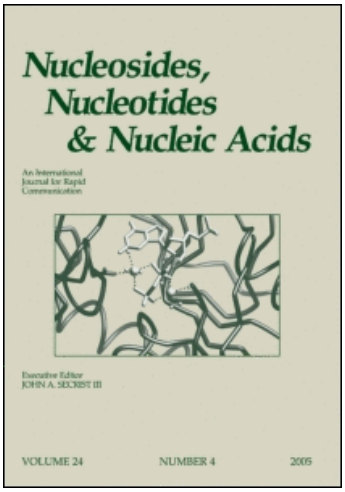

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Synthesis of Novel Bicyclic Nucleosides with 3,6-Anhydro Sugar Moiety

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SYNTHESIS OF NOVEL BICYCLIC NUCLEOSIDES WITH 3,6-ANHYDRO SUGAR MOIETY

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□ *Based on the biological importance of conformationally restricted nucleoside analogues, we have efficiently synthesized 3,6-anhydro sugar moiety with 3-C-hydroxymethyl substituent from 1,2;5,6-di-O-isopropylidene-D-glucose and condensed* ***15*** *with silylated nucleobases to afford the bicyclic nucleoside with 3,6-anhydro skeleton as potential antiviral agent.*

Keywords Bicyclic nucleoside; antiviral agents; intramolecular cyclization

INTRODUCTION

Since 3′-azido-3′-deoxythymidine (AZT) was approved for the treatment of acquired immunodeficiency syndrome (AIDS) by the U.S. Food and Drug Administration (FDA), a number of 2′,3′-dideoxynucleosides have been synthesized and evaluated for antiviral and/or anticancer agents.[1]

It has been suggested that the proper conformation of dideoxynucleosides is required for them to exhibit antiviral activity.[2] The natural nucleosides equilibrate rapidly between S-type (2′-endo/3′-exo) and N-type (2′-exo/3′-endo) conformation in solution state due to the low energy barrier between these two conformers.[3] However, nucleosides adopt only one conformation when binding to the target enzyme. Therefore, a considerable amount of work to probe conformational preference for binding with enzymes and receptors has been done in the synthesis of nucleoside derivatives with fixed sugar-ring puckering.[4]

In particular, nucleoside analogues containing bicyclic carbohydrate moiety have been synthesized to lock the puckering of the furanose

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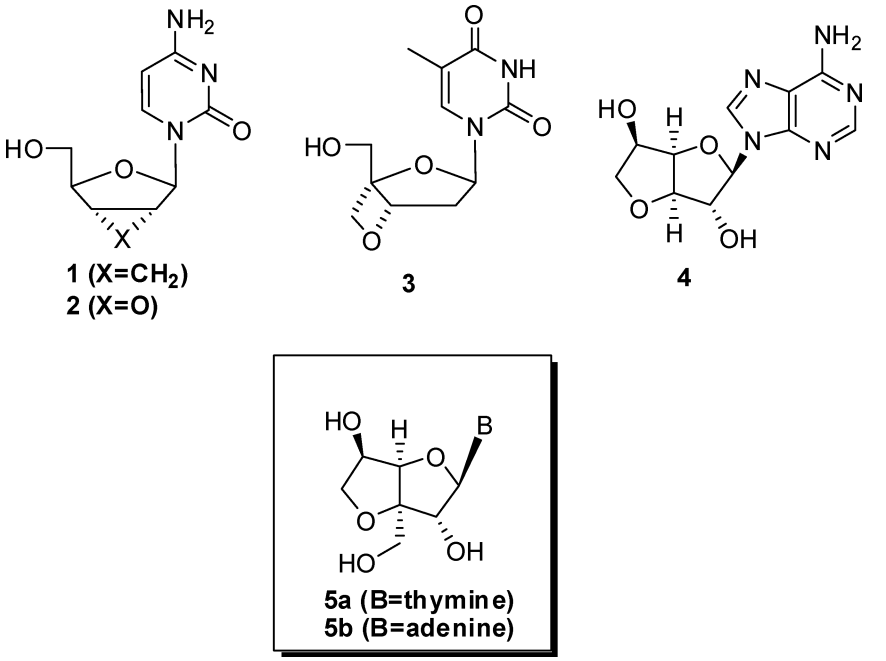


FIGURE 1 The rationale for the design of the target nucleosides.

ring and evaluated for their biological activities. Among them, bicyclic nucleosides fused with cyclopropane (**1**),[5] oxirane (**2**),[6] and oxetane (**3**)[7] have been reported to show anti-HIV activity through inhibition of HIV reversetranscriptase. Similar bicyclic nucleoside (**4**)[8] also has shown antiviral activity (Figure 1) and other nucleosides with bicyclic backbone were synthesized even though no activity was found or reported.

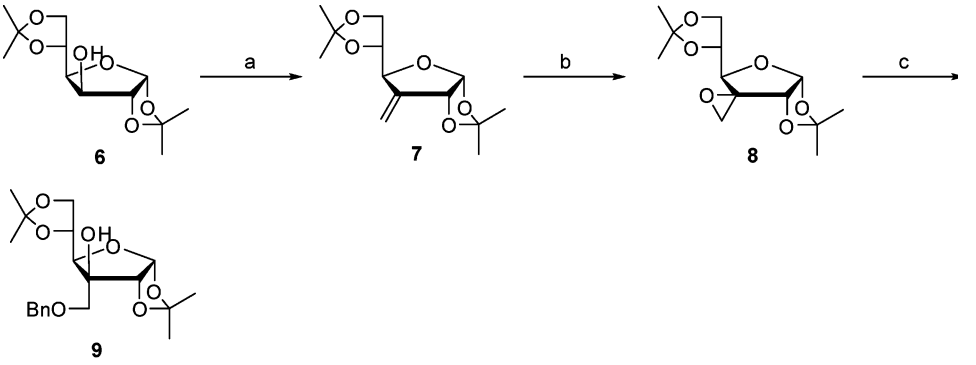
As a part of our ongoing research on the synthesis of conformationally restricted nucleoside derivatives,[9] we wish to report the synthesis of novel 3′-hydroxymethyl bicyclic nucleoside derivatives (**5a** and **5b**) with 3,6-anhydro sugar moiety, starting from 1,2;5,6-di-*O*-isoprpylidene-D-glucose as potential antiviral agent.

RESULTS AND DISCUSSION

Our synthetic strategy to the desired bicyclic nucleoside is to synthesize 3,6-anhydro sugar derivative as the key intermediate, and then to carry out a condensation reaction with nucleosidic base. Synthesis of the key intermediate from 1,2;5,6-di-*O*-isopropylidene-D-glucose is depicted in Schemes 1 and 2.

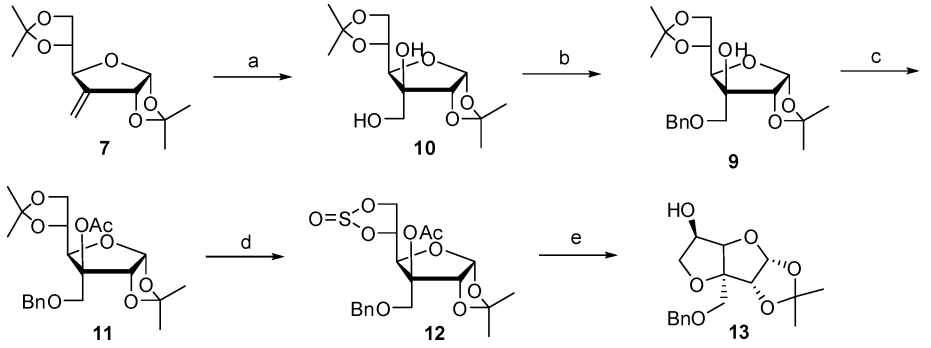
Diacetone-D-glucose **6** was converted to the 3-*C*-methylene derivative **7**[10] by oxidation with pyridinium dichromate/acetic anhydride in CH_2Cl_2 and subsequent Wittig reaction of resulting ketoone with methyl

triphenylphosphonium bromide/n-butyl lithium in THF. The initial attempt to synthesize the 3-*C*-branched sugar derivative via regioselective opening of epoxide ring of **8** with benzyl alcohol in the presence of *n*-BuLi was highly motivated, as it was known in the literature.[11] However, in our hands, the epoxidation of **7** with *m*-CPBA was problematic. The reaction yield was poor and long reaction time was required (Scheme 1).



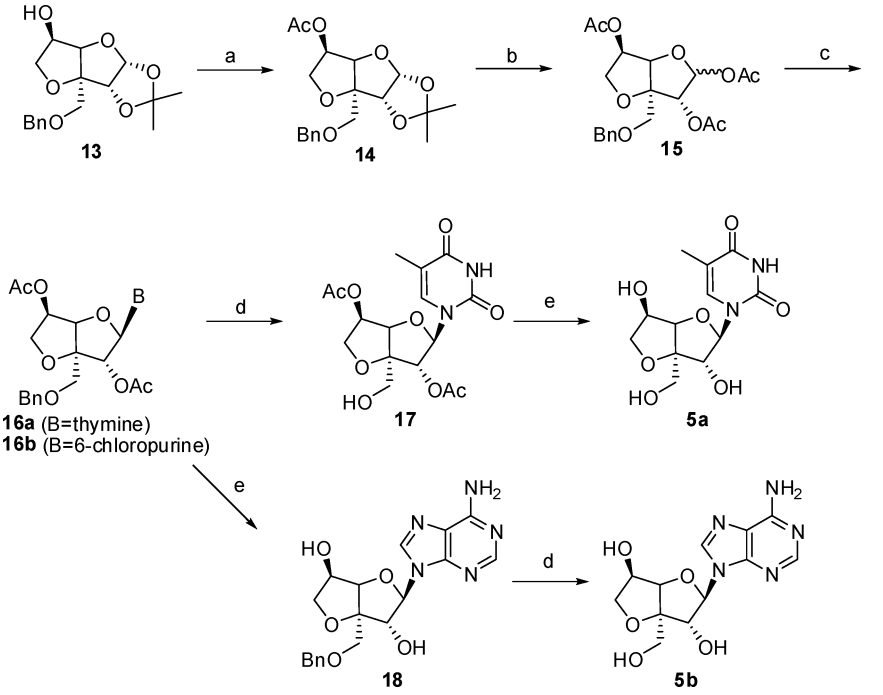
SCHEME 1 (a) i) PDC, Ac_2O, CH_2Cl_2, reflux, 2h; ii) PPh_3PCH_3Br, n-BuLi, THF, −78°C to 55°C; (b) m-CPBA, CH_2Cl_2; (c) $PhCH_2OH$, NaH, THF.

To overcome these difficulties, we attempted the alternative synthetic approach to obtain the 3-*C*-branched sugar derivative as shown in Scheme 2. Stereoselective *cis*-dihydroxylation of **7** using catalytic amount of OsO_4 and NMO led to the diol **10** due to the steric effect of 1,2-isopropylidene group, and primary hydroxy group of **10** was regioselectively benzylated using organotin chemistry[12] to afford monobenzyl ether **9**. Tertiary hydroxy group of **9** was acetylated with acetic anhydride in pyridine in the presence of DMAP at 100°C to give 3-*C*-branched derivative **11**. For the synthesis of the key intermediate, we tried to construct the bicyclic system using the



SCHEME 2 (a) OsO_4, NMO, acetone:H_2O (4:1), rt, 4h, 90%; (b) n-Bu_2SnO, toluene, 140°C, 2 h and then, n-Bu_4NBr, 90°C, overnight, 75%; (c) Ac_2O, pyridine, DMAP, 100°C, overnight, 90%; (d) i) 75% AcOH, 55°C, 2h; ii) $SOCl_2$, pyridine, rt, 3h: (e) NaOMe, MeOH, rt, overnight, 70% from **11**.

intramolecular regioselective ring opening of cyclic sulfite. After selective hydrolysis of 5,6-isopropylidene group in **11** with 75% acetic acid, the resulting diol was treated with thionyl chloride to afford the cyclic sulfite **12**. 3,6-Anhydro sugar **13**, a key intermediate was prepared by treatment of compound **12** with sodium methoxide in MeOH.[13]



SCHEME 3 (a) Ac_2O, pyridine, rt, 3h, 95%; (b) i) 88% HCO_2H, 55°C, 2h; ii) Ac_2O, pyridine, rt, overnight, 90%; (c) thymine or 6-Chloropurine, TMSOTf, DBU, CH_3CN, 60°C, 3h, 70% (**16a**), 75% (**16b**); (d) H_2, Pd/C, EtOH.rt.overnight, 85% (**17**), 60% (**5b** from **16b**); (e) NH_3/MeOH, rt (for **17**) or 80°C (for **16b**), overnight, 85% (**5a**).

With the desired bicyclic sugar derivative in hand, the synthesis of a bicyclic nucleoside with 3,6-anhydro skeleton is shown in Scheme 3. Hydroxy group of **13** was acetylated to give the acetate **14**, which was hydrolyzed with 88% formic acid and then subsequently treated with acetic anhydride in pyridine to afford the glycosyl donor **15**. Condensation of the glycosyl donor **15** with thymine and 6-chloropurine under Vorbrügen conditions gave the protected nucleoside **16a** and **16b**, respectively. Deprotection of benzyl group in **16a** under hydrogenolytic condition afforded the bicyclic nucleoside **17**, which was treated with methanolic ammonia to yield the desired 3,6-anhydro nucleoside **5a**. 6-Chlropurine derivative **16b** was treated with methanolic ammonia at 80°C to give the adenine derivative **18**, in which benzyl group was removed to yield the bcyclic nucleoside **5b**.

The antiviral activity of bicyclic nucleoside analogues **5a** and **5b** were evaluated against HIV-1 in MT-4 cells. However, no significant anti-HIV activity was observed up to 100 μM with no cytotoxicity.

In summary, we have efficiently synthesized 3,6-anhydro bicyclic nucleosides via stereoselective dihydroxylation and regioselective opening of cyclic sulfite, starting from 1,2;5,6-di-*O*-isoporpylidene-D-glucose. This methodology can be used for the synthesis of other bicyclic nucleosides.

EXPERIMETAL

NMR spectra were recorded in a 300 MHz apparatus using tetramethylsilane (TMS) as an internal standard, and the chemical shifts are reported in ppm (δ). Coupling constants are reported in hertz (Hz). Infrared spectra were recorded with a Perkin-Elmer 1710 FTIR spectrophotometer. Mass spectra recorded by FAB (Fast atom bombardment) on a VG Tro-2, GC-MS. TLC were carried out on Merck silica gel 60 F_{254} precoated plates, and silica gel column chromatography was performed on silica gel 60, 230~400 mesh, Merck. All solvents were distilled over CaH_2 or Na/benzophenone prior to use.

3-*C*-hydroxymethyl-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (10)

To a stirred solution of the olefin **7**[10] (2.05 g, 8 mmol) in acetone (40 mL) and water (10 mL) were added dropwise osmium tetroxide (1 mL, 0.08 mmol, 2.5 wt%) and *N*-methyl morpholine-*N*-oxide (5.6 g, 47.8 mmol) at 0°C. The reaction mixture was stirred for 4 hours at room temperature, quenched with saturated aqueous $Na_2S_2O_3$ solution, and then extracted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 10:1) to give the diol **10** (2.09 g, 7.2 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) 5.87 (d, 1H, J = 3.7 Hz), 4.39 (d, 1H, J = 3.5 Hz), 4.23 (m, 1H), 4.15 (dd, 1H, J = 6.0, 8.8 Hz), 4.04 (dd, 1H, J = 4.9, 8.8 Hz), 3.77–3.88 (m, 3H), 3.20–3.29 (m, 2H), 1.52, 1.45, 1.37, 1.31 (4s, 12H); FAB-MS m/z: 313$[M+Na]^+$; Found: C 53.52, H 7.35. Calc. for $C_{13}H_{22}O_7$: C 53.78, H 7.64.

3-*C*-benzyloxymethyl-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (9)

To a stirred solution of the diol **10** (2 g, 6.9 mmol) in toluene (50 mL) was added *n*-Bu_2SnO (2.8 g, 11.25 mmol). The reaction mixture was stirred at 140°C for 2 hours, cooled to 90–100°C, and *n*-Bu_4NBr (1.12 g, 3.47 mmol) and benzyl bromide (1.24 mL, 10.37 mmo1) were added to this mixture.

The reaction mixture was stirred at 90°C overnight and evaporated. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 2:1) to give the benzyl ether **11** (1.97 g, 5.18 mmol, 75%). IR (KBr): 3467, 2986, 1375, 1214, 1072, 1004 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.25–7.41 (m, 5H), 5.85 (d, 1H, J = 3.5 Hz), 4.67 (br s, 1H), 4.61 (d, 1H, J = 2.2 Hz), 4.41 (d, 1H, J = 3.5 Hz), 4.31–4.37 (m, 1H), 4.06 (dd, 1H, J = 6.2, 8.6 Hz), 3.98 (dd, 1H, J = 5.1, 8.7 Hz), 3.74–3.82 (m, 3H), 2.92 (d, 1H, J = 1.1 Hz), 1.50, 1.41, 1.33 (3s, 12H); FAB-MS m/z: 403$[M+Na]^+$; Found: C 62.98, H 7.56. Calc. for $C_{20}H_{28}O_7$: C 63.17, H 7.42.

3-*O*-acetyl-3-*C*-benzyloxymethyl-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (11)

To a stirred solution of **9** (1.9 g, 4.99 mmol) and DMAP (915 mg, 7.49 mmol) in pyridine (30 mL) was added acetic anhydride (0.95 mL, 10.07 mmol). The reaction mixture was stirred at 100°C overnight. After removal of solvent, the residue was diluted with EtOAc and extracted with water. The organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2:1) to give the acetate **11** (1.9 g, 4.50 mmol, 90%). IR (KBr): 2986, 1746, 1373, 1231, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.25–7.37 (m, 5H), 5.89 (d, 1H, J = 3.8 Hz), 4.94 (d, 1H, J = 3.8 Hz), 4.60 (td, 1H, J = 3.1, 6.8 Hz), 4.51 (d, 1H, J = 12.0 Hz), 4.46 (d, 1H, J = 12.0 Hz), 4.36–4.41 (m, 2H), 4.08 (dd, 1H, J = 6.8, 8.2 Hz), 3.98 (dd, 1H, J = 6.8, 8.2 Hz), 3.86 (d, 1H, J = 10.4 Hz), 2.03 (s, 3H), 1.48, 1.43, 1.36, 1.29 (4s, 12H); FAB-MS m/z: 445$[M+Na]^+$; Found: C 62.44, H 7.32. Calc. for $C_{22}H_{30}O_8$: C 62.55, H 7.16.

3,6-Anhydro-3-*C*-benzyloxymethyl-1,2-*O*-isopropylidene-α-D-glucofuranose (13)

A mixture of **11** (1.85 g, 4.38 mmol) in 75% acetic acid (30 mL) was stirred for 2 hours at 55°C. The reaction mixture was cooled to room temperature, evaporated and co-evaporated with toluene to give the diol. This diol was dissolved in pyridine (20 mL) and thionyl chloride (1.6 mL, 21.93 mmol) was added at 0°C. The reaction mixture was stirred for 3 hours at room temperature and evaporated. The residue was partitioned between CH_2Cl_2 and water. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give the cyclic sulfite **12**. To a stirred solution of **12** in MeOH (20 mL) was added 28% sodium methoxide in MeOH (2.11 mL, 10.95 mmol) at 0°C. The reaction mixture was stirred overnight at room temperature and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:1) to give **13** (988 mg, 3.06 mmol, 70%). IR (KBr): 3420, 2934, 1377, 1216, 1074, 1003 cm^{-1}; ^1H

NMR (300 MHz, $CDCl_3$) 7.33–7.42 (m, 5H), 5.88 (d, 1H, $J = 3.7$ Hz), 4.64 (s, 2H), 4.38 (d, 1H, $J = 3.7$ Hz), 3.80–3.95 (m, 5H), 3.75 (m, 1H), 3.57 (d, 1H, $J = 3.5$ Hz), 2.89 (s, 1H), 1.49, 1.31 (2s, 6H). FAB-MS m/z: 323$[M+Na]^+$; Found: C 63.12, H 7.04. Calc. for $C_{17}H_{22}O_6$: C 63.34, H 6.88.

5-*O*-acetyl-3,6-Anhydro-3-*C*-benzyloxymethyl-1,2-*O*-isopropylidene-α-D-glucofuranose (14)

To a stirred solution of **13** (950 mg, 2.95 mmol) in pyridine (20 mL) was added acetic anhydride (0.42 mL, 4.45 mmol) at room temperature, After being stirred for 3 hours at room temperature, the reaction mixture was evaporated. The residue was diluted with EtOAc and washed with water. The organic layer was dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2:1) to give **14** (1.02 g, 2.80 mmol, 95%). IR (KBr): 2986, 1742, 1372, 1239, 1169, 1080, 1003 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.25–7.45 (m, 5H), 5.96 (d, 1H, $J = 3.5$ Hz), 5.27 (td, 1H, $J = 4.1$, 7.7 Hz), 4.77 (d, 1H, $J = 4.1$ Hz), 4/60 (d, 1H, $J = 12.3$ Hz), 4.54 (d, 1H, $J = 12.3$ Hz), 4.46 (d, 1H, $J = 3.5$ Hz), 4.28 (pt, 1H, $J = 8.2$, 7.7 Hz), 3.70–3.79 (m, 3H), 2.11 (s, 3H), 1.45, 1.32 (2s, 6H); FAB-MS m/z: 387$[M+Na]^+$; Found: C 62.39, H 6.73. Calc. for $C_{19}H_{24}O_7$: C 62.63, H 6.64.

1,2,5-*O*-tri-acetyl-3,6-Anhydro-3-*C*-benzyloxymethyl-α-D-glucofuranose (15)

A mixture of **14** (1.01 g, 2.77 mmol) in 88% formic acid (20 mL) was stirred for 2 hours at 55°C. The reaction mixture was cooled to room temperature, evaporated and coevaporated with benzene. The residue was dissolved in pyridine (20 mL) and acetic anhydride (3.4 mL, 36.03 mmol) was added to this mixture. After being stirred overnight at room temperature, the reaction mixture was evaporated. The residue was diluted with EtOAc and washed with water. The organic layer was dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2:1) to give **15** (1.02 g, 2.49 mmol, 90%). ^1H NMR (300 MHz, $CDCl_3$) 7.26–7.39 (m, 5H), 6.11 (s, 1H), 5.07–5.24 (m, 2H), 4.89 (d, 1H, $J = 5.3$ Hz), 4.57 (s, 2H), 4.33 (pt, 1H, $J = 8.1$, 8.4 Hz), 4.00 (pt, 1H, $J = 8.1$, 8.3 Hz), 3.59–3.68 (m, 2H), 2.13, 2.09, 2.05 (3s, 9H); FAB-MS m/z: 431$[M+Na]^+$.

1-(2′,5′-di-*O*-acetyl-3′6′-anhydro-3′-*C*-benzyloxymethyl-β-D-glucofuranosyl)-thymine (16a)

To a stirred mixture of **15** (950 mg, 2.33 mmol) and thymine (352 mg, 2.79 mmol) were added DBU (1.05 mL, 7.02 mmol) and TMSOTf (1.68 mL,

9.30 mmol) at 0°C. after being stirred for 3 hours at 60°C, the reaction mixture was poured into sat. $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:2) to give **16** (779 mg, 1.63 mmol, 70%). IR (KBr): 3743, 1746, 1696, 1458, 1372, 1226, 1053, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 8.30 (s, 1H), 7.29–7.41 (m, 6H), 6.13 (d, 1H, J = 5.1 Hz), 5.27 (d, 1H, J = 5.1 Hz), 4.77 (d, 1H, J = 4.8 Hz), 4.54–4.67 (m, 3H), 4.38 (dd, 1H, J = 7.1, 9.2 Hz), 3.93 (dd, 1H, J = 6.4, 9.2 Hz), 3.66 (d, 1H, J = 10.2 Hz), 3.58 (d, 1H, J = 10.2 Hz), 2.13, 2.06 (2s, 6H), 1.96 (d, 3H, J = 1.1 Hz); FAB-MS m/z: 497$[M+Na]^+$; Found: C 58.08, H 5.72. N 5.84. Calc. for $C_{23}H_{26}N_2O_9$: C 58.22, H 5.52, N 5.90.

6-Chloro-9-(2′,5′-di-*O*-acetyl-3′6′-anhydro-3′-*C*-benzyloxymethyl-β-D-glucofuranosyl)-purine (16b)

Compound **15** (300 mg, 0.73 mmol) was condensed with 6-chloropurine (136 mg, 0.88 mmol) to give compound **16b** (hexane/ethyl acetate = 1:2, 277 mg, 0.55 mmol, 75%) according to the same procedure used in the synthesis of compound **16a**. ^1H NMR (300 MHz, $CDCl_3$) 8.77 (s, 1H), 8.31 (s, 1H), 7.30–7.44 (m, 5H), 6.37 (d, 1H, J = 2.7 Hz), 5.57 (d, J = 2.7 Hz), 5.37 (m, 1H), 4.89 (d, 1H, J = 5.0 Hz), 4.63 (m, 2H), 4.12 (m, 1H), 4.03 (m, 1H), 3.88 (m, 1H), 2.11, 2.05 (2s, 6H); FAB-MS m/z: 525$[M+Na]^+$; Found: C 54.65, H 4.58. N 11.04. Calc. for $C_{23}H_{23}ClN_4O_7$: C 54.93, H 4.61, N 11.24.

1-(2′,5′-di-*O*-acetyl-3′6′-anhydro-3′-*C*-hydroxymethyl-β-D-glucofuranosyl)-thymine (17)

A mixture of **16** (580 mg, 1.21 mmol) and Pd/C (80 mg) in EtOH (15 mL) was degassed and stirred overnight at room temperature under hydrogen atmosphere. The reaction mixture was filtered through a silica gel pad and washed with MeOH. The filtrate was evaporated and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 10:1) to give **17** (397 mg, 1.03 mmol, 85%). ^1H NMR (300 MHz, $CDCl_3$) 8.96 (s, 1H), 7.50 (d, 1H, J = 1.1 Hz), 5.86 (d, 1H, J = 2.9 Hz), 4.85 (d, 1H, J = 4.8 Hz), 4.33–4.66 (m, 4H), 4.09 (m, 1H), 3.83 (m, 1H), 2.16, 2.12 (2s, 6H), 1.95 (d, 3H, J = 1.1 Hz); FAB-MS m/z: 407$[M+Na]^+$; Found: C 49.88, H 5.36. N 7.24 Calc. for $C_{16}H_{20}N_2O_9$: C 50.00, H 5.25, N 7.29.

1-(3′6′-anhydro-3′-*C*-hydroxymethyl-β-D-glucofuranosyl)-thymine (5a)

A solution of **17** (250 mg, 0.65 mmol) in saturated methanolic ammonia (20 mL) was stirred overnight at room temperature and concentrated.

The residue was purified by silica gel column chromatography (methylene chloride/methanol = 6:1) to give **5a** (166 mg, 0.55 mmol, 85%). ^{1}H NMR (300 MHz, DMSO-d_6) 11.36 (s, 1H), 7.72 (s, 1H), 5.79 (d, 1H, J = 7.3 Hz), 5.64 (d, 1H, J = 5.3 Hz), 5.20 (d, 1H, J = 5.9 Hz), 4.73 (t, 1H, J = 5.6 Hz), 4.29 (d, 1H, J = 5.0 Hz), 4.08–4.17 (m, 2H), 3.87 (dd, 1H, J = 5.9, 10.7 Hz), 3.60–3.71 (m, 2H), 3.42 (m, 1H), 1.79 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): 164.1, 151.2, 136.8, 110.0, 91.5, 89.2, 82.1, 79.0, 72.5, 71.3, 61.2, 12.6; FAB-MS m/z: 323[M+Na]$^+$; Found: C 47.89, H, 5.25, N 9.23. Calc. for $C_{12}H_{16}N_2O_7$: C 48.00, H 5.37, N 9.33.

6-Amino-(3′6′-anhydro-3′-*C*-hydroxymethyl-β-D-glucofuranosyl)-purine (5b)

A solution of compound **16b** (200 mg, 0.40 mmol) in methanolic ammonia (20 mL) was heated in a sealed steal reaction vessel overnight at 80°C, cooled to room temperature, and concentrated to give compound **18**. The residue was dissolved in EtOH (20 mL) and Pd/C (70 mg) was added. This mixture was degassed and stirred overnight at room temperature under hydrogen atmosphere. The reaction mixture was filtered through a silica gel pad and washed with MeOH. The filtrate was evaporated and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 5:1) to give **5b** (74 mg, 0.24 mmol, 60%). ^{1}H NMR (300 MHz, CD_3OD) 8.58 (s, 1H), 8.35 (s, 1H), 6.16 (d, 1H, J = 6.5 Hz), 4.18 (d, 1H, J = 5.1 Hz), 3.94–4.03 (m, 2H), 3.77 (m, 1H), 3.66–3.75 (m, 2H), 3.49 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD): 156.1, 152.4, 149.8, 140.3, 119.4, 97.4, 91.6, 85.1, 75.1, 74.9, 74.8, 62.1; FAB-MS m/z: 332[M+Na]$^+$; Found: C 46.38, H, 4.96, N 22.58. Calc. for $C_{12}H_{15}N_5O_5$: C 46.60, H 4.89, N 22.64.

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