1.4. (+)-(1R,5S)-1-((4-Methoxybenzyloxy)methyl)-3-oxabicyclo[3.1.0]hexan-2-ol (**9**).* To a stirred solution of PMB ether **8** (8.88 g, 35.77 mmol) in anhydrous methylene chloride (100 mL) was

added diisobutylaluminum hydride (Dibal-H, 71.53 mL, 71.53 mmol, 1.0 M solution in hexanes) at −78 °C, and the reaction mixture was stirred for 30 min at the same temperature. MeOH (71.50 mL) was added and the resulting mixture was stirred overnight, allowing it to reach room temperature. The gel generated was filtered off through a pad of Celite, and the filtrate collected was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using hexane and ethyl acetate (1.8:1) to give lactol **9** (8.53 g, 95%) as a colorless oil: $[\alpha]_D^{25}$ +4.45 (*c* 1.34, $CHCl_3$); IR (neat): *ν* 3387, 3085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.22 (d, 2H, *J*=8.8 Hz, Ar), 6.85 (d, 2H, *J*=8.4 Hz, Ar), 5.25 (d, 1H, *J*=5.6 Hz, anomeric H), 4.48 (d, 1H, *J*=11.6 Hz, PMPC*H*H), 4.44 (d, 1H, *J*=11.6 Hz, PMPCH*H*), 4.32 (d, 1H, *J*=5.6 Hz, OH), 4.04 (dd, 1H, *J*=2.8, 7.6 Hz, 4-*H*H), 3.77 (s, 3H, OCH_3), 3.72–3.68 (m, 2H, 4-H*H*, C*H*HOPMB), 3.61 (d, 1H, *J*=10.4 Hz, CH*H*OPMB), 1.58–1.54 (m, 1H, 5-H), 0.66 (dd, 1H, *J*=4.8, 8.0 Hz, 6-*H*H), 0.56 (t, 1H, *J*=4.4 Hz, 6-H*H*); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.5, 129.9, 129.7, 114.1, 99.5, 73.0, 70.2, 67.5, 55.5, 32.6, 20.4, 13.3; LRMS(FAB+) *m*/*z* 251 $(M+H)^+$; HRMS(FAB+) *m*/*z* $C_{14}H_{19}O_4$ $(M+H)^+$ calcd 251.1283, obsd 251.1290.

*5.1.5. (+)-(1R,2S)-2-((tert-Butyldiphenylsilyloxy)methyl)-1-((4-methoxybenzyloxy) methyl)cyclopropanecarbaldehyde (**10**).* To a solution of lactol **9** (8.53 g, 34.07 mmol) and imidazole (4.87 g, 71.56 mmol) in anhydrous methylene chloride (150 mL) was added *tert*-butyldiphenylsilylchloride (9.30 mL, 39.19 mmol) dropwise at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was extracted with methylene chloride. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using hexane and ethyl acetate (12:1) to give silyl ether **10** (14.70 g, 97%) as a colorless oil: $[\alpha]_D^{25}$ +17.49 (*c* 1.22, $CHCl_3$); IR (neat): *ν* 3089, 1737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 9.49 (s, 1H, CHO), 7.68–7.37 (m, 10H, 2×Ph), 7.27 (d, 2H, *J*=8.5 Hz, Ar), 6.89 (d, 2H, *J*=9.0 Hz, Ar), 4.51 (s, 2H, PMPCH_2), 4.00 (dd, 1H, *J*=6.0, 12.0 Hz, TBDPSOC*H*H), 3.91 (d, 1H, *J*=10.0 Hz, C*H*HOPMB), 3.82 (s, 3H, OCH_3), 3.66 (dd, 1H, *J*=8.5, 11.5 Hz, TBDPSOCH*H*), 3.49 (d, 1H, *J*=10.5 Hz, CH*H*OPMB), 1.79–1.73 (m, 1H, 2-H), 1.44 (dd, 1H, *J*=5.5, 7.0 Hz, 3-*H*H), 1.23 (dd, 1H, *J*=5.5, 9.0 Hz, 3-H*H*), 1.04 (s, 9H, *tert*-butyl); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 201.0, 159.4, 135.8, 133.8, 133.5, 130.5, 129.9, 129.5, 128.0, 127.9, 114.0, 72.8, 70.8, 61.7, 55.5, 36.53, 31.2, 27.0, 19.4, 17.6; LRMS(FAB+) *m*/*z* 489 $(M+H)^+$; HRMS(FAB+) *m*/*z* $C_{30}H_{37}O_4Si$ $(M+H)^+$ calcd 489.2461, obsd 489.2457.

*5.1.6. (-)-((1S,2S)-2-((tert-Butyldiphenylsilyloxy)methyl)-1-((4-methoxybenzyloxy) methyl)cyclopropyl)methanol (**11**).* To a stirred solution of **10** (14.70 g, 30.08 mmol) in MeOH (100 mL) was added sodium borohydride (0.57 g, 15.04 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 10 min. After being evaporated under reduced pressure, the reaction mixture was extracted between ethyl acetate and H_2O, and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (5:1) to give alcohol **11** (14.09 g, 95%) as a colorless oil: $[\alpha]_D^{25}$ −5.51 (*c* 0.58, $CHCl_3$); IR (neat): *ν* 3392, 3086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.68–7.35 (m, 10H, 2×Ph), 7.26 (d, 2H, *J*=8.8 Hz, Ar), 6.87 (d, 2H, *J*=8.4 Hz, Ar), 4.53 (d, 1H, *J*=11.6 Hz, PMPC*H*H), 4.44 (d, 1H, *J*=11.6 Hz, PMPCH*H*), 4.08 (t, 1H, *J*=11.2 Hz, OH), 4.01 (dd, 1H, *J*=5.6, 11.6 Hz, TBDPSOC*H*H), 3.99 (d, 1H, *J*=10.8 Hz, TBDPSOCH*H*), 3.79 (s, 3H, OCH_3), 3.42 (t, 1H, *J*=11.2 Hz, C*H*HOH), 3.42 (dd, 1H, *J*=1.6, 10.4 Hz, CH*H*OH), 3.37 (dd, 1H, *J*=1.6, 10.4 Hz, C*H*HOPMB), 2.93 (d, 1H, *J*=9.6 Hz, CH*H*OPMB), 1.03 (s, 9H, *tert*-butyl), 1.03 (m, 1H, 2-H, overlapped by *tert*-butyl), 0.70 (dd, 1H, *J*=5.6, 8.4 Hz, 3-*H*H), 0.37 (t, 1H, *J*=5.2 Hz, 3-H*H*); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.3, 135.8, 135.7, 133.2, 133.1, 130.8, 130.1, 130.1, 129.4, 128.1, 128.0, 114.0, 75.0, 72.9, 65.0, 64.2, 55.5, 28.2, 27.0, 22.6, 19.3, 14.6; LRMS(FAB+) *m*/*z* 491 $(M+H)^+$; HRMS(FAB+) *m*/*z* $C_{30}H_{39}O_4Si$ $(M+H)^+$ calcd 491.2618, obsd 491.2629.

*5.1.7. (+)-((1R,2S)-2-((tert-Butyldiphenylsilyloxy)methyl)-1-((4-methoxybenzyloxy)methyl)cyclopropyl)methyl benzoate (**12**).* To a stirred solution of **11** (5.03 g, 10.25 mmol) and DMAP (0.13 g, 1.02 mmol) in methylene chloride (70 mL) and pyridine (4.14 mL, 51.24 mmol) was treated dropwise benzoyl chloride (1.31 mL, 12.81 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 8 h. After being evaporated under reduced pressure, the reaction mixture was extracted with ethyl acetate, washed with 0.5 M HCl solution and a saturated $NaHCO_3$ solution, dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give an oil, which was purified by silica gel column chromatography using hexane and ethyl acetate (15:1) to give compound **12** (5.79 g, 95%) as a colorless oil: $[\alpha]_D^{25}$ +17.30 (*c* 1.17, $CHCl_3$); IR (neat): *ν* 3086, 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.97–7.29 (m, 15H, 3×Ph), 7.22 (d, 2H, *J*=8.4 Hz, Ar), 6.79 (d, 2H, *J*=8.8 Hz, Ar), 4.60 (d, 1H, *J*=11.6 Hz, C*H*HOBz), 4.50 (d, 1H, *J*=11.6 Hz, PMPC*H*H), 4.46 (d, 1H, *J*=11.6 Hz, PMPCH*H*), 4.35 (d, 1H, *J*=11.6 Hz, CH*H*OBz), 3.84 (dd, 1H, *J*=6.0, 11.6 Hz, TBDPSOC*H*H), 3.73 (s, 3H, OCH_3), 3.72 (dd, 1H, *J*=7.2, 11.2 Hz, TBDPSOCH*H*), 3.43 (d, 1H, *J*=10.0 Hz, C*H*HOPMB), 3.38 (d, 1H, *J*=10.4 Hz, CH*H*OPMB), 1.26–1.15 (m, 1H, 2-H), 0.99 (s, 9H, *tert*-butyl), 0.72 (dd, 1H, *J*=5.6, 14.0 Hz, 3-*H*H), 0.55 (t, 1H, *J*=5.6 Hz, 3-H*H*); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 166.8, 159.3, 135.8, 133.9, 133.8, 132.9, 130.7, 130.6, 129.9, 129.4, 128.5, 127.9, 127.8, 113.9, 74.2, 72.4, 65.4, 63.5, 55.4, 27.0, 24.5, 24.3, 19.4, 13.5; LRMS(FAB+) *m*/*z* 595 $(M+H)^+$; HRMS(FAB+) *m*/*z* $C_{37}H_{43}O_5Si$ $(M+H)^+$ calcd 595.2880, obsd 595.2874.

*5.1.8. (+)-((1R,2S)-2-(Hydroxymethyl)-1-((4-methoxybenzyloxy)-methyl)cyclopropyl)methyl benzoate (13) and (+)-((1S,2S)-2-(hydroxymethyl)-2-((4-methoxybenzyloxy)methyl)cyclopropyl)methyl benzoate (**14**).* To a stirred solution of **12** (5.66 g, 9.51 mmol) in THF (60 mL) and acetic acid (0.65 mL, 11.41 mmol) was added *n*-tetrabutylammonium fluoride (11.4 mL, 11.4 mmol, 1 M solution in THF). And the reaction mixture was stirred at room temperature for 7 h. After the reaction mixture was evaporated under reduced pressure, the reaction mixture was extracted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using hexane and ethyl acetate (2:1) to give **13** (3.62 g, 100%) as a colorless oil: compound **13**: $[\alpha]_D^{25}$ +15.56 (*c* 0.91, $CHCl_3$); IR (neat): *ν* 3376, 3100, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.95–7.38 (m, 5H, Ph), 7.21 (d, 2H, *J*=8.8 Hz, Ar), 6.79 (d, 2H, *J*=8.8 Hz, Ar), 4.78 (d, 1H, *J*=11.6 Hz, C*H*HOBz), 4.47 (d, 1H, *J*=11.6 Hz, PMPC*H*H), 4.42 (d, 1H, *J*=12.0 Hz, PMPCH*H*), 4.17 (d, 1H, *J*=11.6 Hz, CH*H*OBz), 3.85 (dd, 1H, *J*=5.6, 12.0 Hz, HOC*H*H), 3.71 (s, 3H, OCH_3), 3.58 (d, 1H, *J*=9.6 Hz, C*H*HOPMB), 3.51 (dd, 1H, *J*=9.2, 11.6 Hz, HOCH*H*), 3.17 (d, 1H, *J*=10.0 Hz, CH*H*OPMB), 2.08 (br s, 1H, OH), 1.32–1.24 (m, 1H, 2-H), 0.85 (dd, 1H, *J*=5.2, 8.8 Hz, 3-*H*H), 0.55 (t, 1H, *J*=6.0 Hz, 3-H*H*); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 166.8, 159.3, 133.3 130.4, 130.2, 129.8, 129.5, 128.7, 113.9, 79.9, 72.8, 65.4, 62.7, 55.4, 24.7, 24.3, 13.9; LRMS(FAB+) *m*/*z* 357 $(M+H)^+$; HRMS(FAB+) *m*/*z* $C_{21}H_{25}O_5$ $(M+H)^+$ calcd 357.1702, obsd 357.1698. Compound **14** (benzoyl-migrating compound, generated in the absence of acetic acid): $[\alpha]_D^{25}$ +15.48 (*c* 1.95, $CHCl_3$); IR (neat): *ν* 3384, 3088, 1731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 8.05–7.42 (m, 5H, Ph), 7.24 (d, 2H, *J*=8.5 Hz, Ar), 6.87 (d, 2H, *J*=8.5 Hz, Ar), 4.61 (dd, 1H, *J*=6.5, 11.5 Hz, C*H*HOBz), 4.50 (d, 1H, *J*=11.5 Hz, PMPC*H*H), 4.46 (d, 1H, *J*=11.5 Hz, PMPCH*H*), 4.28 (dd, 1H, *J*=8.5, 12.0 Hz, CH*H*OBz), 3.98 (dd, 1H, *J*=6.0, 12.0 Hz, C*H*HOH), 3.81 (s, 3H, OCH_3), 3.63 (dd, 1H, *J*=5.0, 11.5 Hz, CH*H*OH), 3.50 (d, 1H, *J*=10.0 Hz, C*H*HOPMB), 3.40 (d, 1H, *J*=10.0 Hz, CH*H*OPMB), 2.70 (t, 1H, *J*=6.0 Hz, OH) 1.40–1.34 (m, 1H, 2-H), 0.82 (dd, 1H, *J*=5.5, 8.5 Hz, 3-*H*H), 0.61 (t, 1H, *J*=5.0 Hz, 3-H*H*); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 166.8, 159.5, 133.3 130.4, 130.2, 129.8, 129.4, 128.6, 114.1, 76.7, 72.9, 65.3, 64.9, 55.5, 24.6, 20.9, 13.9; LRMS(FAB+) *m/z* 357 $(M+H)^+$; HRMS(FAB+) *m/z* $C_{21}H_{25}O_5$ $(M+H)^+$ calcd 357.1702, obsd 357.1703.

*5.1.9. (+)-((1R,2S)-2-Formyl-1-((4-methoxybenzyloxy)methyl)cyclopropyl) methylbenzoate (**15**).* To a stirred solution of oxalyl chloride (1.51 mL, 17.26 mmol) in anhydrous methylene chloride (100 mL) was added a solution of dimethyl sulfoxide (2.67 mL, 37.56 mmol) in anhydrous methylene chloride (30 mL) at −78 °C, and the mixture was stirred at the same temperature for 20 min. To this mixture was added a solution of **13** (3.62 g, 10.15 mmol) in anhydrous methylene chloride (40 mL), and the reaction mixture was stirred at −78 °C for 1 h. After the addition of triethylamine (9.76 mL, 70.05 mmol) at −78 °C, the mixture was gradually warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with a saturated NH_4Cl solution (50 mL) and then extracted with methylene chloride. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using hexane and ethyl acetate (15:1) as eluent to give aldehyde **15** (3.38 g, 94%) as a colorless oil: $[\alpha]_D^{25}$ +71.24 (*c* 1.16, $CHCl_3$); IR (neat): ν 3094, 1734, 1724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.58 (d, 1H, *J*=4.5 Hz, CHO) 7.95–7.41 (m, 5H, Ph), 7.22 (d, 2H, *J*=9.0 Hz, Ar), 6.83 (d, 2H, *J*=9.0 Hz, Ar), 4.86 (d, 1H, *J*=12.0 Hz, C*H*HOBz), 4.47 (d, 1H, *J*=12.0 Hz, PMPC*H*H), 4.44 (d, 1H, *J*=11.5 Hz, PMPCH*H*), 4.27 (d, 1H, *J*=12.0 Hz, CH*H*OBz), 3.75 (s, 3H, OCH_3), 3.61 (d, 1H, *J*=9.5 Hz, C*H*HOPMB), 3.37 (d, 1H, *J*=10.0 Hz, CH*H*OPMB), 2.12–2.08 (m, 1H, 2-H), 1.62 (t, 1H, *J*=5.5 Hz, 3-*H*H), 1.36 (dd, 1H, *J*=5.0, 8.0 Hz, 3-H*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 166.1, 159.3, 133.1 129.8, 129.7, 129.6, 129.3, 128.4, 113.8, 72.8, 71.8, 63.3, 55.2, 32.5, 31.4, 13.6; LRMS(FAB+) *m/z* 355 $(M+H)^+$; HRMS(FAB+) *m/z* $C_{21}H_{23}O_5$ $(M+H)^+$ calcd 355.1545, obsd 355.1552.

*5.1.10. (+)-(1S,2S,5R)-5-((4-Methoxybenzyloxy)methyl)-3-oxabicyclo[3.1.0]hexan-2-ol (**16**).* To a solution of aldehyde **15** (3.38 g, 9.54 mmol) in MeOH (40 mL) was added 1 M sodium methoxide (2.86 mL, 2.86 mmol). After the reaction mixture was stirred at room temperature for 4 h, the reaction mixture was extracted with methylene chloride and washed with NH_4Cl, and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using hexane and ethyl acetate (2:1) to give lactol **16** (2.37 g, 99%) as a colorless oil: $[\alpha]_D^{25}$ +39.07 (*c* 1.78, $CHCl_3$); IR (neat): ν 3397, 3083 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, 2H, *J*=8.5 Hz, Ar), 6.88 (d, 2H, *J*=8.5 Hz, Ar), 5.17 (d, 1H, *J*=5.5 Hz, anomeric H), 4.48 (s, 2H, $PMPCH_2$), 4.04 (d, 1H, *J*=8.0 Hz, 4-*H*H), 3.87 (d, 1H, *J*=5.5 Hz, OH), 3.82 (d, 1H, *J*=8.0 Hz, 4-H*H*), 3.80 (s, 3H, OCH_3), 3.65 (d, 1H, *J*=10.5 Hz, PMBOC*H*H), 3.55 (d, 1H, *J*=10.5 Hz, PMBOCH*H*), 1.51 (dd, 1H, *J*=4.0, 8.0 Hz, 1-H), 0.71 (dd, 1H, *J*=4.5, 8.0 Hz, 6-*H*H), 0.56 (t, 1H, *J*=4.5 Hz, 6-H*H*); ^{13}C NMR (120 MHz, $CDCl_3$) δ 159.3, 130.0, 129.4, 113.8, 98.7, 72.5, 70.7, 69.3, 55.3, 27.6, 27.3, 12.7; LRMS(FAB+) *m/z* 251 $(M+H)^+$; HRMS(FAB+) *m/z* $C_{14}H_{19}O_4$ $(M+H)^+$ calcd 251.1283, obsd 251.1289.

*5.1.11. (+)-(1S,2S,5R)-5-(Hydroxymethyl)-3-oxabicyclo[3.1.0]hexan-2-ol (**17**).* To a solution of lactol **16** (2.37 g, 9.47 mmol) in 1,4-dioxane (10.0 mL) was added 3 M HCl (10.0 mL) solution. And the reaction mixture was stirred at room temperature for two days. After being neutralized with triethylamine, the reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography using ethyl acetate and MeOH (40:1) as eluent to give diol **17** (803.8 mg, 66%) as a colorless oil: $[\alpha]_D^{25}$ +77.59 (*c* 3.44, $CHCl_3$); IR (neat): ν 3399 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 5.11 (s, 1H, anomeric H), 3.97 (d, 1H, *J*=8.0 Hz, 4-*H*H), 3.83 (d, 1H, *J*=12.0 Hz, HOC*H*H), 3.76 (d, 1H, *J*=8.0 Hz, 4-H*H*), 3.63 (d, 1H, *J*=12.0 Hz, HOCH*H*), 1.47 (dd, 1H, *J*=4.0, 8.0 Hz, 1-H), 0.77–0.75 (m, 1H, 6-*H*H), 0.45 (t, 1H, *J*=4.5 Hz, 6-H*H*); ^{13}C NMR (100 MHz, CD_3OD) δ 98.5, 68.8, 62.9, 29.8, 26.9, 11.7; LRMS(FAB+) *m/z* 131 $(M+H)^+$; HRMS(FAB+) *m/z* $C_6H_{11}O_3$ $(M+H)^+$ calcd 131.0708, obsd 131.0715.

*5.1.12. (+)-((1S,4R,5S)-4-Acetoxy-3-oxabicyclo[3.1.0]hexan-1-yl) methyl acetate (**18**).* To a stirred solution of diol **17** (803.8 mg, 6.27 mmol) in pyridine was added dropwise acetic anhydride (2.07 mL, 21.9 mmol) at 0 °C and the reaction mixture was stirred at room temperature overnight. After the reaction mixture was evaporated under reduced pressure, the reaction mixture was extracted with EtOAc, washed with 0.5 M HCl solution and a saturated $NaHCO_3$ solution, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography using hexane and ethyl acetate (3:1) as eluent to give diacetate **18** (946 mg, 70%) as a colorless oil: $[\alpha]_D^{25}$ +102.82 (*c* 1.93, $CHCl_3$); IR (neat): ν 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (s, 1H, anomeric H), 4.35 (d, 1H, *J*=11.6 Hz, AcOC*H*H), 4.11 (d, 1H, *J*=11.6 Hz, AcOCH*H*), 3.97 (d, 1H, *J*=8.4 Hz, 2-*H*H), 3.86 (d, 1H, *J*=8.0 Hz, 2-H*H*), 2.04 (s, 3H, Ac), 2.03 (s, 3H, Ac), 1.65 (dd, 1H, *J*=4.4, 8.8 Hz, 5-H), 0.86 (dd, 1H, *J*=5.2, 8.0 Hz, 6-*H*H), 0.63 (t, 1H, *J*=10.0 Hz, 6-H*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.5, 95.9, 71.3, 65.2, 27.0, 26.6, 21.5, 21.0, 12.8; LRMS(FAB+) *m/z* 215 $(M+H)^+$; HRMS(FAB+) *m/z* $C_{10}H_{15}O_5$ $(M+H)^+$ calcd 215.0919, obsd 215.0924.

*5.1.13. ((1S,4R/S,5S)-4-(2,4-Dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-oxabicyclo[3.1.0]hexan-1-yl)methyl acetate (**19α/β**).* A mixture of uracil (121.7 mg, 1.09 mmol), HMDS (5 mL), and a catalytic amount of ammonium sulfate was refluxed overnight. The resultant clear solution was concentrated to dryness under reduced pressure and anhydrous conditions to give a silylated uracil. A solution of diacetate **18** (155.1 mg, 0.72 mmol) in dry acetonitrile (7 mL) and TMSOTf (0.15 mL, 1.09 mmol) were successively added to the residue at 0 °C. The reaction mixture was stirred for 2 h, poured into a saturated $NaHCO_3$ solution, and filtered through Celite. The resulting mixture was evaporated, extracted with CH_2Cl_2, washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography using methylene chloride and methanol (20:1) as eluent to give inseparable α- and β-uracil nucleoside mixture **19α/β** (161.0 mg, 84%) as a colorless oil: UV (MeOH) λ_{max} 262 nm; IR (thin film): ν 1735, 1702, 1654 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.76 (d, 1H, *J*=8.4 Hz, H-6, minor), 7.73 (d, 1H, *J*=7.6 Hz, H-6, major), 5.98 (d, 1H, *J*=2.8 Hz, anomeric H, minor), 5.94 (s, 1H, anomeric H, major), 5.70 (d, 1H, *J*=7.6 Hz, H-5, major), 5.64 (d, 1H, *J*=8.4 Hz, H-5, minor), 4.43 (d, 1H, *J*=12.0 Hz, AcOC*H*H, major), 4.28 (d, 1H, *J*=11.6 Hz, AcOC*H*H, minor), 4.22 (d, 1H, *J*=12.4 Hz, AcOCH*H*, major), 4.17 (d, 1H, *J*=12.4 Hz, AcOCH*H*, minor), 4.08–4.03 (m, 2H, 2-*H*H, major, minor), 3.97 (d, 1H, *J*=8.4 Hz, 2-H*H*, minor), 3.90 (d, 1H, *J*=8.8 Hz, 2-H*H*, major), 2.06 (s, 3H, CH_3CO, major), 2.04 (s, 3H, CH_3CO, minor), 1.91 (dd, 1H, *J*=4.0, 8.4 Hz, 5-H, major), 1.91 (m, 1H, 5-H, minor), 1.10 (m, 1H, 6-*H*H, major), 0.98–0.91 (m, 2H, 6-H_2, minor), 0.74 (t, 1H, *J*=4.4 Hz, 6-H*H*, major); ^{13}C NMR (100 MHz, CD_3OD) δ 171.5, 171.3, 165.1, 164.9, 151.3, 151.1, 141.2, 141.0, 101.4, 100.7, 87.1, 85.9, 70.9, 65.8, 64.5, 28.9, 28.3, 25.8, 24.8, 19.5, 13.3, 9.9; LRMS(FAB+) *m/z* 267 $(M+H)^+$; HRMS(FAB+) *m/z* $C_{12}H_{15}N_2O_5$ $(M+H)^+$ calcd 267.0981, obsd 267.0983.

*5.1.14. ((1S,4R/S,5S)-4-(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-oxabicyclo[3.1.0]hexan-1-yl)methyl acetate (**20α/β**).* A mixture of thymine (131.9 mg, 1.05 mmol), HMDS (5 mL), and a catalytic amount of ammonium sulfate was refluxed overnight. The resultant clear solution was concentrated to dryness under reduced pressure and anhydrous conditions to give a silyated thymine. A solution of diacetate **18** (149.3 mg, 0.70 mmol) in dry acetonitrile

(7 mL) and TMSOTf (0.19 mL, 1.05 mmol) were successively added to the residue at 0 °C. The reaction mixture was stirred for 2 h, poured into a saturated $NaHCO_3$ solution, and filtered through Celite. The resulting mixture was evaporated, extracted with CH_2Cl_2, washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography using methylene chloride and methanol (25:1) as eluent to give inseparable α- and β-thymine nucleoside mixture **20α/β** (170.3 mg, 87%) as a colorless oil: UV (MeOH) λ_{max} 266 nm; IR (thin film): ν 1736, 1707, 1692 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.55 (d, 1H, J=1.2 Hz, H-6, minor), 7.51 (d, 1H, J=0.8 Hz, H-6, major), 5.98 (d, 1H, J=2.4 Hz, anomeric H, minor), 5.98 (s, 1H, anomeric H, major), 4.49 (d, 1H, J=12.4 Hz, AcOC*H*H, major), 4.28 (d, 1H, J=12.4 Hz, AcOC*H*H, minor), 4.18 (d, 2H, J=12.0 Hz, AcOCH*H*, major, minor), 4.09 (d, 1H, J=8.4 Hz, 2-*H*H, major), 4.04 (d, 1H, J=8.4 Hz, 2-*H*H, minor), 3.95 (d, 1H, J=8.4 Hz, 2-H*H*, minor), 3.88 (d, 1H, J=8.4 Hz, 2-H*H*, major), 2.08 (s, 3H, CH_3CO, major), 2.04 (s, 3H, CH_3CO, minor), 1.92–1.89 (m, 2H, 5-H, major, minor), 1.90 (d, 3H, J=0.8 Hz, CH_3, major), 1.86 (d, 3H, J=0.8 Hz, CH_3, minor), 1.09–1.06 (ddd, 1H, J=0.8, 5.2, 8.4 Hz, 6-*H*H, major), 1.01 (t, 1H, J=4.8 Hz, 6-*H*H, minor), 0.95–0.91 (m, 1H, 6-H*H*, minor), 0.93 (t, 1H, J=4.4 Hz, 6-H*H*, major); ^{13}C NMR (100 MHz, CD_3OD) δ 171.5, 171.4, 165.2, 165.1, 151.5, 151.3, 136.8, 136.5, 110.2, 109.6, 86.9, 85.7, 70.8, 70.7, 65.1, 64.5, 29.1, 28.1, 25.7, 24.7, 19.6, 19.5, 13.2, 11.5, 11.3, 10.0; LRMS(FAB+) m/z 281 $(M+H)^+$; HRMS(FAB+) m/z $C_{13}H_{17}N_2O_5$ $(M+H)^+$ calcd 281.1137, obsd 231.1129.

*5.1.15. ((1S,4R/S,5S)-4-(4-Benzamido-2-oxopyrimidin-1(2H)-yl)-3-oxabicyclo[3.1.0]hexan-1-yl)methyl acetate (**21**α/β).* A mixture of N^4-benzoylcytosine (226.8 mg, 1.24 mmol), HMDS (5 mL), and a catalytic amount of ammonium sulfate was refluxed overnight. The resultant clear solution was concentrated to dryness under reduced pressure and anhydrous conditions to give a silylated N^4-benzoylcytosine. A solution of diacetate **18** (177.0 mg, 0.83 mmol) in dry acetonitrile (7 mL) and TMSOTf (0.15 mL, 1.09 mmol) were successively added to the residue at 0 °C. The reaction mixture was stirred for 2 h, poured into a saturated $NaHCO_3$ solution, and filtered through Celite. The resulting mixture was evaporated, extracted with CH_2Cl_2, washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography using methylene chloride and methanol (20:1) as eluent to give inseparable α- and β-N^4-benzoylcytosine nucleoside mixture **21α/β** (194.6 mg, 64%) as a white solid: UV (MeOH) λ_{max} 260, 304 nm; IR (thin film): ν 1734, 1708, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (br s, 1H, N*H*Bz), 7.89–7.84 (m, 3H, Ar, H-6), 7.62–7.58 (m, 1H, Ar), 7.52–7.48 (m, 3H, Ar, H-5), 5.99 (s, 1H, anomeric H), 4.31 (d, 1H, J=12.0 Hz, AcOC*H*H), 4.15 (d, 1H, J=8.4 Hz, 2-*H*H), 4.13 (d, 1H, J=12.0 Hz, AcOCH*H*), 4.07 (d, 1H, J=8.8 Hz, 2-H*H*), 2.09–2.05 (m, 1H, 5-H), 2.04 (s, 3H, CH_3CO), 1.10 (dd, 1H, J=5.2, 8.8 Hz, 6-*H*H), 0.87 (t, 1H, J=4.8 Hz, 6-H*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 166.6, 162.5, 155.2, 144.4, 143.7, 133.5, 129.3, 127.8, 96.5, 89.5, 72.5, 64.7, 28.7, 28.1, 20.9, 14.7; LRMS(FAB+) m/z 370 $(M+H)^+$; HRMS(FAB+) m/z $C_{19}H_{20}N_3O_5$ $(M+H)^+$ calcd 370.1403, obsd 370.1407.

*5.1.16. ((1S,4R/S,5S)-4-(6-Benzamido-9H-purin-9-yl)-3-oxabicyclo[3.1.0]hexan-1-yl)methyl acetate (**22**α/β).* A mixture of N^6-benzoyladenine (268.5 mg, 1.12 mmol), HMDS (5 mL), and a catalytic amount of ammonium sulfate was refluxed overnight. The resultant clear solution was concentrated to dryness under reduced pressure and anhydrous conditions to give a silylated N^6-benzoyladenine. A solution of diacetate **18** (160.3 mg, 0.75 mmol) in dry acetonitrile (7 mL) and TMSOTf (0.20 mL, 1.12 mmol) were successively added to the residue at 0 °C. The reaction mixture was stirred for 2 h, poured into a saturated $NaHCO_3$ solution, and filtered through Celite. The resulting mixture was evaporated, extracted with CH_2Cl_2, washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography using methylene chloride and methanol (30:1) as eluent to give give inseparable α- and β-N^6-benzoyladenine nucleoside mixture **22α/β** (261 mg, 89%) as a colorless oil: UV (MeOH) λ_{max} 280 nm; IR (thin film): ν 3086, 1740, 1670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.05 (s, 1H, NHBz), 8.81 (s, 1H, H-8), 8.32 (s, 1H, H-2), 8.03–7.51 (m, 5H, Ar), 6.29 (s, 1H, anomeric H), 4.56 (d, 1H, J=12.0 Hz, AcOC*H*H), 4.33 (d, 1H, J=12.0 Hz, AcOCH*H*), 4.11 (d, 1H, J=8.5 Hz, 2-*H*H), 4.04 (d, 1H, J=9.0 Hz, 2-H*H*), 2.15 (s, 3H, CH_3CO), 2.13 (dd, 1H, J=4.5, 8.5 Hz, 5-H), 1.13 (ddd, 1H, J=0.5, 4.4, 8.0 Hz, 6-*H*H), 0.99 (t, 1H, J=4.5 Hz, 6-H*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 164.8, 153.0, 152.2, 149.7, 141.2, 133.8, 133.0, 129.1, 128.1, 123.6, 85.1, 70.8, 64.8, 28.9, 26.1, 21.9, 13.7; LRMS(FAB+) m/z 394 $(M+H)^+$; HRMS(FAB+) m/z $C_{20}H_{20}N_5O_4$ $(M+H)^+$ calcd 394.1515, obsd 394.1522.

*5.1.17. (+)-1-((1S,2S,5R)-5-(Hydroxymethyl)-3-oxabicyclo[3.1.0]hexan-2-yl)pyrimidine-2,4(1H,3H)-dione (1β) and (+)-1-((1S,2R,5R)-5-(hydroxymethyl)-3-oxabicyclo[3.1.0]hexan-2-yl)-pyrimidine-2,4(1H,3H)-dione (**1**α).* To a stirred solution of **19α** and **19β** mixture (161.0 mg, 0.60 mmol) in MeOH (2 mL) was added 1 M sodium methoxide (0.12 mL, 0.12 mmol) at 0 °C and the reaction mixture was stirred at room temperature overnight. After the reaction mixture was concentrated in vacuo, the resulting residue was purified by silica gel column chromatography using methylene chloride, ether and methanol (20:10:1.5) as eluent to give the final β-anomer of uracil nucleoside **1β** (97.4 mg, 72%) as a white solid along with its α-anomer **1α** (31.5 mg, 23%) as a white solid: compound **1β** (less polar material, β-anomer): mp 196.8–197.5 °C; UV (MeOH) λ_{max} 261 nm; $[\alpha]_D^{25}$ +88.54 (c 0.80, MeOH); IR (thin film): ν 3348, 1700, 1659 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 8.01 (d, 1H, J=8.0 Hz, H-6), 6.00 (s, 1H, anomeric H), 5.68 (d, 1H, J=8.0 Hz, H-5), 4.13 (d, 1H, J=8.0 Hz, 4-*H*H), 3.99 (d, 1H, J=12.0 Hz, HOC*H*H), 3.88 (d, 1H, J=8.0 Hz, 4-H*H*), 3.60 (d, 1H, J=12.0 Hz, HOCH*H*), 1.77 (dd, 1H, J=4.0, 8.5 Hz, 1-H), 1.01 (ddd, 1H, J=1.0, 5.5, 8.5 Hz, 6-*H*H), 0.68 (t, 1H, J=4.5 Hz, 6-H*H*); ^{13}C NMR (100 MHz, CD_3OD) δ 165.0, 151.5, 141.7, 101.3, 86.6, 70.5, 61.4, 31.9, 24.9, 12.9; LRMS(FAB+) m/z 225 $(M+H)^+$; HRMS(FAB+) m/z $C_{10}H_{13}N_2O_4$ $(M+H)^+$ calcd 225.0875, obsd 225.0882; Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.71; H, 5.42; N, 12.27; compound **1α** (more polar material, α-anomer): mp 177.6–178.5 °C; UV (MeOH) λ_{max} 262 nm; $[\alpha]_D^{25}$ +133.96 (c 0.78, MeOH); IR (thin film): ν 3336, 1701, 1653 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.78 (d, 1H, J=8.0 Hz, H-6), 5.99 (d, 1H, J=2.8 Hz, anomeric H), 5.64 (d, 1H, J=8.4 Hz, H-5), 4.05 (d, 1H, J=8.4 Hz, 4-*H*H), 4.02 (d, 1H, J=8.0 Hz, 4-H*H*), 3.68 (s, 2H, $HOCH_2$), 1.94–1.90 (m, 1H, 1-H), 0.89–0.84 (m, 2H, 6-H_2); ^{13}C NMR (100 MHz, CD_3OD) δ 165.1, 151.2, 141.1, 100.6, 86.4, 70.9, 62.3, 31.2, 24.1, 9.6; LRMS(FAB+) m/z 225 $(M+H)^+$; HRMS(FAB+) m/z $C_{10}H_{13}N_2O_4$ $(M+H)^+$ calcd 225.0875, obsd 225.0879.

*5.1.18. (+)-1-((1S,2S,5R)-5-(Hydroxymethyl)-3-oxabicyclo[3.1.0]-hexan-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (2β) and (+)-1-((1S,2R,5R)-5-(hydroxymethyl)-3-oxabicyclo[3.1.0]hexan-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**2**α).* To a stirred solution of **20α** and **20β** mixture (170.3 mg, 0.61 mmol) in MeOH (2 mL) was added 1 M sodium methoxide (0.12 mL, 0.12 mmol) at 0 °C and the reaction mixture was stirred at room temperature overnight. After the reaction mixture was concentrated in vacuo, the resulting residue was purified by silica gel column chromatography using ethyl acetate as eluent to give the final β-anomer of thymine nucleoside **2β** (77.5 mg, 54%) as a colorless sticky oil along with its α-anomer **2α** (51.9 mg, 36%) as a white solid: compound **2β** (less polar material, β-anomer): UV (MeOH) λ_{max} 267 nm; $[\alpha]_D^{25}$ +84.43 (c 1.16, MeOH); IR (thin film): ν 3334, 1694, 1684 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.98 (d, 1H, J=1.6 Hz, H-6), 6.00 (s, 1H, anomeric H), 4.13 (d, 1H, J=8.4 Hz, 4-*H*H), 4.05 (d, 1H, J=12.4 Hz, HOC*H*H), 3.84 (d, 1H, J=8.8 Hz, 4-H*H*), 3.52 (d, 1H, J=11.6 Hz, HOCH*H*), 1.85 (d, 3H,

J=1.2 Hz, CH_3), 1.73 (dd, 1H, J=4.4, 8.8 Hz, 1-H), 0.99–0.96 (ddd, 1H, J=0.8, 4.8, 8.0 Hz, 6-*H*H), 0.65 (t, 1H, J=4.4 Hz, 6-H*H*); ^{13}C NMR (100 MHz, CD_3OD) δ 165.2, 151.7, 137.5, 110.2, 86.1, 70.0, 61.4, 31.9, 24.8, 12.9, 11.2; LRMS(FAB+) m/z 239 $(M+H)^+$; HRMS(FAB+) m/z $C_{11}H_{15}N_2O_4$ $(M+H)^+$ calcd 239.1032, obsd 239.1020; Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.42; H, 6.10; N, 11.88; compound **2α** (more polar material, α-anomer): mp 154.3–155.1 °C; UV (MeOH) λ_{max} 268 nm; $[\alpha]_D^{25}$ +103.18 (c 0.65, MeOH); IR (thin film): ν 3327, 1698, 1675 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 (s, 1H, H-6), 5.99 (d, 1H, J=2.8 Hz, anomeric H), 4.05 (d, 1H, J=8.0 Hz, 4-*H*H), 4.00 (d, 1H, J=8.4 Hz, 4-H*H*), 3.68 (s, 2H, HOCH_2), 1.89 (ddd, 1H, J=2.8, 4.4, 8.0 Hz, 1-H), 1.86 (d, 3H, J=0.8 Hz, CH_3), 0.92 (t, 1H, J=4.8 Hz, 6-*H*H), 0.85 (dd, 1H, J=5.2, 8.0 Hz, 6-H*H*); ^{13}C NMR (100 MHz, CD_3OD) δ 165.3, 151.3, 136.7, 109.5, 86.1, 70.8, 62.3, 30.9, 24.0, 11.2, 9.6; LRMS(FAB+) m/z 239 $(M+H)^+$; HRMS(FAB+) m/z $C_{11}H_{15}N_2O_4$ $(M+H)^+$ calcd 239.1032, obsd 239.1022.

*5.1.19. (+)-4-Amino-1-((1S,2S,5R)-5-(hydroxymethyl)-3-oxabicyclo[3.1.0]hexan-2-yl)pyrimidin-2(1H)-one (3β) and (+)-4-amino-1-((1S,2R,5R)-5-(hydroxymethyl)-3-oxabicyclo[3.1.0]hexan-2-yl)pyrimidin-2(1H)-one (**3α**).* To a stirred solution of **21α** and **21β** mixture (194.6 mg, 0.53 mmol) in MeOH (2 mL) was added 1 M sodium methoxide (0.11 mL, 0.11 mmol) at 0 °C and the reaction mixture was stirred at room temperature overnight. After the reaction mixture was concentrated in vacuo, the resulting residue was purified by silica gel column chromatography using methylene chloride and methanol (6:1) as eluent to give the final β-anomer of cytosine nucleoside **3β** (97.5 mg, 83%) as a white solid along with its α-anomer **3α** (15.5 mg, 13%) as a colorless sticky oil: compound **3β** (more polar material, β-anomer): mp 220.6–222.8 °C; UV (MeOH) λ_{max} 273 nm; $[\alpha]_D^{25}$ +54.22 (c 0.98, MeOH); IR (thin film): ν 3339, 1704 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.91 (d, 1H, J=7.6 Hz, H-6), 6.00 (s, 1H, anomeric H), 5.88 (d, 1H, J=7.2 Hz, H-5), 4.11 (dd, 1H, J=0.8, 8.4 Hz, 4-*H*H), 3.93 (d, 1H, J=12.0 Hz, HOC*H*H), 3.87 (d, 1H, J=8.4 Hz, 4-H*H*), 3.57 (d, 1H, J=12.0 Hz, HOCH*H*), 1.75 (dd, 1H, J=4.0, 8.4 Hz, 1-H), 0.97 (ddd, 1H, J=0.8, 4.8, 8.4 Hz, 6-*H*H), 0.65 (t, 1H, J=4.8 Hz, 6-H*H*); ^{13}C NMR (100 MHz, CD_3OD) δ 166.5, 157.5, 141.7, 94.8, 87.5, 70.5, 61.6, 31.8, 25.6, 13.0; LRMS(FAB+) m/z 224 $(M+H)^+$; HRMS(FAB+) m/z $C_{10}H_{14}N_3O_3$ $(M+H)^+$ calcd 224.1035, obsd 224.1028; Anal. Calcd for $C_{10}H_{13}N_3O_3\cdot 0.1H_2O$: C, 53.37; H, 5.91; N, 18.67. Found: C, 53.34; H, 6.05; N, 18.53; compound **3α** (less polar material, α-anomer): UV (MeOH) λ_{max} 271 nm; $[\alpha]_D^{25}$ +155.49 (c 1.37, MeOH); IR (thin film): ν 3352, 1706 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (d, 1H, J=7.6 Hz, H-6), 5.99 (d, 1H, J=2.8 Hz, anomeric H), 5.85 (d, 1H, J=7.6 Hz, H-5), 4.07 (d, 1H, J=8.4 Hz, 4-*H*H), 4.04 (d, 1H, J=8.0 Hz, 4-H*H*), 3.68 (d, 1H, J=12.0 Hz, HOC*H*H), 3.65 (d, 1H, J=12.0 Hz, HOCH*H*), 2.02–1.98 (m, 1H, 1-H), 0.78–0.77 (m, 2H, 6-H_2); ^{13}C NMR (100 MHz, CD_3OD) δ 166.5, 157.1, 141.3, 94.0, 87.1, 71.1, 62.4, 31.3, 24.7, 9.3; LRMS(FAB+) m/z 224 $(M+H)^+$; HRMS(FAB+) m/z $C_{10}H_{14}N_3O_3$ $(M+H)^+$ calcd 224.1035, obsd 224.1026.

*5.1.20. (+)-((1R,4S,5S)-4-(6-Amino-9H-purin-9-yl)-3-oxabicyclo[3.1.0]hexan-1-yl) methanol (4β) and (+)-((1R,4R,5S)-4-(6-amino-9H-purin-9-yl)-3-oxabicyclo[3.1.0]hexan-1-yl)methanol (**4α**).* To a stirred solution of **22α**/**β** mixture (250 mg, 0.64 mmol) in MeOH (2 mL) was added 1 M sodium methoxide (3.83 mL, 3.83 mmol) at 0 °C and the reaction mixture was stirred at room temperature 15 h. After the reaction mixture was concentrated in vacuo, the resulting residue was purified by silica gel column chromatography using methylene chloride and methanol (10:1→7:1) as eluent to give the final β-anomer of adenine nucleoside **4β** (137 mg, 87%) as a white solid along with its α-anomer **4α** (18 mg, 11%) as a colorless sticky oil: compound **4β** (less polar material, β-anomer): mp 247.7–249.0 °C; UV (MeOH) λ_{max} 260 nm; $[\alpha]_D^{25}$ +47.56 (c 0.42, MeOH); IR (thin film): ν 3354, 3091 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 8.55 (s, 1H, H-8), 8.20 (s, 1H, H-2), 6.18 (s, 1H, anomeric H), 4.17 (d, 1H, J=8.5 Hz, 2-*H*H), 4.10 (d, 1H, J=12.0 Hz, HOC*H*H), 3.93 (d, 1H, J=8.5 Hz, 2-H*H*), 3.70 (d, 1H, J=12.0 Hz, HOCH*H*), 2.06 (dd, 1H, J=4.0, 8.0 Hz, 5-H), 1.05 (ddd, 1H, J=1.0, 4.4, 8.5 Hz, 6-*H*H), 0.81 (t, 1H, J=4.0 Hz, 6-H*H*); ^{13}C NMR (100 MHz, CD_3OD) δ 156.2, 152.6, 150.6, 140.0, 118.4, 85.0, 69.6, 61.7, 31.5, 25.1, 12.6; LRMS(FAB+) m/z 248 $(M+H)^+$; HRMS(FAB+) m/z $C_{11}H_{14}N_5O_2$ $(M+H)^+$ calcd 248.1147, obsd 248.1141; Anal. Calcd for $C_{11}H_{13}N_5O_2\cdot 0.2H_2O$: C, 52.67; H, 5.38; N, 27.92. Found: C, 52.70; H, 5.36; N, 27.83; compound **4α** (more polar material, α-anomer): UV (MeOH) λ_{max} 261 nm; $[\alpha]_D^{25}$ +139.13 (c 0.19, MeOH); IR (thin film): ν 3347, 3086 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 8.32 (s, 1H, H-8), 8.21 (s, 1H, H-2), 6.30 (d, 1H, J=3.0 Hz, anomeric H), 4.11 (s, 2H, 2-H_2), 3.76 (s, 2H, HOCH_2), 2.09–2.06 (m, 1H, 5-H), 1.13 (t, 1H, J=4.5 Hz, 6-*H*H), 1.01 (t, 1H, J=5.0, 7.5 Hz, 6-H*H*); ^{13}C NMR (100 MHz, CD_3OD) δ 156.8, 152.7, 149.5, 138.8, 118.8, 84.99, 70.84, 62.22, 31.8, 24.39, 10.46; LRMS(FAB+) m/z 248 $(M+H)^+$; HRMS(FAB+) m/z $C_{11}H_{14}N_5O_2$ $(M+H)^+$ calcd 248.1147, obsd 248.1152.

5.2. X-ray crystallography

Crystal of appropriate dimensions was obtained by crystallization from 50% methanol solution. Preliminary examination and data collection were performed using a Bruker SMART CCD Detector single crystal X-ray diffractometer using a graphite monochromated Mo Kα radiation (λ=0.71073 Å) source equipped with a sealed tube X-ray source at −80 °C. The SMART and SAINT software packages[34] were used for data collection and integration, respectively. The collected data were corrected for absorbance using SADABS,[35] based upon Laue symmetry, using equivalent reflections. Structures were solved by direct methods and refined by full-matrix least-squares calculations with the SHELXS97[36] and SHELXL97,[37] respectively. Refinement of the structure converged at a final $R1$=0.0340 for 2445 reflections with $I>2\sigma(I)$; $R1$=0.0375, and $wR2$=0.0814 for all 2637 reflections. The largest difference in peak and hole were 0.21 and −0.19 e Å^{-3}, respectively.

5.2.1. Crystal data. $C_{10}H_{13}N_3O_3(H_2O)$: Mr=241.25, orthorhombic, space group $P2_12_12_1$ (no. 19), a=9.4008(14) Å, b=10.5659(15) Å, c=11.2820(16) Å, V=1120.6(3) Å^3, T=193(2) K, Z=4, ρ_{calcd}=1.430gcm^{-3}, $F(000)$=512, crystal dimension 0.50×0.25×0.18 mm^3, μ(Mo Kα)=0.11 mm^{-1}. 7091 data (2637 unique, R_{int}=0.021) were collected in the range 2.6<θ<28.3°. $wR2$=0.0814, $R1$=0.0340 (the 2445 reflections having $Fo^2>2\sigma(Fo^2)$), Goodness of fit on F^2=1.052. CCDC No. 744745.

6. Supplementary data

Crystallographic data have been deposited with Cambridge Crystallographic Data Center as supplementary publication number CCDC 744745. The data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK [Tel: (+44)1223 336 408, Fax: (+44)1223 336 033 or e-mail: deposit@ccdc.cam.ac.uk].

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