Stereocontrolled Syntheses of Carbocyclic *C*-Nucleosides and Related Compounds

Byoung K. Chun, Gyu Y. Song, and Chung K. Chu*

Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy, The University of Georgia, Athens, Georgia 30602

dchu@rx.uga.edu

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Carbocyclic 9-deazapurine nucleosides (**1**−**4**), a spiranic pyrimidone carbocyclic compound (**5**), and an unusual carbocyclic isonucleoside (**6**) were prepared as enantiomerically pure compounds via the key intermediates **10** and **21** from 1,4-γ-ribonolactone. The key intermediate **10** was prepared by stereoselective reduction with Bu_3SnH and then converted to carbocyclic *C*-ribonucleosides **1**, **3**, and **4**. 2′,3′-Didehydro-2′,3′-dideoxycarbocyclic 9-deazainosine (**2**) was prepared from a 2′,3′-dimesylate **17** by treatment with Li_2Te followed by an acidic deprotection. The key bicyclic intermediate **21** was prepared from a diol **20** by an intramolecular cyclization using CHI_3−Ph_3P−imidazole and converted to the spiranic compound **5** and an olefinic nucleoside **6** by the construction of the heterocyclic moiety followed by deprotection.

Introduction

Syntheses of natural carbocyclic and *C*-nucleoside analogues have been inspired by their interesting biological activities as well as by their chemical and enzymatic stability. *C*-Nucleosides are a unique class of nucleosides in which the heterocycle is connected to a sugar moiety by a C−C bond instead of the C−N bond of the natural nucleosides. As a result, they are resistant to the chemical and the enzymatic hydrolytic cleavage of the glycosidic bond. *C*-Nucleosides have received considerable attention due not only to the chemical stability but also to the interesting biological activities of naturally occurring compounds such as showdomycin, formycins, oxazinomycin, pyrazomycin, etc.[1] Also, several biologically active synthetic *C*-nucleosides such as pseudoisocytidine,[2] thiazofurin,[3] and 9-deazaadenosine[4] have been reported. These *C*-nucleosides have shown both antitumor and antiviral activities. Carbocyclic nucleosides are another class of metabolically stable nucleosides in which a methylene group replaces the oxygen in the furan ring of the natural nucleosides. The biologically active carbocyclic nucleosides such as aristeromycin[5] and neplanocin[6,7] were isolated from microorganisms and were found to possess various interesting biological activities including antiviral and antitumor activity. The synthetic carbocyclic nucleosides, abacavir,[8] BMS-200475,[9] and lobucavir,[10] also show promising antiviral activities. Abacavir has recently been approved by the FDA as an anti-HIV agent.

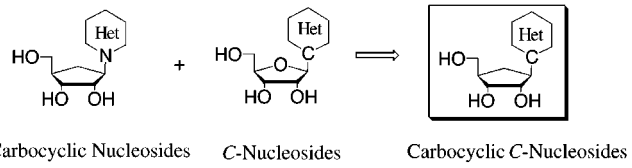

Figure 1. Structure of carbocyclic *C*-nucleoside.

On the basis of these interesting chemical and biological properties of *C*-nucleosides and carbocyclic nucleosides, it was of interest to synthesize hybrid nucleosides, carbocyclic *C*-nucleosides (Figure 1). Although some carbocyclic and *C*-nucleosides are naturally occurring, so far no natural carbocyclic *C*-nucleosides have been reported. The history of synthesis of carbocyclic *C*-nucleosides dates back to the 1960s.[11] Despite the long history of both carbocyclic and *C*-nucleosides, only a few carbo-

* Corresponding author tel: 706-542-5379; fax: 706-542-5381.

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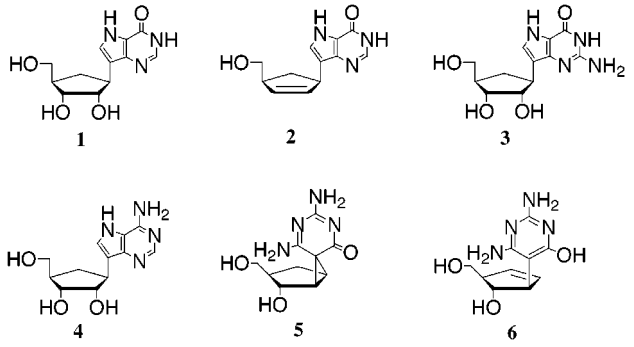

Figure 2. Structure of target compounds **1**−**6**.

cyclic *C*-nucleosides have been synthesized,[12] probably due to the synthetic difficulties of these nucleosides.

Although no significant biological activities have been observed so far, it was of interest to explore further the carbocyclic *C*-nucleosides because most of the hitherto known carbocyclic *C*-nucleosides possess only unnatural heterocyclic moieties. Furthermore, many of them have been synthesized as racemic mixtures, probably due to the synthetic difficulties. Therefore, enantiomeric synthesis of the carbocyclic *C*-nucleosides would be synthetically challenging and biologically interesting. Also, during our synthetic studies, we observed some interesting chemistry. On the basis of our findings herein, we report the synthesis of a novel purine carbocyclic *C*-nucleoside, 2′,3′-didehydro-2′,3′-dideoxyinosine; a spiranic carbocyclic *C*-nucleoside; and an unsaturated nucleoside as enantiomerically pure forms (Figure 2). Preliminary results for the synthesis of the adenosine derivative have been previously reported.[13]

Results and Discussion

For the synthesis of various carbocyclic *C*-nucleosides, we utilized the key intermediate **10**[13] as a chiral starting material, which was stereoselectively prepared by Bu_3SnH−AIBN reduction of the olefinic intermediate **9**, obtained by treating the ketone **8**[13,14] with ethyl cyanoacetate and potassium *tert*-butoxide in EtOH in 76% yield (Scheme 1). Several reduction conditions from **9** to **10** were investigated, of which the Bu_3SnH method provided the best result in terms of obtaining the desired β product **10**.[13] Thus, treatment of **9** with Bu_3SnH−AIBN in benzene with refluxing conditions gave the desired β isomer **10** with high stereoselectivity (**10**/**11** = 7/1) in 62% yield. Although Bu_3SnH reduction of α,β-unsaturated carbonyl compounds is well-known,[15] few studies on the regioselectivity of the reaction have been reported. The regioselectivity of the radical reduction **9** to **10** may be explained by a thermodynamically stable transition state in which the 5-substituent and the isopropylidene group are in a trans relationship to minimize the sterically unfavorable interactions between the two groups. The stereochemistry of each isomer was determined by NOESY experiments.[13] The $NaBH_4$ and H_2−Pd/C methods produced more α isomer as the major product because of the stereoelectronic effects of the isopropylidene group, which is consistent with previously reported results.[16,17]

The carbocyclic 9-deazainosine (**1**) was prepared in four steps from **10**. The intermediate **10** was converted to the enamine **12** by DIBALH reduction followed by treating $H_2NCH_2CO_2Et$·HCl in MeOH. N-protection of **12** with ethyl chloroformate and DBU in CH_2Cl_2 followed by cyclization with NaOEt gave the pyrrole derivative **13** in 41% yield from **10**. Treatment of **13** with $H_2NC(=NH)$·HOAc gave the protected 9-deazainosine (**14**), which was deprotected with aqueous CF_3CO_2H to afford the target compound, carbocyclic 9-deazainosine (**1**) in 68% yield.

The 2′,3′-didehydro-2′,3′-dideoxycarbocyclic 9-deazainosine (**2**) was prepared in four steps from **14**. The isopropylidene group of **14** was selectively deprotected with dilute HCl in MeOH to give the 2′,3′-diol **15** in 72% yield (Scheme 1). Various reductive eliminations of 2′,3′-vicinal diols have been reported.[18−23] Among them, several possible synthetic approaches to the olefinic nucleoside **2** including the direct conversion of vicinal diol, reductive elimination of cyclic thionocarbonate, and vicinal dimesylate were investigated. To provide the appropriate intermediate for the reductive elimination, the diol **15** was converted to the cyclic thionocarbonate **16** by treating it with thiocarbonyldiimidazole in refluxing toluene or the dimesylate **17** by treating it with MsCl in pyridine. Direct conversion of the diol **15** with I_2−PPh_3−imidazole[22] and reductive olefination of the cyclic thiocarbonate **16** with trimethyl phosphite to **18** resulted in poor yields. However, Li_2Te reduction of the mesylate **17** gave the desired olefinic carbocyclic *C*-nucleoside **18** in 65% yield.[21] Deprotection of **18** with aqueous CF_3CO_2H afforded the target compound, **2**, in 60% yield.

For the synthesis of carbocyclic 9-deazaguanosine (**3**), we utilized the pyrrole **13** as the intermediate. Treatment of **13** with *N*-benzoylisothiocyanate and MeI, followed by treating with NH_3(g) in a steel bomb at 95 °C, gave the protected carbocyclic 9-deazaguanosine (**19**) in 57% yield.

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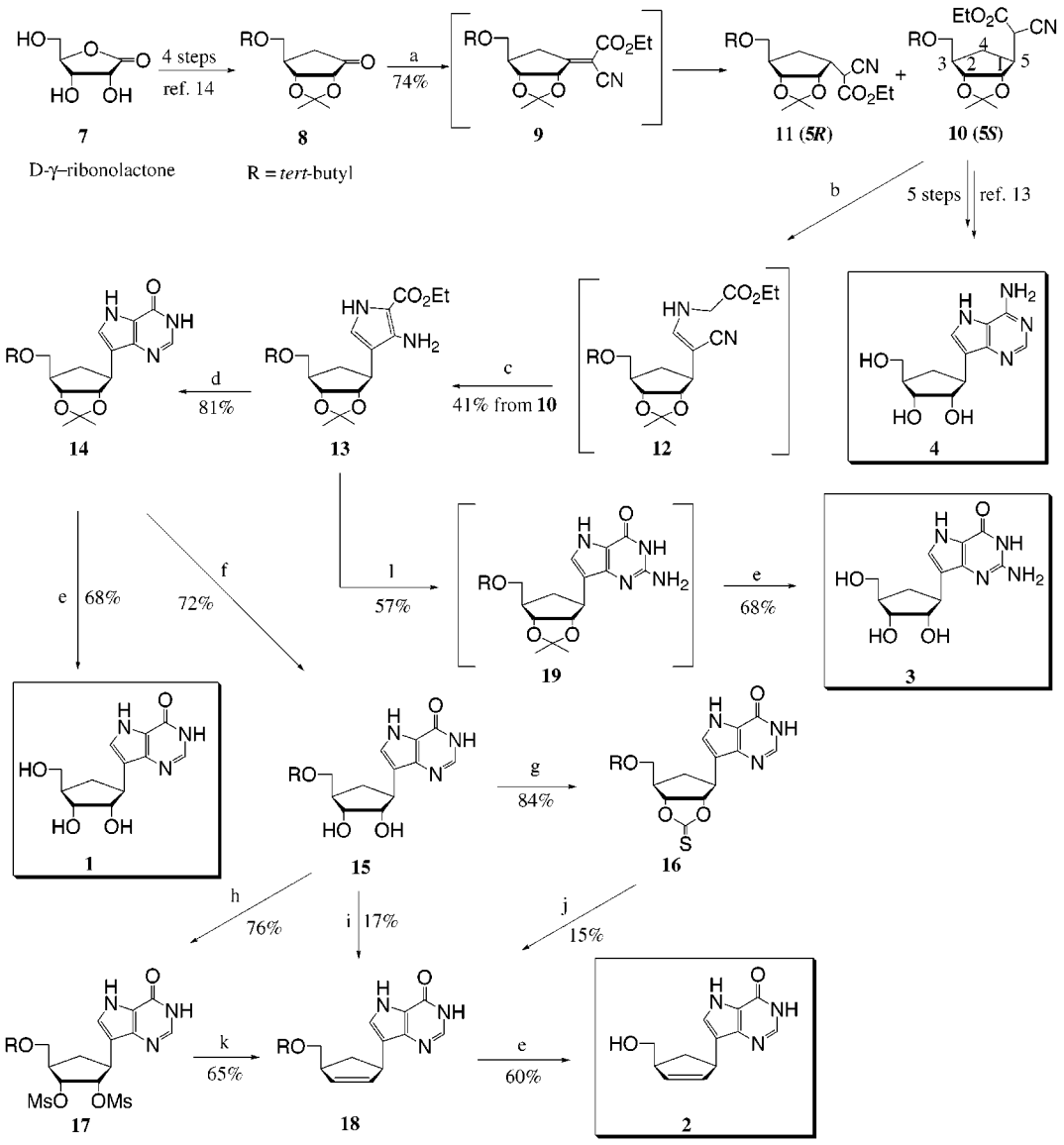
Scheme 1[a]

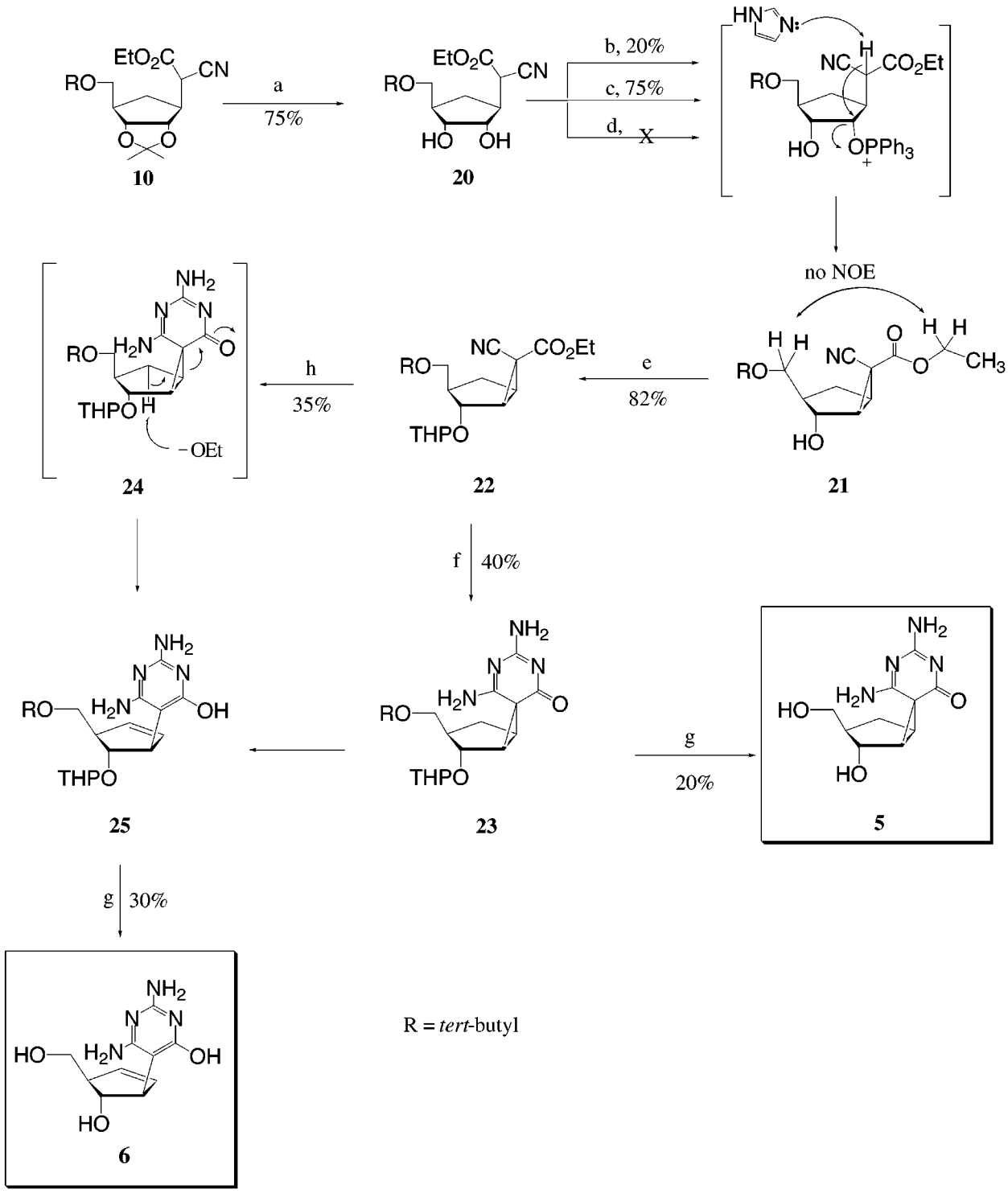


[a] Key: (a) $NCCH_2CO_2Et$, KO*t*-Bu, EtOH, 1 h. (b) 1: DIBAL-H, Et_2O, −78 °C, 10 min. 2: $H_2NCH_2CO_2Et$·HCl, MeOH, 2 h. (c) 1: $ClCO_2Et$, DBU, CH_2Cl_2, 2 h. 2: NaOMe, MeOH, 40 min. (d) $HC(=NH)NH_2$·HOAc, EtOH, reflux, 4 days. (e) CF_3CO_2H/H_2O (2:1, v/v), 50 °C, 3 h. (f) *c*-HCl, MeOH, rt, 2 h. (g) $CS(Im)_2$, toluene, reflux, 1 h. (h) MsCl, pyridine, rt, 4 h. (i) Ph_3P, CHI_3, Im, CH_3CN, toluene, DMF, reflux, 12 h. (j) $(MeO)_3P$, 140 °C, 4 h. (k) Te, Et_3BHLi, THF, 50 °C, 7 h. (l) 1: BzN=C=S, CH_2Cl_2. 2: MeI, DBN. 3: NH_3/MeOH, 90 °C, 16 h.

Deprotection of **19** with aqueous CF_3CO_2H gave the target compound, **3**, in 68% yield. Preparation of the carbocyclic 9-deazaadenosine (**4**) was previously reported by our group as a communication.[13]

As part of the investigation for the unsaturated carbocyclic *C*-nucleosides, the diol **20**, obtained from **10**, was subjected to I_2-PPh_3−imidazole[22] to prepare the unsaturated nucleosides such as **2** (Scheme 2). From this reaction, however, we obtained the spiro intermediate **21**, 6-cyanobicyclic[3.1.0]hexane-6-carboxylic acid methyl ester, in 20% yield instead of an expected 1,2-olefinic compound. This bicyclic intermediate **21** was probably generated from an intramolecular S_N2''-type cyclization reaction involving the cyanoacetate moiety and the 2-hydroxy group under the reaction conditions as shown in Scheme 2. The structure was determined based on 1-D and 2-D NMR, mass spectroscopy, and elemental analysis. The chemical behavior of **21** also supported the proposed structure; DIBALH reduction of the ethoxycarbonyl group of **21** gave a sharp aldehyde peak as a singlet at 9.3 ppm without any indication of enolization in the NMR spectrum, which indicated that the aldehyde possesses a quaternary α-carbon. The stereochemistry shown at the quaternary α-carbon of the ethoxycarbonyl moiety is proposed based on the steric effect of the bulkier side chain, the ethoxycarbonyl group, which may protrude outward as shown in the structure of **21**. This assignment was supported by a NOESY spectrum where there was no NOE between the protons of the ethoxycarbonyl group and the methylene protons of the *tert*-butoxymethyl side chain. As the bicyclic compound **21** can be utilized as an intermediate for the novel nucleosides such as conformationally restricted nucleosides,[24] we tried to improve the reaction condition (I_2-PPh_3−imidazole), which had originally been used for the preparation of an unsaturated compound from vicinal diols. The replacement of I_2 with iodoform (CHI_3) significantly improved the yield up to 75% (Scheme 2, c route). However, the Mitsunobu reaction failed to give any detectable amount of the bicyclic compound **21**. To our best knowledge, this is

Scheme 2[a]



[a] Key: (a) HCl, EtOH, rt, 3 h. (b) PPh_3, I_2, Im, CH_3CN−benzene, 50 °C, 2 h. (c) PPh_3, CHI_3, Im, CH_3CH, 50 °C, 10 h. (d) DEAD, PPh_3, THF, rt or 50 °C. (e) DHP, PPTs, rt, 2 h. (f) Guanidine hydrochloride, DBN, EtOH, reflux, 20 min. (g) CF_3CO_2H/H_2O (2:1, v/v), 50 °C, 4 h. (h) Guanidine hydrochloride, NaOEt, EtOH, reflux, 4 h.

probably the first example of an application of CHI_3−PPh_3−imidazole[25] for the preparation of a cyclopropane derivative from a vicinal diol. After the improvement of the cyclopropanation preparation, the bicyclic intermediate **21** was used for the preparation of the conformationally fixed spiranic compound (Scheme 2). To achieve the synthesis of our target compound **5**, the intermediate **21** was protected with 3,4-dihydro-2*H*-pyran (DHP) to give the intermediate **22** in 82% yield. Treatment of **22** with guanidine hydrochloride in the presence of DBN gave **23** under short refluxing conditions (ca. 20 min) in 42% yield, which was also found to undergo an elimination reaction to generate the olefinic diaminopyrimidone nucleoside **25**. Meanwhile, replacing DBN with a stronger base, sodium ethoxide, resulted in the unsaturated product **25** as a major product in 35% yield. The olefinic product **25** appears to be generated from E2 elimination of **22**. Deprotection of **23** and **24** with aqueous CF_3CO_2H gave

spiranic compound **5** and olefinic nucleoside **6**, respectively.

The anti-HIV activity of synthesized nucleosides was evaluated in peripheral blood mononuclear (PBM) cells. None of them showed any significant antiviral activity.

In summary, we have developed synthetic methodologies for the appropriately functionalized carbocyclic intermediate **10** as well as the bicyclic carbocyclic intermediate **21**, both of which were successfully utilized for the syntheses of various carbocyclic *C*-nucleosides.

Experimental Section

Melting points were determined on a Mel-temp II apparatus and are uncorrected. NMR spectra were recorded on a Bruker 400 AMX spectrometer at 400 (^{1}H) and 100 MHz (^{13}C) in the indicated solvents. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Mass spectra were recorded on a Micromass Autospec high-resolution mass spectrometer in FAB mode. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Column chromatography was performed using either silica gel 60 (220−400 mesh) for flash column chromatography or silica gel G (TLC grade, 400 mesh) for vacuum flash column chromatography. UV spectra were obtained on a Beckman DU 650 spectrophotometer. Elemental analyses were performed by Atlantic Microlab, Inc. Numbering of nucleosides was done according to the convention for that of usual nucleosides.

Ethyl (2*R*/*S*,1′*S*,2′*R*,3′*R*,5′*S*)-2-(3′-*tert*-Butoxymethyl-1′,2′-isopropylidene-dioxycyclopentan-5′-yl)-2-cyanoacetate (10) and Ethyl (2*R*/*S*,1′*S*,2′*R*,3′*R*,5′*R*)-2-(3′-*tert*-Butoxymethyl-1′,2′-isopropylidene-dioxycyclopentan-5′-yl)-2-cyanoacetate (11). Method 1. Potassium *tert*-butoxide (7.4 g, 66.0 mmol) was added to a solution of **8** (3.2 g, 13.20 mmol) and ethyl cyanoacetate (7.0 mL, 65.78 mmol) in ethanol (80 mL) at 0 °C. The resulting mixture was stirred for 1 h. After the salt was removed by filtration, the filtrate was concentrated to a residue, which was purified by silica gel column chromatography (hexanes:EtOAc = 3:1) to give **9** as a crude product. The crude product was dissolved in benzene (250 mL) and degassed with vacuum for 30 min, and then Bu_3SnH (5 mL, 18.58 mmol) and ′AIBN (500 mg, 3.04 mmol) were added. The reaction mixture was refluxed for 2 h. After being concentrated, a small amount of the residue was roughly purified by silica gel column chromatography to determine the **10**/**11** ratio (7:1, determined by NMR). The residue was purified by silica gel column chromatography (hexanes:EtOAc = 30:1) to give **10** (1.37 g, 41.3%) and **11** (0.19 g, 5.8%) as a syrup.

Method 2. A mixture of **9** (500 mg, 1.48 mmol), 10% Pd/C (33 mg), and MeOH (20 mL) was stirred under a hydrogen balloon for 4 h. After being concentrated, the residue was purified by silica gel column chromatography (hexanes:EtOAc = 30:1) to give **11** (232 mg, 46%) and **10** (194 mg, 39%).

Method 3. $NaBH_4$ (8 mg, 0.19 mmol) was slowly added to a solution of **9** (50 mg, 0.13 mmol) in EtOH (2 mL). The reaction mixture was stirred for 1 h. After being concentrated, the residue was purified by silica gel column chromatography (hexanes:EtOAc = 10:1) to give **11** (37 mg, 72%) along with a small amount of **10** (**10**:**11** = 1/10, determined by NMR). Compound **10**: ^{1}H NMR ($CDCl_3$): δ 4.52−4.41 (m, 2H, H-1′,2′), 4.28 (m, 2H, OCH_2CH_3), 3.86 (d, 0.55H, J = 6.94 Hz, CHCN), 3.77 (m, 0.45H, J = 6.80 Hz, CHCN), 3.39 (m, 2H, H-6′), 2.60 (m, 1H, H-5′), 2.30 (m, 1H, H-3′), 2.23 (m, 1H, H-4′), 1.53 (m, 1H, H-4″), 1.45−1.15 (m, 18H, OCH_2CH_3, $(CH_3)_2C$, $(CH_3)_3C$). FABMS (m/z): $(M + H)^+$ 340. Anal. Calcd for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13. Found: C, 63.47; H, 8.52; N, 3.97. Compound **11**: ^{1}H NMR ($CDCl_3$): δ 4.70−4.48 (m, 2H, H-1′,2′), 4.28 (m, 2H, OCH_2CH_3), 3.72 (d, 0.6H, J = 9.66 Hz, CHCN), 3.53 (m, 0.4H, J = 10.78 Hz, CHCN), 3.24 (m, 2H, H-6′), 2.75 (m, 1H, H-5′), 2.26 (m, 1H, H-3′), 1.98−1.79 (m, 1H, H-4′), 1.45−1.15 (m, 19H, H-4″, OCH_2CH_3, $(CH_3)_2C$, $(CH_3)_3C$). FABMS (m/z): $(M + H)^+$ 340. Anal. Calcd for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13. Found: C, 63.75; H, 8.52; N, 3.95.

(1′*S*,2′*R*,3′*R*,5′*S*)-[3-Amino-4-(3′-*tert*-butoxymethyl-1′,2′-isopropylidene-dioxycyclopentan-5′-yl)-1*H*-pyrrole]-2-carboxylic Acid Ethyl Ester (13). DIBALH (1 M in hexanes, 4.86 mL) was added to a solution of **10** (1.65 g, 4.86 mmol) in anhyd ethyl ether at −78 °C over 10 min. The resulting mixture was stirred for 10 min and quenched with MeOH (20 mL). After the solvent was removed, the solid cake was suspended in EtOAc−MeOH (20:1), stirred vigorously for 30 min, and filtered. The filtrate was concentrated to a residue, which was dissolved in MeOH (50 mL). Ethylglycinate hydrochloride (1.68 g, 12.0 mmol) and $NaOAc{\cdot}3H_2O$ (1.6 g, 11.6 mmol) were added. The reaction mixture was evaporated slowly with a rotary evaporator to a white solid at rt and coevaporated with MeOH (50 mL, 3×) to complete the reaction. The obtained white solid was suspended in EtOAc (100 mL) and stirred for 20 min. After being filtered and concentrated, the residue was purified by flash silica gel column chromatography (hexanes:EtOAc = 4:1 to 3:1) to give a glycinate, **12** (1.66 g, 89%), as a syrup. DBU (12 mL, 76.42 mmol) and ethyl chloroformate (4.4 mL, 46.02 mmol) were added to a solution of **12** (1.66 g, 4.34 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The reaction mixture was stirred for 2 h at rt, washed with water (20 mL, 3×), and concentrated. The obtained residue was purified with 1% MeOH in CH_2Cl_2 and dissolved in EtOH (100 mL) containing NaOEt (6.5 mL, 1 M solution in MeOH). The reaction mixture was stirred for 40 min at rt and concentrated. The residue was purified by silica gel column chromatography (hexanes:EtOAc = 10:1 to 5:1) to give **13** (750 mg, 41% from **10**) as a semisolid: $[\alpha]^{25}_D$ −32.08 (*c* 0.15, MeOH). ^{1}H NMR ($CDCl_3$): δ 7.97 (s, 1H, HN-1), 6.49 (s, 1H, H-8), 4.79 (bs, 2H, HN_2-3), 4.42 (m, 1H, H-2′), 4.28 (m, 3H, H-1′, CH_3CH_2O), 3.52−3.37 (m, 2H, H-6′), 2.98 (m, 1H, H-5′), 2.38 (m, 1H, H-3′), 2.24 (m, 1H, H-4′), 1.79−1.19 (m, 19H, H-4″, $(CH_3)_2C$, CH_3CH_2O, $(CH_3)_3C$). FABMS (m/z): $(M + H)^+$ 381.

Carbocyclic *O*-*tert*-Butyl-2′,3′-isopropylidene-9-deazainosine (14). A solution of **13** (200 mg, 0.53 mmol) and formamidine acetate (219 mg, 2.10 mmol) in EtOH (10 mL) was refluxed for 4 days and concentrated. The obtained residue was purified by silica gel column chromatography (hexanes:EtOAc = 30:1) to give **14** (155 mg, 81%) as a white solid that was recrystallized from EtOAc: mp 300 °C; $[\alpha]^{25}_D$ −46.12 (*c* 0.20, MeOH). UV (MeOH) λ_{max}, nm: 235.0, 262.5. ^{1}H NMR ($CDCl_3$): δ 7.90 (s, 1H, H-2), 7.24 (s, 1H, H-8), 4.84 (t, 1H, J = 6.7 Hz, H-2′), 4.51 (t, 1H, J = 4.6, 7.0 Hz, H-3′), 3.50 (m, 1H, H-6′), 3.39 (m, 2H, H-6″, H-1′), 2.38 (m, 2H, H-4′, H-5′), 1.88 (m, 1H, H-5″) 1.56 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.18 (s, 9H, $(CH_3)_3C$). HRMS−FAB (m/z): $(M + H)^+$ calcd for $C_{19}H_{28}N_3O_4$, 362.2079; found, 362.2076. Anal. Calcd for $C_{19}H_{27}N_3O_4{\cdot}0.3$EtOAc: C, 62.55; H, 7.64; N, 10.83. Found: C, 62.78; H, 7.79; N, 10.76.

Carbocyclic 9-Deazainosine (1). A solution of **14** (200 mg, 0.55 mmol) in 8 mL of CF_3CO_2H−water (3:1, v/v) was stirred for 3 h at 50 °C and concentrated. The residue was coevaporated with toluene (5 mL, 4×) to give a yellowish oil (100 mg, 68%) that was washed with EtOAc and recrystallized from EtOAc−MeOH (5:1) to give **1** (30 mg, 20%) as a white crystal: mp 210 °C; $[\alpha]^{25}_D$ −39.38 (*c* 0.48, H_2O). UV (MeOH) λ_{max}, nm (ϵ): 234, 234.0 (27 615, pH 7), 230.5 (25 792, pH 11), 241.5 (27 815, pH 2). ^{1}H NMR (DMSO-d_6): δ 11.81 (s, 1H, HN-1), 7.79 (s, 1H, H-2), 7.17 (d, 1H, J = 2.4 Hz, H-8), 4.55 (bs, 1H, HO-), 4.52 (bs, 1H, HO-), 3.89 (dd, 1H, J = 5.2, 8.3 Hz, H-2′), 3.74 (t, 1H, J = 4.9 Hz, H-3′), 3.43 (dd, 1H, J = 6.2, 10.6 Hz, H-6′), 3.35 (dd, 1H, J = 6.3, 10.5 Hz, H-6″), 3.13 (dd, 1H, J = 8.2, 18.6 Hz, H-1′), 2.12 (m, 1H, H-5′), 1.99 (m, 1H, H-4′), 1.39 (m, 1H, H-5″). HRMS−FAB (m/z): $(M + H)^+$ calcd for $C_{12}H_{16}N_3O_4$, 266.1140; found, 266.1160. Anal. Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.42; H, 5.84; N, 15.75.

Carbocyclic 2′,3′-Di-*O*-thionocarbonyl-*O*-*tert*-butyl-9-deazainosine (16). Compound **14** (300 mg, 0.83 mmol) was dissolved in MeOH containing *c*-HCl (0.5 mL). The solution was stirred for 2 h at rt, neutralized with $NaCO_3$ powder, and concentrated. The obtained residue was purified by silica gel column chromatography ($CHCl_3$:MeOH = 20:1) to give **15** (192 mg, 72%) as a white solid. A mixture of **15** (90 mg, 0.28 mmol)

and thiocarbonyldiimidazole (108 mg, 0.61 mmol) in toluene (10 mL) was refluxed for 1 h and concentrated. The obtained residue was purified by silica gel column chromatography ($CHCl_3$:MeOH = 30:1 to 10:1) to give **16** (85 mg, 84%) as a syrup. ^{1}H NMR (DMSO-d_6): δ 7.82 (s, 1H, H-2), 7.38 (d, 1H, J = 2.4 Hz, H-8), 5.42 (m, 1H, H-2′), 5.23 (m, 1H, H-3′), 3.35−3.44 (m, 3H, H-6′, H-1′), 2.20 (m, 1H, H-4′), 1.69 (m, 1H, H-5′), 1.16 (m, 1H, H-5″). FABMS (m/z): $(M + H)^+$ 364.

Carbocyclic 5′-*O*-*tert*-Butyl-2′,3′-didehydro-2′,3′-dideoxy-9-deazainosine (18). MsCl (0.15 mL, 1.93 mmol) was added to a solution of **15** (80 mg, 0.25 mmol) in anhyd pyridine. The resulting mixture was stirred for 4 h at rt and concentrated. The obtained residue was purified by silica gel column chromatography ($CHCl_3$:MeOH = 30:1 to 10:1) to give **17** (120 mg, 76%) as a syrup. Method 1 for **18**: Lithium triethylborohydride solution (1.28 mL, 1 M solution in THF) was added to tellurium (82 mg, 0.64 mmol) in a three-neck flask equipped with a condenser at rt under nitrogen atmosphere. The reaction mixture was stirred for 5 h at rt, and **17** (120 mg, 0.18 mmol) was added dropwise. The reaction mixture was stirred for 7 h at 50 °C and concentrated. The obtained residue was purified by silica gel column chromatography (hexanes:EtOAc = 1:1) to give **18** (34 mg, 65%) as a white solid. Method 2 for **18**: Imidazole (39 mg, 0.57 mmol), triphenylphosphine (282 mg, 1.07 mmol), and iodoform (0.54 mmol) were added to a suspension of **15** (90 mg, 0.28 mmol) in toluene−CH_3CN−DMF (5, 2, and 1 mL, respectively) at rt. The resulting reaction mixture was refluxed for 12 h and concentrated. The obtained residue was purified by silica gel column chromatography (hexanes:EtOAc = 1:1) to give **18** (4.4 mg, 17%) as a white solid. Method 3 for **18**: A solution of **16** (80 mg, 0.22 mmol) in trimethyl phosphite (10 mL) was stirred for 4 h at 140 °C and concentrated. The obtained residue was purified by silica gel column chromatography (hexanes:EtOAc = 1:1) to give **18** (9.5 mg, 15%) as a white solid: mp 183−185 °C. UV (MeOH) λ_{max}, nm: 237, 263. ^{1}H NMR (DMSO-d_6): δ 11.81 (s, 1H, HN-1), 11.77 (s, 1H, HN-7), 7.76 (d, 1H, J = 3.2 Hz, H-2), 6.94 (d, 1H, J = 2.4 Hz, H-8), 5.83 (t, 1H, J = 3.6 Hz, H-2′), 5.76 (t, 1H, J = 3.6 Hz, H-3′), 4.17 (d, 1H, J = 8.4 Hz, H-1′), 2.99 (t, 1H, J = 8.4 Hz, H-6′), 2.97 (t, 1H, J = 8.4 Hz, H-6′), 2.56 (m, 1H, H-4′), 2.38 (m, 1H, H-5′), 2.27 (m, 1H, H-5″), 1.75 (s, 9H, $(CH_3)_3C$). ^{13}C NMR (DMSO-d_6): δ 157.2, 146,7, 144.2, 137.1, 133.3, 128.7, 121.2, 119.6, 74.9, 65.8, 45.0, 39.2, 30.8, 30.5. FABMS (m/z): $(M + H)^+$ 288.

Carbocyclic 2′,3′-Didehydro-2′,3′-dideoxy-9-deazainosine (2). A solution of **18** (113 mg, 0.39 mmol) in 10 mL of $CF_3COOH-H_2O$ (2/1, v/v) was stirred for 3 h at 50 °C and concentrated under reduced pressure. The residue was coevaporated with toluene to give a residue that was dissolved in MeOH (1 mL) and neutralized with triethylamine. After being concentrated, the residue was purified by silica gel column chromatography ($CHCl_3$:MeOH = 10:1) to give **2** (50 mg, 55%): mp 186−189 °C. UV λ_{max}, nm (ϵ): 234.0 (28 038, pH 7), 230.5 (26 111, pH 11), 241.5 (27 925, pH 2). ^{1}H NMR (DMSO-d_6): δ 11.86 (s, 1H, HN-1), 7.80 (s, 1H, H-2), 6.90 (s, 1H, H-8), 5.89 (m, 1H, H-2′), 5.79 (m, 1H, H-3′), 4.27 (t, 1H, J = 4.1 Hz, HO-), 4.12 (m, 1H, H-1′), 3.06 (m, 1H, H-6′), 2.86 (m, 1H, H-6″), 2.55 (m, 1H, H-4′), 2.37 (m, 1H, H-5′), 2.22 (m, 1H, H-5″). ^{13}C NMR (DMSO-d_6): δ 157.1, 147.5, 146.3, 136.8, 133.9, 128.6, 119.2, 66.1, 47.6, 44.7, 38.5. HRMS−FAB (m/z): $(M + H)^+$ calcd for $C_{12}H_{15}N_3O_2$, 232.1074; found, 232.1086. Anal. Calcd for $C_{12}H_{14}N_3O_2 \cdot 1.0H_2O$: C, 57.82; H, 6.00; N, 16.56. Found: C, 57.80; H, 5.65; N, 16.24.

Carbocyclic 9-Deazaguanosine (3). *N*-Benzoylisothiocyanate (0.1 mL, 0.74 mmol) was added to a solution of **13** (147 mg, 0.39 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was stirred for 40 min at rt and concentrated. The obtained residue was purified by silica gel column chromatography ($CHCl_3$ to 1% MeOH in $CHCl_3$) to give a residue (380 mg). After being dried under high vacuum, the residue was dissolved in CH_2Cl_2 and treated consecutively with DBN (0.5 mL, 3.87 mmol) and MeI (0.5 mL, 1.54 mmol). The resulting reaction mixture was stirred for 2 h at rt, diluted with CH_2Cl_2 (50 mL), washed with water (20 mL, 2×), dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH = 30:1) to give a residue. The residue was dissolved in MeOH (50 mL), saturated with NH_3-(g) at −78 °C in a steel bomb under anhyd conditions, and then heated for 16 h at 95 °C under tight sealing. After being cooled to rt, the reaction mixture was concentrated, and the residue was purified by silica gel column chromatography ($CHCl_3$:MeOH = 60:1) to give **19** (120 mg, 57%) as a solid. **19** was dissolved in 4 mL of $CF_3CO_2H-H_2O$ (3:1), and the resulting mixture was stirred for 3 h at 50 °C. The solvent was concentrated and coevaporated with toluene (5 mL, 4×) to a yellowish solid, which was recrystallized from MeOH to give **3** (60 mg, 68%): mp 290 °C; $[\alpha]^{25}_D$ −21.50 (c 0.3, H_2O). UV λ_{max}, nm (ϵ): 231 (17 002, pH 7), 266 (8376, pH 7), 264.5 (8048, pH 11), 234.5 (13 530, pH 2), 273.0 (11 600, pH 2). ^{1}H NMR (DMSO-d_6): δ 11.30 (s, 1H, HN-1), 7.00 (s, 1H, H-8), 6.20 (s, 1H, HN-7), 3.71 (m, 2H, H-2′, 3′), 4.57 (s, 1H, HO-), 4.12 (s, 1H, HO-), 3.45 (m, 2H, H-6″), 3.01 (m, 1H, H-1′), 2.20 (m, 1H, H-5′), 1.99 (m, 1H, H-4′), 1.25 (m, 1H, H-5″). HRMS−FAB (m/z): $(M + H)^+$ calcd for $C_{12}H_{17}N_4O_4$, 281.1250; found, 281.1257. Anal. Calcd for $C_{12}H_{16}N_4O_4 \cdot CF_3CO_2H$: C, 42.64; H, 4.39; N, 14.20. Found: C, 42.65; H, 4.74; N, 13.81.

Carbocyclic 9-Deazadenosine (4). Compound **4** was prepared from D-γ-ribonolactone in 11 steps:[13] mp 240 °C; $[\alpha]^{25}_D$ −45.46 (c 0.35, MeOH). UV (MeOH) λ_{max}, nm (ϵ): 275 , 274.0 (11 760, pH 7), 271.5 (11 720, pH 11), 275 (18 530, pH 2). ^{1}H NMR (DMSO-d_6): δ 10.59 (s, 1H, HN-5, D_2O exchangeable), 7.93 (s, 1H, H-2), 7.14 (d, 1H, J = 2.0 Hz, H-8), 6.61 (s, 2H, H_2N-4, D_2O exchangeable), 4.00 (s, 1H), 3.73 (m, 1H, H-2′), 3.65 (m, 1H, H-3′), 3.04 (m, 2H, H-6′), 2.02 (m, 1H, H-5′), 1.90 (m, 1H, H-4′), 1.31 (m, 1H, H-5″). FABMS (m/z): $(M + H)^+$ 265. Anal. Calcd for $C_{12}H_{16}N_4O_3 \cdot 0.3H_2O$: C, 53.44; H, 6.20; N, 20.77. Found: C, 53.44; H, 6.20; N, 20.22.

(1*S*,2*S*,3*R*,5*R*,6*S*)-2-Hydroxy-3-*tert*-butoxymethyl-6-cyanobicyclic[3.1.0]hexane-6-carboxylic Acid Ethyl Ester (21). A solution of **10** (1.85 g, 5.45 mmol) in EtOH (200 mL) containing *c*-HCl (3 mL) was stirred for 3 h, neutralized with saturated $NaHCO_3$, and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH = 30:1) to give **20** (0.93 g, 74%). Method 1 for **21**: I_2 was added (873 mg, 3.44 mmol) to a solution of triphenylphosphine (902 mg, 3.44 mmol) and imidazole (117 mg, 1.72 mmol) in benzene−CH_3CN (72 mL, 2:1). The resulting mixture was stirred for 5 min at rt to give a white suspension to which **20** (258 mg, 0.86 mmol) was added. The resulting reaction mixture was stirred for 2 h at 40 °C and concentrated. The obtained residue was purified by silica gel column chromatography (hexanes:EtOAc = 10:1 to 5:1) to give **21** (149 mg, 20%) as a syrup. Method 2 for **21**: CHI_3 was added (1.70 g, 4.24 mmol) to a solution of triphenylphosphine (1.10 g, 4.24 mmol) and imidazole (288 mg, 4.24 mmol) in anhyd CH_3CN (10 mL). The reaction mixture was stirred until a solution was obtained. Compound **20** (320 mg, 1.06 mmol) in anhyd CH_3CN (10 mL) was added to the solution in one portion. The resulting mixture was stirred for 10 h at 50 °C. After the precipitated solid was filtered, the solid cake was extracted with EtOAc (200 mL, 3×), and the combined filtrate was concentrated. The obtained residue was purified by silica gel column chromatography (hexanes:EtOAc = 10:1 to 5:1) to give **21** (224 mg, 75%) as a syrup: $[\alpha]^{25}_D$ +11.82 (c 2.5, MeOH). ^{1}H NMR ($CDCl_3$): δ 4.25 (m, 2H, CH_3CH_2O-), 4.19 (m, 1H, H-3′), 3.45 (m, 2H, H-6′), 2.24−2.41 (m, 4H, H-1′,2′,4′,5′), 1.45−1.12 (m, 13H, H-5″, CH_3-CH_2-, $(CH_3)_3C$). ^{13}C NMR ($CDCl_3$): δ 166.0, 115.1, 79.0, 73.4, 64.1, 62.7, 61.2, 55.8, 42.8, 36.2, 27.9, 27.4, 14.1. HRMS−FAB (m/z): $(M + H)^+$ calcd for $C_{15}H_{24}NO_4$, 282.1811; found, 282.1807. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 63.75; H, 8.28; N, 4.89.

(1*S*,2*S*,3*R*,5*R*,6*S*)-2-*O*-(1-Tetrahydropyranosyl)-3-*tert*-butoxymethyl-6-cyanobicyclic[3.1.0]hexane-6-carboxylic Acid Ethyl Ester (22). A mixture of **21** (670 mg, 2.38 mmol), dihydropyran (0.43 mL, 4.76 mol), and pyridinium *p*-toluenesulfonate (catalytic amount) in CH_2Cl_2 (70 mL) was stirred for 1 h at rt and concentrated. The obtained residue was purified by silica gel column chromatography (hexanes:EtOAc = 30:1) to give **22** (713 mg, 82%) as a syrup. ^{1}H NMR ($CDCl_3$): δ 4.21 (m, 2H, CH_3CH_2O-), 4.12−3.78 (m, 2H, H-3′,

anomeric THP), 3.65−3.30 (m, 4H, H-6′, CH_2O−THP), 2.75−2.26 (m, 4H, H-1′,2′,4′,5′), 1.75−1.25 (m, 7H, H-5″, $(CH_2)_3$−THP), 1.23 (m, 3H, CH_3CH_2O-), 1.12 (s, 9H, $(CH_3)_3C$). FABMS (*m*/*z*): $(M + H)^+$ 336.

(5*R*,1′*S*,3′*R*,5′*R*)-Spiro[[2′-(1-tetrahydropyranosyl)-3′-*tert*-butoxymethylbicyclic[3.1.0]hexane]-5,6′-(2,6-diamino-5*H*-pyrimidine-4-one)] (23). 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN, 0.40 mL, 3.2 mmol) was added to a solution of **22** (240 mg, 0.66 mmol) and guanidine hydrochloride (1.00 g, 10.46 mmol) in EtOH (20 mL). The mixture was refluxed for 20 min and concentrated to a residue, which was purified by silica gel column chromatography ($CHCl_3$:MeOH = 30:1) to give **23** (99 mg, 40%) as a syrup. UV (MeOH) λ_{max}, nm: 235.0. ^{1}H NMR ($CDCl_3$): δ 6.52 (bs, 2H, H_2N-), 4.0−3.81 (m, 2H, H-3′ and anomeric THP), 3.60−3.31 (m, 4H, H-6′, CH_2−THP), 2.75−2.24 (m, 4H, H 1′,2′,4′,5′), 2.12−1.15 (m, 16H, H-5″, $(CH_2)_3$−THP, $(CH_3)_3C$). HRMS−FAB (*m*/*z*): $(M + H)^+$ calcd for $C_{19}H_{31}N_4O_4$, 379.2409; found, 379.2345.

(5*R*,1′*S*,3′*R*,5′*R*)-Spiro[[2′-hydroxy-3′-hydroxymethylbicyclic[3.1.0]hexane]-5,6′-(2,6-diamino-5*H*-pyrimidine-4-one)] (5). A solution of **23** (120 mg, 0.32 mmol) in 5 mL of $CF_3CO_2H-H_2O$ (2:1, v/v) was stirred for 4 h at 50 °C and concentrated under reduced pressure. The residue was coevaporated with toluene (5 mL, 4×), treated with Et_3N (1 mL), and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH = 10:1) to give **5** (16 mg, 20%) as a white solid: mp 167−170 °C; $[\alpha]^{25}_D$ −12.30 (*c* 0.4, H_2O). UV (MeOH) λ_{max}, nm: 235.0. ^{1}H NMR (D_2O): δ 3.92 (m, 1H, H-3′), 3.67−3.44 (m, 2H, H-6′), 2.54−2.39 (m, 3H, H-2′,4′,5′), 2.25 (m, 1H, H-1′), 1.37 (m, 1H, H-1′). ^{13}C NMR (D_2O): δ 176.7, 163.0, 119.3, 76.6, 63.2, 57.0, 43.4, 36.9, 29.7, 9.19. HRMS−FAB (*m*/*z*): $(M + H)^+$ calcd for $C_{10}H_{15}N_4O_3$, 239.1147; found, 239.1144. Anal. Calcd for $C_{10}H_{14}N_4O_3$: C, 50.41; H, 5.92; N, 23.52. Found: C, 50.22; H, 5.96; N, 23.25.

(1′*S*,2′*R*,5′*S*)-5-[1-*O*-(1-Tetrahydrofuranosyl)-2-*tert*-butoxymethylcyclopent-3-en-5-yl]-2,6-diaminopyrimidine-4-one (25). NaOEt (1.3 mL, 0.2 M solution in MeOH) was added to a mixture of **22** (40 mg, 0.11 mmol) and guanidine hydrochloride (20 mg, 0.21 mmol) in EtOH (5 mL) at rt. The mixture was refluxed for 1 h, neutralized with *c*-HCl, and concentrated. The obtained residue was purified by silica gel column chromatography ($CHCl_3$:MeOH = 30:1) to give **25** (15 mg, 35%) as a semiwhite solid. UV (MeOH) λ_{max}, nm: 213.0, 241.5, 277.5. ^{1}H NMR ($CDCl_3$): δ 11.28 (bs, 1H, HN-), 5.76 (bs, 2H, H_2N-), 5.64−5.51 (m, 2H, H-4′,5′), 5.03 (bs, 2H, H_2N-), 4.76−4.43 (m, 2H, H-2′, anomeric THP), 4.24 (m, 1H, H-1′), 3.92−3.31 (m, 4H, H-6′, CH_2O−THP), 2.92 (m, 1H, H-3′), 1.85−1.54 (m, 6H, $(CH_2)_3$−THP), 1.16 (s, 9H, $(CH_3)_3C$). FABMS (*m*/*z*): $(M + H)^+$ 379.

(1′*S*,2′*R*,5′*S*)-5-[1-Hydroxy-2-hydroxymethylcyclopent-3-en-5-yl]-2,6-diaminopyrimidine-4-one (6). A solution of **25** (150 mg, 0.39 mmol) in 6 mL of $CF_3CO_2H-H_2O$ (3:1, v/v) was stirred for 4 h at 50 °C and concentrated under reduced pressure. The residue was coevaporated with toluene (10 mL, 5×), treated with Amberlite IRA-900 ion-exchange resin (strongly basic), filtered, and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH = 5:1) to give **6** (28 mg, 30%): mp 172−174 °C; $[\alpha]^{25}_D$ −22.32 (*c* 0.2, MeOH). UV (MeOH) λ_{max}, nm: 213.0, 241.5, 277.5. ^{1}H NMR (DMSO-d_6): δ 9.82 (s, 1H, HO-4, D_2O exchangeable), 5.99 (s, 2H, HN_2-, D_2O exchangeable), 5.59 (m, 1H, H-5′), 5.51 (m, 3H, HN_2-, H-4′), 4.76 (d, 1H, J = 6.41 Hz, HO-2′, D_2O exchangeable), 4.70 (t, 1H, J = 4.82 Hz, HO-6′, D_2O exchangeable), 4.16 (m, 2H, H-6′), 3.84 (m, 1H, H-2′), 3.61 (m, 1H, H-1′), 3.43 (m, 1H, H-3′). FABMS (*m*/*z*): $(M + H)^+$ 239. Anal. Calcd for $C_{10}H_{14}N_4O_3 \cdot 0.1H_2O$: C, 50.04; H, 5.96; N, 23.34. Found: C, 50.08; H, 5.87; N, 23.05.

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