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Note

Facile synthesis of 1′,2′-*cis*-β-pyranosyladenine nucleosides

Takayuki Ando,[a] Hisashi Shinohara,[b] Xiong Luo,[b] Mahmoud Kandeel[b] and Yukio Kitade[a,b,c,*]

[a]*Center for Emerging Infectious Diseases, Gifu University, Yanagido 1-1, Gifu 501-1193, Japan*
[b]*Department of Biomolecular Science, Faculty of Engineering, Gifu University, Yanagido 1-1, Gifu 501-1193, Japan*
[c]*Center for Advanced Drug Research, Gifu University, Yanagido 1-1, Gifu 501-1193, Japan*

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Abstract—1′,2′-*cis*-β-Glycosyladenine nucleosides, such as β-altroside, β-mannoside, and β-idoside, were efficiently synthesized from the corresponding 1′,2′-*trans*-β-6-chloropurine derivatives, β-glucoside, and β-galactoside. Nucleophilic substitution of the *O*-trifluoromethanesulfonyl groups at the C-2′ and/or 3′ was carried out using tetrabutylammonium acetate or cesium acetate under mild conditions. Subsequent deprotection and amidation afforded the desired compounds, 1′,2′-*cis*-β-pyranosyladenine nucleosides.

Keywords: Pyranosyladenine; 1′,2′-*cis*-Glycoside; Pyranosyl nucleoside

Various nucleosides containing pyranosyl rings instead of furanosyl ones for the sugar portion have been synthesized along with their analogues[1] in order to develop antileukemia,[2] antitumor,[3] and antimicrobial[4] reagents, and enzyme inhibitors.[5] In addition, amidite derivatives of pyranosyl nucleosides were used as modified oligonucleotides to clarify the importance of the core sugar structure.[6–11]

It has been reported that 1′,2′-*trans*-pyranosyl nucleosides are more abundant than 1′,2′-*cis*-pyranosyl ones. For example, β-glucosyladenine **1**,[12] β-galactosyladenine **2**,[13] and β-allosyladenine **3**[14] (Fig. 1) were easily synthesized under various coupling conditions, and they were subsequently deprotected. Due to C-2′ acyl group having strong neighboring participation, 1′,2′-*trans*-glycosides were selectively synthesized. On the other hand, it is more difficult to synthesize 1′,2′-*cis*-β-glycosides, such as β-altroside **4**, β-mannoside **5**,[15] and β-idoside **6**, because both anomeric effect and neighboring participation act to construct thermodynamically stable α-glycoside formation during the glycosylation reaction (Scheme 1). Several synthetic methods involving direct glycosylation using the corresponding glycosyl donor and an insoluble silver salt,[16] and intramolecular aglycon delivery (IAD)[17–19] were developed to facilitate construction of 1,2-*cis*-glycosides for O-glycosylation. However, idose and altrose are considered as rare sugars and are therefore expensive for use in the optimization of reaction conditions and as starting materials.

We have devised a versatile method for the synthesis of 1′,2′-*cis*-β-pyranosyladenine nucleosides from the corresponding protected 1′,2′-*trans*-β-glycosyl-6-chloropurine derivatives (Scheme 2). Glucose and galactose are relatively inexpensive starting materials used in the synthetic step. The hydroxy group was epimerized by S_N2 substitution of the *O*-trifluoromethanesulfonyl (TfO) group with either tetrabutylammonium acetate (TBAA) or CsOAc under mild conditions. Subsequent deprotection and amidation at the 6-position yielded the title compounds.

Under reflux condition, peracetylated glucose (glc) or galactose (gal) was transformed with trimethylsilyl trifluoromethanesulfonate (TMSOTf) into reactive cations, that were combined with silylated 6-chloropurine to yield peracetylated β-glucosyl- and β-galactosyl-6-chloropurine derivatives (Scheme 3). Deacetylation was carried out using methanolic ammonia at 0 °C.

* Corresponding author. Tel./fax: +81 58 2932640; e-mail: ykkitade@gifu-u.ac.jp

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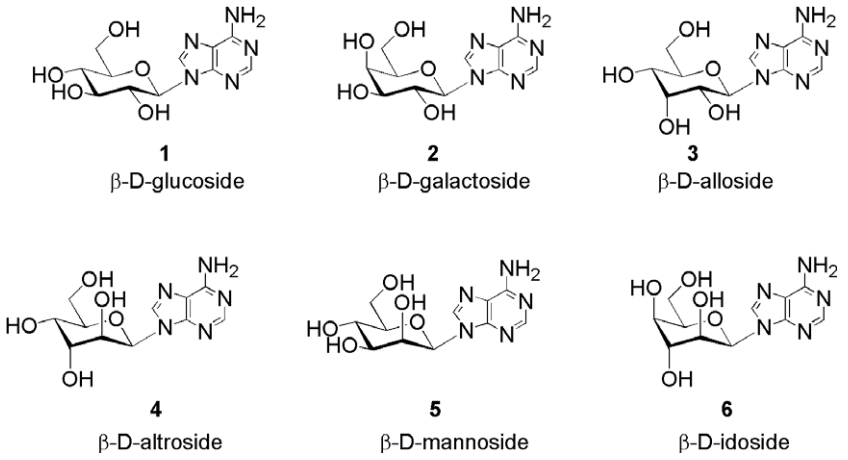
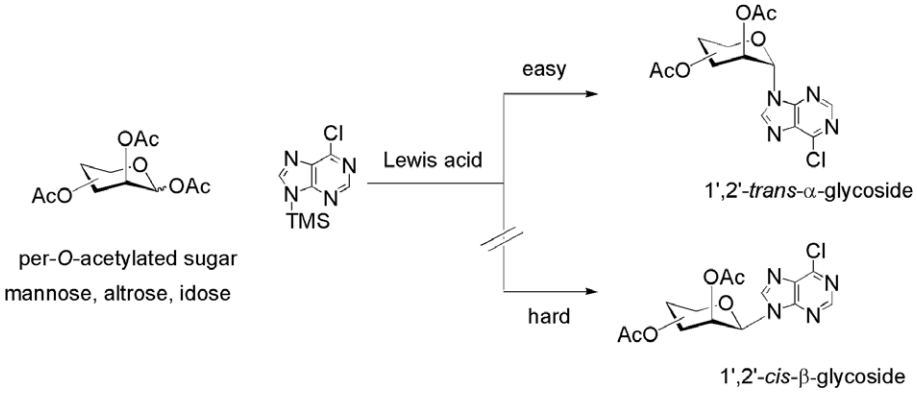
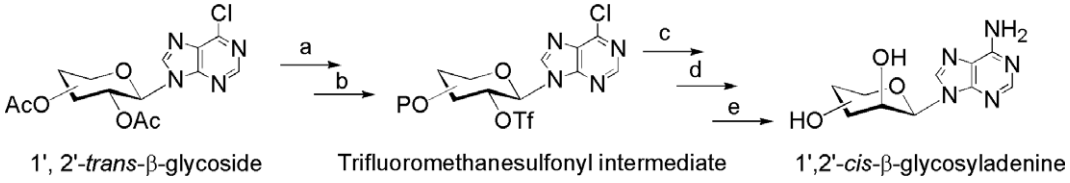


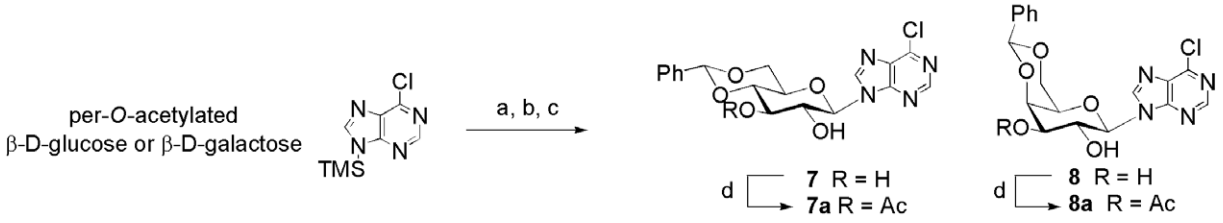
Figure 1. Various pyranosyladenine nucleosides.



Scheme 1.



Scheme 2. Synthetic plan for 1′,2′-*cis*-β-D-glycosyladenine nucleosides.



Scheme 3. Reagents and conditions: (a) TMSOTf, $ClCH_2CH_2Cl$, rt, 5 h; (b) NH_3–MeOH, 0 °C, 3 h; (c) BDA, CSA, CH_3CN, rt, 18 h; (d) Ac_2O, pyridine, rt, 5 h.

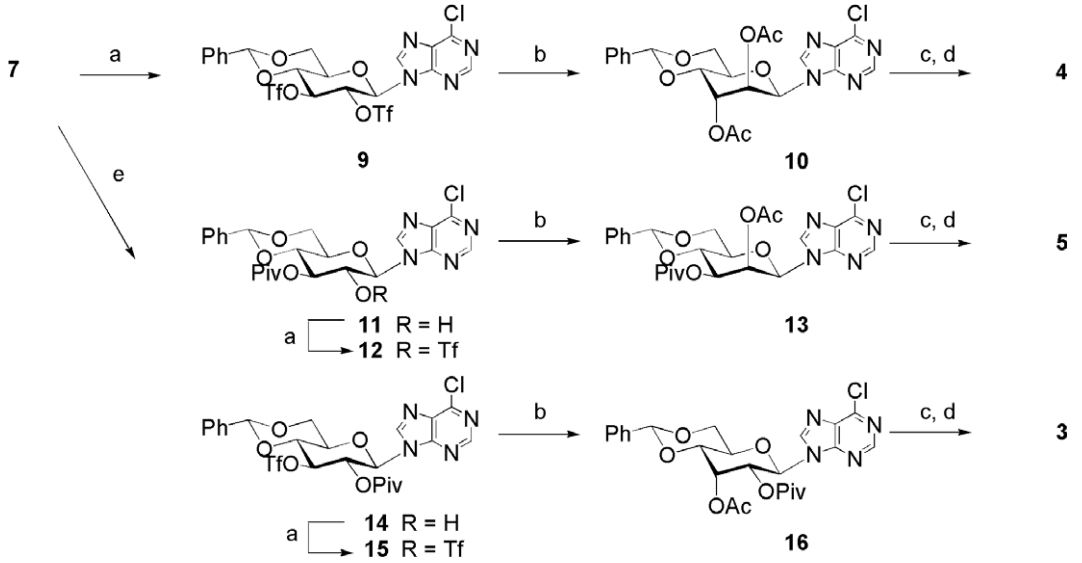
Compounds **7** and **8** were obtained by the introduction of a benzylidene group at the 4′ and 6′ positions, respectively. The structures of these compounds were determined based on the spectra of the corresponding acetylated derivatives **7a** and **8a**. Significant signals in the ^1H NMR spectra were those of doublet anomeric

protons ($J_{1',2'}$ 9.6 Hz, for glc, 9.2 Hz for gal) that indicated the β-glycosidic linkage. Treatment of **7** with trifluoromethanesulfonic anhydride (Tf_2O) and pyridine in CH_2Cl_2 at 0 °C yielded the 2′,3′-di-*O*-trifluoromethanesulfonyl intermediate **9** at 95% yield. The inversion of the 2′ and 3′ positions of **9** by nucleophilic substitution with the acetoxy anion from TBAA or CsOAc was carried out in DMF.[20] The protected β-altrosyl-6-chloropurine **10** was obtained as a single isomer in 65% (by TBAA method) and 86% yield (by the CsOAc method) (Scheme 4).

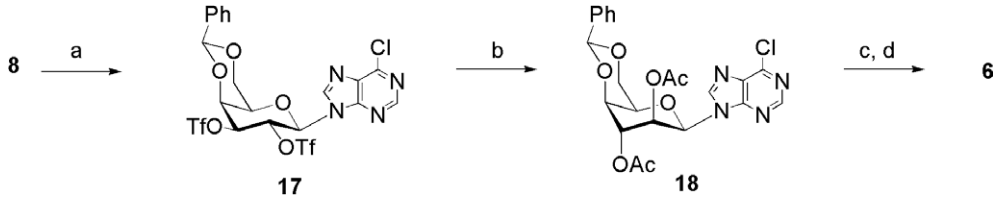
A mixture of trimethylacetyl chloride and pyridine in CH_2Cl_2 were used for the selective monoprotection of the hydroxy group of compound **7**. The desired 3′-OH protected compound **11** (32%), 2′-OH protected compound **14** (37%), and the unreacted starting material (28%) were obtained. The 2′,3′-di-*O*-trimethylacetylated compound was not obtained. However, the regioselectivity of protection was not very high; the undesired 2′-*O*-trimethylacetyl-3′-*O*-trifluoromethanesulfonyl compound **15** obtained from **14** was also an important intermediate in the synthesis of β-allopyranosyladenine. Further, the separation of these regioisomers by silica gel chromatography was relatively easy. Compounds **11** and **14** were treated with Tf_2O and pyridine in CH_2Cl_2 to afford the corresponding trifluoromethanesulfonyl intermediates **12** and **15**, respectively. Inversion of triflated positions of **12** and **15** to yield β-mannosyl- and β-allosyl-6-chloropurine at 90% (for **13**) and 88% (for **16**) yield, respectively, was achieved as described. Finally, *O*-deacetylation, amidation of the 6 position, and removal of the benzylidene group yielded 1′,2′-*cis*-β-glycosyladenine derivatives (**4** and **5)** and β-allosyladenine **3**, respectively.

Similarly, treatment of β-galactosyl-6-chloropurine **8** with Tf_2O and pyridine, followed by nucleophilic substitution with TBAA, deprotection, and amidation afforded the desired β-idosyladenine **6** (Scheme 5).

The $J_{1',2'}$, $J_{2',3'}$ and $J_{3',4'}$ values were analyzed (summarized in Table 1) in order to define the stereochemistry of hydroxy groups. The $J_{1',2'}$ values of **10**, **13**, and **18** (1.6–2.0 Hz) demonstrated that the relationships between H-1′ and H-2′ supported the 1′,2′-*cis*-β assignment. Furthermore, the $J_{2',3'}$ and $J_{3',4'}$ values of **10**, **16**, and **18** were less (2.0–3.6 Hz) than those of the corresponding compounds **7a** and **8a** (9.6 and 9.2 Hz, respectively). This information indicated that the ring proton at C-3′ of **10**, **16**, and **18** was located in the equatorial



Scheme 4. Reagents and conditions: (a) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 30 min (for **9**) or 10 min (for **12** and **15**); (b) TBAA, DMF, 40 °C, 24 h (for **10**) or 0 °C, 30 min (for **13**) AcOCs, DMF, 40 °C, 1 h (for **16**); (c) NH_3–MeOH, 120 °C, 24 h; (d) CSA, MeOH, rt, 18 h; (e) PivCl, pyridine, CH_2Cl_2, 0 °C, 18 h.



Scheme 5. Reagents and conditions: (a) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 30 min; (b) TBAA, DMF, 40 °C, 24 h; (c) NH_3–MeOH, 120 °C, 24 h; (d) CSA, MeOH, rt, 18 h.

Table 1. Coupling constants

Compound	Coupling constant (Hz)		
	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$
7a	9.6	9.2	9.6
10	2.0	3.6	3.6
13	1.6	3.6	10.8
16	9.6	3.2	2.8
8a	9.2	10.0	3.6
18	2.0	3.2	2.0

position, and that the configuration of 3′-OH group was axial.

In conclusion, we successfully synthesized 1′,2′-*cis*-β-glycosyladenine nucleosides by inverting the configuration of the hydroxy group. Nucleophilic substitution yielded considerably higher amounts of the glucose derivative than the galactose derivative. It is assumed that the 4′ axial hydroxy group and 4′,6′-*O*-benzylidene group caused steric hindrance around the 2′ position of the galactose moiety. Changing the protective group of the galactose portion may solve this problem and increase the inversion yield; this technique is currently under investigation.

The synthetic method described in this paper may be applied to other bases, such as guanine, thymine, cytosine, and uracil. Furthermore, trifluoromethanesulfonyl intermediates may also be useful for modification of the sugar portion with various nucleophiles in order to introduce various functional groups and construct double bond in the pyranose ring.

1. Experimental

1.1. General methods

Specific rotations were determined with a Horiba SEPA-300 high sensitive polarimeter at 25 °C. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz on a JEOL AL-400 (operated at 400 and 100 MHz, respectively) by using $CDCl_3$ with TMS as the internal standard, DMSO-d_6, and CD_3OD. The spin multiplicities are indicated by the following symbols s (singlet), d (doublet), dd (doublet of doublet), t (triplet), ddd (doublet of doublet of doublet), q (quartet), m (multiplet), and br (broad). Coupling constants (*J*) are expressed in Hertz. Mass spectra (EIMS and HRESIMS) were recorded at 70 eV on Shimadzu GCMS QP 2010A and a JEOL JMS-700/GI spectrometer. Reactions were monitored by thin-layer chromatography using E. MERCK Silica Gel 60F_{254} glass plate. Silica gel column chromatography was carried out on Wako gel C-300. HPLC was performed using the Shimadzu HPLC 10A VP-series attached with a YMC ODS-AM column (250 mm × 20 mm) for separation or an YMC ODS-M80 column (150 mm × 8 mm) for analysis.

1.2. General procedure

1.2.1. General procedure A for the silylation of 6-chloropurine. To a suspended solution of 6-chloropurine (6-CP) in dichloroethane (10 mL for 100 mg of 6-CP) was added *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 1.5 equiv for 6-CP) and the mixture was stirred under reflux conditions for 30 min. The reaction solution was directly used for the coupling reaction with peracetylated sugar.

1.2.2. General procedure B for deacetylation and amidation of the 6-chloro group. The compound was treated with methanolic ammonia (50 mL, 27–32% w/w) at 120 °C in a sealed tube for 24 h. The reaction mixture was evaporated under reduced pressure.

1.2.3. General procedure C for removal of the benzylidene group. Camphorsulfonic acid (CSA, 0.01 equiv for starting material) was added to a solution of the residue obtained after general procedure B in MeOH (10 mL) and the mixture was stirred for 18 h at rt. After neutralization with Et_3N, the reaction mixture was concentrated.

1.3. 9-(4′,6′-*O*-Benzylidene-β-D-glucopyranosyl)-*H*-6-chloropurine (7)

To a solution of silylated 6-CP in dichloroethane, which was obtained from 6-CP (300 mg, 1.94 mmol) by using general procedure (A) were added 1,2,3,4,6-penta-*O*-acetyl-β-D-glucose (1.14 g, 2.91 mmol) and TMSOTf (528 μL, 2.91 mmol), and the stirring was continued for 2 h under reflux condition. The mixture was neutralized with triethylamine and concentrated. Column chromatography ($CHCl_3$–MeOH, 150:1 to 70:1) of the residue on silica gel gave acetylated glucosyl 6-CP derivative. Deacetylation was performed under the treatment with methanolic ammonia at 0 °C for 3 h. The reaction mixture was evaporated under the reduced pressure, and the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 3:1) and crystallization from MeOH. To a suspended solution of deacetylated compound were added benzaldehydedimethyl acetal (1.31 mL, 8.73 mmol) and CSA (34 mg, 0.15 mmol) and the mixture was stirred at rt for 18 h. The mixture was neutralized with Et_3N, concentrated, and extracted with EtOAc. The extract was washed with water, dried (Na_2SO_4), and concentrated. The crystallization from EtOAc gave **7** (230 mg, 74%). $[\alpha]_D$ −35 (*c* 0.01 $CHCl_3$); ^{1}H NMR (DMSO-d_6): δ 8.91 (s, 1H, H-2), 8.82 (s, 1H, H-8), 7.48–7.36 (m, 5H, *Ph*CH), 5.77 (d, 1H, $J_{1',2'}$ 9.6 Hz, H-1′), 5.64 (s, 1H, PhC*H*), 4.25–4.18 (m, 2H, H-2′, H-3′), 3.80–3.62 (m, 4H, H-4′, 5′, 6′ax, 6′eq); ^{13}C NMR (DMSO-d_6): δ 152.0, 149.4, 146.4, 137.6, 131.1, 128.9, 128.2, 128.0 (2C, Ph), 126.4 (2C, Ph),

100.8, 94.2, 84.1, 80.2, 73.0, 71.9, 68.8; EI MS (*m*/*z*, relative intensity): 403 (M^-, 4.8), 250 (25.5), 197 (18), 183 (72), 155 (100), 119 (17), 105 (51.8); HRESIMS *m*/*z* calcd for $C_{18}H_{18}ClN_4O_5$ $[M+H]^+$: 405.0966. Found, 405.0987.

1.4. 9-(2′,3′-Di-*O*-acetyl-4′,6′-*O*-benzylidene-β-D-glucopyranosyl)-*H*-6-chloropurine (7a)

To a solution of **7** (50 mg, 124 μmol) in pyridine (1 mL) was added Ac_2O (1 mL), and the mixture was stirred for 5 h at rt. After completion of the reaction, MeOH was added, and the mixture was stirred for 20 min, concentrated, and extracted with CH_2Cl_2. The extract was washed with 2 M HCl, satd Na_2CO_3, and water, dried (Na_2SO_4), and concentrated. The crystallization from EtOAc–hexane gave **7a** (54 mg, 111 μmol) in 90% yield as white crystal. $[\alpha]_D$ −32.5 (*c* 0.01, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.81 (s, 1H, H-2), 8.30 (s, 1H, H-8), 7.48–7.38 (m, 5H, *Ph*CH), 5.99 (d, 1H, $J_{1',2'}$ 9.6 Hz, H-1′), 5.73 (d, 1H, $J_{2',3'}$ 9.2 Hz, H-2′), 5.60 (s, 1H, PhC*H*), 5.60 (t, 1H, $J_{3',4'}$ 9.6 Hz, H-3′) 4.40 (br q, 1H, H-4′), 3.99–3.82 (m, 2H, H-6′ax, 6′eq), 2.09 and 1.80 (2s, 6H, $2CH_3CO$); ^{13}C NMR ($CDCl_3$): δ 169.8, 169.2, 152.6, 151.7, 151.6, 143.0, 136.3, 129.4, 128.4 (2C, Ph), 126.1 (2C, Ph), 101.8, 81.7, 77.9, 71.7, 70.8, 69.8, 68.0, 67.3; HRESIMS *m*/*z* calcd for $C_{22}H_{22}ClN_4O_7$ $[M+H]^+$: 489.1177. Found, 489.1201.

1.5. 9-(4′,6′-*O*-Benzylidene-β-D-galactopyranosyl)-*H*-6-chloropurine (8)

Compound **8** (240 mg, 593 μmol) was prepared from 1,2,3,4,6-penta-*O*-acetyl-β-D-galactose (300 mg, 769 μmol) in 77% yield as described from **7** after crystallization from EtOAc. $[\alpha]_D$ −30 (*c* 0.01, $CHCl_3$); ^1H NMR (DMSO-d_6): δ 8.89 (s, 1H, H-2), 8.86 (s, 1H, H-8), 8.31–7.36 (m, 5H, Ph), 5.68 (d, 1H, $J_{1',2'}$ 9.6 Hz, H-1′), 5.39 and 5.29 (2d, 2H, $J_{H',OH'}$ 5.4, 5.6 Hz, OH-2′, OH-3′), 4.49 (dt, $J_{2',3'}$ 9.6 Hz 1H, H-2′), 4.24 (d, 1H, H-4′), 4.00 (q, 2H, H-6′a, H-6′b), 3.91 (s, 1H, H-5′), 3.78 (ddd, 1H, H-3′); ^{13}C NMR (DMSO-d_6): δ 152.1, 151.9, 149.3, 146.3, 138.7, 131.1, 128.8, 128.0 (2C, Ph), 126.8 (2C, Ph), 100.3, 84.0, 75.8, 72.2, 68.6, 68.1, 67.8; EI MS (*m*/*z*, relative intensity): 405 (2.6), 298 (2.8), 269 (3.3), 250 (13.6), 183 (75), 155 (100), 107 (46), 91 (10.7), 79 (15.7); HRESIMS *m*/*z* calcd for $C_{18}H_{18}ClN_4O_5$ $[M+H]^+$: 405.0966. Found, 405.0933.

1.6. 9-(2′,3′-Di-*O*-acetyl-4′,6′-*O*-benzylidene-β-D-galactopyranosyl)-*H*-6-chloropurine (8a)

To a solution of **8** (50 mg, 124 μmol) in pyridine (1 mL) was added Ac_2O (1 mL), and the mixture was stirred for 5 h at rt. After completion of the reaction, MeOH was added, and the mixture was stirred for 20 min, concentrated, and extracted with CH_2Cl_2. The extract was washed with 2 M HCl, satd Na_2CO_3, and water, dried (Na_2SO_4), and concentrated. The crystallization from EtOAc–hexane gave **8a** (57 mg, 117 μmol) in 95% yield as white crystal. $[\alpha]_D$ −30 (*c* 0.01, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.78 (s, 1H, H-2), 8.46 (s, 1H, H-8), 7.48–7.41 (m, 5H, *Ph*CH), 5.98 (d, 1H, $J_{1',2'}$ 9.2 Hz, H-1′), 5.91 (t, 1H, $J_{2',3'}$ 10.0 Hz, H-2′), 5.60 (s, 1H, PhC*H*), 5.25 (dd, 1H, $J_{3',4'}$ 3.6 Hz, H-3′), 4.59 (d, 1H, H-4′), 4.32 and 4.12 (2d, 2H, H-6′$_a$, H-6′$_b$), 3.90 (s, 1H, H-5′), 2.12 and 1.77 (2s, 6H, $2CH_3CO$); ^{13}C NMR ($CDCl_3$): δ 170.4, 169.0, 152.3, 151.5, 143.4, 137.1, 133.7, 131.5, 129.5, 128.4 (2C, Ph), 126.2 (2C, Ph), 101.2, 81.0, 73.0, 71.8, 69.1, 68.5, 67.8, 20.8, 20.2; HRESIMS *m*/*z* calcd for $C_{22}H_{22}ClN_4O_5$ $[M+H]^+$: 488.1177. Found, 488.1154.

1.7. 9-(4′,6′-*O*-Benzylidene-2′,3′-di-*O*-trifluoromethanesulfonyl-β-D-glucopyranosyl)-*H*-6-chloropurine (9)

To a suspended solution of **7** (30 mg, 74 μmol) in CH_2Cl_2 (3 mL) was added Tf_2O (37 μL, 222 μmol) and pyridine (36 μL, 444 μmol) and the mixture was stirred at 0 °C for 30 min. After completion of the reaction, MeOH was added, and the mixture was stirred for 10 min at rt, concentrated, and extracted with $CHCl_3$. The extract was washed with 2 M HCl, satd aq $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated. Column chromatography (EtOAc–hexane, 1:3) of the residue on silica gel gave **9** (47 mg, 95%) as white solid. $[\alpha]_D$ −19.2 (*c* 0.013, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.81 (s, 1H, H-2), 8.20 (s, 1H, H-8), 6.00 (br t, 1H, H-2′), 5.32 (1H, t, $J_{2',3'}$ 9.6 Hz, $J_{3',4'}$ 10.0 Hz), 4.48 (dd, 1H, J_{gem} 16 Hz, $J_{5',6'ax}$ 9.6 Hz, H-6′ax), 4.22 (t, 1H, $J_{4',5'}$ 9.6 Hz, H-4′), 3.88 (m, 2H, H-5′, H-6′eq), ^{13}C NMR ($CDCl_3$): δ 152.8, 152.2, 151.6, 143.3, 135.3, 132.0, 129.7, 129.0, 128.4 (2C, Ph), 126.0 (2C, Ph), 102.2, 82.3, 82.1 78.5, 77.2, 76.7, 69.0, 67.5; EI MS (*m*/*z*, relative intensity) 667 (M^-, 8), 413 (12.4), 385 (49.4), 263 (100), 241 (8), 229 (13.7), 155 (23), 105 (86); HRESIMS *m*/*z* calcd for $C_{20}H_{16}F_6N_4O_5S_2$ $[M+H]^+$: 668.9951. Found, 668.9975.

1.8. 9-(2′,3′-Di-*O*-acetyl-4′,6′-*O*-benzylidene-β-D-altropyranosyl)-*H*-6-chloropurine (10)

To a solution of **9** (400 mg, 598 μmol) in DMF (4 mL) was added CsOAc (344 mg, 1.79 mmol) and 18-crown-6 (473 mg, 1.79 mmol) or TBAA (540 mg, 1.79 mmol), and the mixture was stirred at 40 °C for 24 h and was concentrated. Column chromatography (EtOAc–hexane 1:2) of the residue on silica gel gave **10** (190 mg, 65% from CsOAc method, 250 mg 86% from TBAA methods) as white solid. $[\alpha]_D$ −33.9 (*c* 0.053, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.78 (s, 1H, H-2), 8.30 (s, 1H, H-8), 7.46–7.38 (m, 5H, Ph), 6.47 (d, 1H, $J_{1',2'}$ 2.0 Hz, H-1′), 5.68

(s, 1H, PhC*H*), 5.62 (t, 1H, $J_{3',4'}$ 3.6 Hz, H-3′), 5.29 (dd, 1H, $J_{2',3'}$ 3.6 Hz, H-2′), 4.44 (dd, 1H, J_{gem} 10.4 Hz, $J_{5',6'eq}$ 9.2 Hz, H-6′eq), 4.32 (dt, 1H, $J_{4',5'}$ 5.2 Hz, H-5′), 3.95 (t, 1H, $J_{5',6'ax}$ 10.0 Hz, H-6′ax), 2.28 and 2.09 (2s, 6H, $2CH_3CO$); ^{13}C NMR ($CDCl_3$): δ 168.8, 168.1, 152.4, 151.4, 150.4, 143.0, 136.6, 131.2, 129.3, 128.4 (2C, Ph), 126.0 (2C, Ph), 102.1, 79.5, 76.7, 74.3, 68.9, 68.4, 67.4, 66.6, 20.9, 20.5; EI MS (*m*/*z*, relative intensity): 487 (M^-, 26), 428 (12), 369 (14), 339 (46), 322 (24), 295 (18), 263 (42), 237 (79), 209 (27), 183 (34), 155 (100), 105 (99), 77 (22.7), 55 (11.6); HRESIMS *m*/*z* calcd for $C_{22}H_{22}ClN_4O_5$ $[M+H]^+$: 489.1177. Found, 489.1215.

1.9. 9-(4′,6′-*O*-Benzylidene-3′-*O*-trimethylacetyl-β-D-glucopyranosyl)-*H*-6-chloropurine (11) and 9-(4′,6′-*O*-benzylidene-2′-*O*-trimethylacetyl-β-D-glucopyranosyl)-*H*-6-chloropurine (14)

To a solution of **7** (92 mg, 227 μmol) in CH_2Cl_2 (10 mL) was added trimethylacetyl chloride (55 μL, 454 μmol) and pyridine (368 μL, 4.54 mmol), and the mixture was stirred at 0 °C for 18 h. After completion of the reaction, MeOH was added, and the mixture was stirred for 10 min at rt, concentrated, and extracted with $CHCl_3$. The extract was washed with 2 M HCl, satd aq $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated. Column chromatography (EtOAc–hexane, 1:1) of the residue on silica gel gave **11** (71 mg, 32%) and **14** (82 mg 37%) as white solid. **11**: $[\alpha]_D$ −46.9 (*c* 0.016, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.79 (s, 1H, H-2), 8.34 (s, 1H, H-8), 7.46–7.36 (m, 5H, Ph), 5.97 (d, 1H, $J_{1',2'}$ 9.6 Hz, H-1′), 5.63 (s, 1H, PhC*H*), 5.31 (t, 1H, $J_{2',3'}$ 9.6 Hz, H-3′), 4.50 (ddd, 1H, $J_{2',3'}$ 8.8 Hz, H-2′), 3.98 (br t, 1H, H-4′), 3.88–3.81 (m, 3H, H-5′, H-6′ax, H-6′eq), 1.25 (1s, 9H, $3CH_3CO$); ^{13}C NMR ($CDCl_3$): δ 180.1, 152.3, 151.6, 143.8, 136.5, 131.8, 129.2, 128.3 (2C, Ph), 125.8 (2C, Ph), 101.2, 85.1, 77.8, 75.2, 72.0, 69.5, 68.1, 39.2, 27.1 (3C, $3CH_3$); HRESIMS *m*/*z* calcd for $C_{23}H_{26}ClN_4O_6$ $[M+H]^+$: 489.1541. Found, 489.1484. Compound **14**: $[\alpha]_D$ −17.4 (*c* 0.023, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.78 (s, 1H, H-2), 8.33 (s, 1H, H-8), 7.52–7.39 (m, 5H, Ph), 5.96 (d, 1H, $J_{1',2'}$ 9.6 Hz, H-1′), 5.63 (s, 1H, PhC*H*), 5.59 (t, 1H, $J_{2',3'}$ 9.2 Hz, H-2′), 4.40 (br t, 1H, H-4′), 3.87–3.82 (m, 3H, H-5′, H-6′ax, H-6′eq), 1.25 (1s, 9H, $3CH_3CO$); ^{13}C NMR ($CDCl_3$): δ 180.1, 152.3, 151.6, 143.8, 136.5, 131.8, 129.2, 128.3 (2C, Ph), 125.8 (2C, Ph), 101.4, 85.1, 77.9, 75.0, 72.0, 69.5, 68.1, 39.4, 27.2 (3C, $3CH_3$); HRESIMS *m*/*z* calcd for $C_{23}H_{26}ClN_4O_6$ $[M+H]^+$: 489.1541. Found, 489.1501.

1.10. 9-(4′,6′-*O*-Benzylidene-2′-*O*-trifluoromethanesulfonyl-3′-*O*-trimethylacetyl-β-D-glucopyranosyl)-*H*-6-chloropurine (12)

To a suspended solution of **11** (200 mg, 410 μmol) in CH_2Cl_2 (5 mL) was added Tf_2O (136 μL, 810 μmol) and pyridine (0.65 mL, 8.1 mmol), and the mixture was stirred at 0 °C for 10 min. After completion of the reaction, MeOH was added, and the mixture was stirred for 10 min at rt, concentrated, and extracted with $CHCl_3$. The extract was washed with 2 M HCl, satd aq $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated. Column chromatography (EtOAc–hexane, 1:1) of the residue on silica gel gave **12** (230 mg, 91%) as white solid. $[\alpha]_D$ −44.4 (*c* 0.02, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.84 (s, 1H, H-2), 8.25 (s, 1H, H-8), 7.42–7.37 (m, 5H, Ph), 6.00 (d, 1H, $J_{1',2'}$ 9.6 Hz, H-1′), 5.90 (br t, 1H, H-2′), 5.76 (t, 1H, $J_{2',3'}$, $J_{3',4'}$ 9.6 Hz, H-3′), 5.61 (s, 1H, $PhCH_2$), 4.40 (ddd, 1H, $J_{4',5'}$ 9.6 Hz, H-5′), 4.04 (br t, 1H, H-4′), 3.92–3.83 (m, 2H, H-6′ax, H-6′eq), 1.25 (1s, 9H, 3C*H*$_3$); ^{13}C NMR ($CDCl_3$): δ 176.6, 152.5, 151.6, 151.4, 142.9, 135.7, 131.3, 129.5, 128.3 (2C, Ph), 125.9 (2C, Ph), 101.8, 83.4, 81.6, 77.2, 69.6, 69.4, 67.8, 38.8, 26.6 (3C, 3*C*H$_3$); HRESIMS *m*/*z* calcd for $C_{24}H_{25}ClF_3N_4O_8S$ $[M+H]^+$: 621.1034. Found, 621.1075.

1.11. 9-(2′-*O*-Acetyl-4′,6′-*O*-benzylidene-3′-*O*-trimethylacetyl-β-D-mannopyranosyl)-*H*-6-chloropurine (13)

To a suspended solution of **12** (65 mg, 105 μmol) in DMF (5 mL), was added CsOAc (60 mg, 314 μmol) and 18-crown-6 (83 mg, 314 μmol), and the mixture was stirred at 0 °C for 30 min. After completion of the reaction, the mixture was concentrated, and extracted with $CHCl_3$. The extract was washed with 2 M HCl, satd aq $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated. Column chromatography (EtOAc–hexane, 1:1) of the residue on silica gel gave **13** as white powder (50 mg, 90%). $[\alpha]_D$ −8.4 (*c* 0.018, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.70 (s, 1H, H-2), 8.30 (s, 1H, H-8), 7.47–7.37 (m, 5H, Ph), 6.34 (d, 1H, $J_{1',2'}$ 1.6 Hz, H-1′), 5.75 (dd, 1H, $J_{2',3'}$ 3.6 Hz, H-2′), 5.69 (s, 1H, PhC*H*), 5.47 (dd, 1H, $J_{3',4'}$ 10.8 Hz, H-3′), 4.45 (dd, 1H, J_{gem} 10.4 Hz, $J_{5',6'eq}$ 4.8 Hz, H-6′eq), 4.23 (t, 1H, $J_{4',5'}$ 10.0 Hz, H-4′), 4.00 (1H, t, $J_{5',6'ax}$ 9.6 Hz, H-6′ax), 3.87 (dt, 1H, H-5′), 2.10 (s, 3H, CH_3CO), 1.17 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$): δ 176.9, 168.7, 152.4, 151.4, 150.3, 142.8, 136.5, 131.0, 129.2, 128.3 (2C, Ph), 125.8 (2C, Ph), 101.6, 81.0, 75.2, 70.7, 69.5, 69.1, 67.9, 38.9, 26.9 (3C, $3CH_3$), 20.4; EI MS (*m*/*z*, relative intensity): 529.2 (M, 0.5), 263.0 (5.4), 183 (5.0), 157 (4.0), 105.1 (15.5), 85.2 (20.0), 69.0 (5.3), 57.1 (100); HRESIMS *m*/*z* calcd for $C_{25}H_{28}ClN_4O_7$ $[M+H]^+$: 531.1647. Found, 531.1623.

1.12. 9-(4′,6′-*O*-Benzylidene-3′-*O*-trifluoromethanesulfonyl-2′-*O*-trimethylacetyl-β-D-glucopyranosyl)-*H*-6-chloropurine (15)

Compound **15** (240 mg, 386 μmol) was prepared from **14** (200 mg, 410 μmol) as described from **12** in 94% yield

after silica gel chromatography (EtOAc–hexane, 1:3). $[\alpha]_D$ −13.8 (*c* 0.014, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.82 (s, 1H, H-2), 8.30 (s, 1H, H-8), 7.50–7.40 (m, 5H, Ph), 6.00 (d, 1H, $J_{1',2'}$ 9.2 Hz, H-1′), 5.91 (t, 1H, $J_{2',3'}$ 9.2 Hz, H-2′), 5.68 (s, 1H, PhC*H*), 5.32 (t, 1H, $J_{3',4'}$ 9.2 Hz, H-3′), 4.45 and 3.90 (2q, 2H, H-6′ax, H-6′eq), 4.16 (t, 1H, $J_{4',5'}$ 9.2 Hz, H-4′), 3.90 (m, 1H, H-5′), 1.25 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$): δ 176.5, 152.7, 151.8, 151.5, 142.9, 135.7, 131.3, 129.5, 128.3 (2C, Ph), 125.9 (2C, Ph), 101.8, 83.2, 81.3, 77.3, 69.6, 69.4, 67.8, 38.8, 26.6 (3C, $3CH_3$); HRESIMS *m*/*z* calcd for $C_{24}H_{25}ClF_3N_4O_8S$ $[M+H]^+$: 621.1034. Found, 621.1054.

1.13. 9-(3′-*O*-Acetyl-4′,6′-*O*-benzylidene-2′-*O*-trimethylacetyl-β-D-allopyranosyl)-*H*-6-chloropurine (16)

To a solution of **15** (35 mg, 105 μmol) in DMF (5 mL) was added CsOAc (32 mg, 314 μmol), and the mixture was stirred at 40 °C for 1 h, and was concentrated. Column chromatography (EtOAc–hexane 1:2) of the residue on silica gel gave **16** (24 mg, 80%) as white powder. $[\alpha]_D$ +5.6 (*c* 0.018, MeOH); ^1H NMR ($CDCl_3$): δ 8.81 (s, 1H, H-2), 8.27 (s, 1H, H-8), 7.46–7.37 (m, 5H, Ph), 6.21 (d, 1H, $J_{1',2'}$ 9.6 Hz, H-1′), 6.02 (t, 1H, $J_{2',3'}$ 3.2 Hz, $J_{3',4'}$ 2.8 Hz, H-3′), 5.68 (dd, 1H, H-2′), 5.64 (s, 1H, PhC*H*), 4.42 (dd, 1H, J_{gem} 10.4 Hz, H-6′eq), 4.31 (m, 1H, H-5′), 4.04 (dd, 1H, $J_{4',5'}$ 9.6 Hz, H-4′), 3.84 (t, 1H, H-6′ax), 2.23 (s, 3H, CH_3CO), 0.82 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$): δ 176.1, 169.4, 152.5, 151.7, 143.2, 136.4, 131.5, 129.3, 128.3 (2C, Ph), 126.1 (2C, Ph), 101.8, 79.6, 68.5, 68.5, 67.5, 67.2, 38.6, 26.5 (3C, $3CH_3$), 20.8; HRESIMS *m*/*z* calcd for $C_{25}H_{28}ClN_4O_7$ $[M+H]^+$: 531.1647. Found, 531.1665.

1.14. 9-(4′,6′-*O*-Benzylidene-2′,3′-di-*O*-trifluoromethanesulfonyl-β-D-galactopyranosyl)-*H*-6-chloropurine (17)

Compound **17** (804 mg, 1.20 mmol) was prepared from **8** (546 mg, 1.35 mmol) as described from **9** in 89% yield after silica gel chromatography (EtOAc–Hexane, 1:3). $[\alpha]_D$ +16.7 (*c* 0.033, $CHCl_3$); ^1H NMR (DMSO-d_6): δ 8.81 (s, 1H, H-2), 8.36 (s, 1H, H-8), 7.58–7.46 (m, 5H, Ph), 6.11 (d, 1H, $J_{1',2'}$ 9.2 Hz, H-1′), 5.78 (br t, 1H, H-2′), 5.27 (dd, 1H, $J_{2',3'}$ 9.6 Hz, $J_{3',4'}$ 3.6 Hz, H-3′), 4.83 (d, 1H, H-5′), 4.40 and 4.19 (2dd, 2H, J_{gem} 13.2 Hz, H-6′ax, H-6′eq), 3.96 (s, 1H, H-5′); ^{13}C NMR (DMSO-d_6): 152.8, 152.0, 151.7, 142.6, 136.0, 131.5, 129.8, 128.6 (2C, Ph), 126.0 (2C, Ph), 101.4, 81.3, 78.2, 76.9, 76.7, 73.8, 68.7, 67.9; EI MS (*m*/*z*, relative intensity): 668 (M^-, 6), 535 (17.7), 413 (31.6), 369 (11.5), 234 (24.3), 229 (14.5), 183 (19.3), 155 (29.1), 105 (100), 69 (31.0); HRESIMS *m*/*z* calcd for $C_{20}H_{16}ClFN_4O_9S_2$ $[M+H]^+$: 668.9951. Found, 668.9934.

1.15. 9-(2′,3′-*O*-Acetyl-4′,6′-*O*-benzylidene-β-D-idopyranosyl)-*H*-6-chloropurine (18)

Compound **18** (40 mg, 60 μmol) was prepared from **17** (201 mg, 300 μmol) as described from **10** in 20% yield after silica gel chromatography (EtOAc). $[\alpha]_D$ +22.2 (*c* 0.022, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.79 (s, 1H, H-2), 8.47 (s, 1H, H-8), 7.50–7.41 (m, 5H, *Ph*CH), 6.30 (d, 1H, $J_{1',2'}$ 2.0 Hz, H-1′), 5.95 (t, 1H, $J_{2',3'}$ 3.2 Hz, H-2′), 5.60 (s, 1H, PhC*H*), 5.35 (dd, 1H, $J_{3',4'}$ 2.0 Hz, H-3′), 4.59 (d, 1H, H-4′), 4.32 and 4.12 (2d, 2H, H-6′$_a$, 6′$_b$), 3.90 (s, 1H, H-5′), 2.14 and 1.83 (2s, 6H, CH_3CO); ^{13}C NMR ($CDCl_3$): δ 170.5, 168.9, 152.2, 151.3, 143.1, 137.1, 133.7, 131.5, 129.5, 128.4 (2C, Ph), 126.2 (2C, Ph), 101.4, 80.9, 73.0, 71.5, 69.5, 68.1, 67.5, 20.9, 20.1; HRESIMS *m*/*z* calcd for $C_{22}H_{22}ClN_4O_5$ $[M+H]^+$: 488.1177. Found, 488.1198.

1.16. 9-β-D-Altropyranosyladenine (4)

Compound **4** (45 mg, 0.15 mmol) was obtained from **10** (80 mg, 0.164 mmol) using general procedure (B) and (C) in 92% followed by preparative HPLC (MeOH–H_2O, 7:93) and recrystallization from MeOH. $[\alpha]_D$ +52.8 (*c* 0.018, MeOH); ^1H NMR (DMSO-d_6): δ 8.24 (s, 1H, H-2), 8.12 (s, 1H, H-8), 6.05 (s, 1H, $J_{1',2'}$ 2.0 Hz, H-1′), 5.64, 5.28, and 4.69 (3d, 3H, OH-2′, OH-3′, OH-4′), 4.49 (t, 1H, OH-6′), 3.87–3.46 (m, 6H, H-2′, 3′, 4′, 5′, 6′a, and 6′b); ^{13}C NMR (DMSO-d_6): δ 155.9, 152.4, 148.6, 140.1, 117.9, 78.5, 77.2, 71.0, 70.5, 63.6, 61.4: EI MS (*m*/*z*, relative intensity) 297 (M, 3.7), 164 (100), 148 (8.8), 135 (88.7), 119 (6), 108 (17.5); HRESIMS *m*/*z* calcd for $C_{11}H_{16}N_5O_5$ $[M+H]^+$: 297.2673. Found, 297.2648.

1.17. 9-β-D-Mannopyranosyladenine (5)

Compound **5** (24 mg, 80 μmol) was obtained from **13** (50 mg, 94 μmol) in 85% using general procedure (B) and (C) followed by preparative HPLC (MeOH–H_2O, 5:95) and recrystallization from MeOH. $[\alpha]_D$ +14.8 (*c* 0.024, H_2O); ^1H NMR (DMSO-d_6): δ 8.24 (s, 1H, H-2), 8.12 (s, 1H, H-8), 5.88 (s, 1H, $J_{1',2'}$ 1.6 Hz, H-1′), 5.63, 5.25, and 4.77 (3d, 3H, OH-2′, OH-3′, OH-4′), 4.40 (t, 1H, OH-6′), 3.87–3.46 (m, 6H, H-2′, 3′, 4′, 5′, 6′a, and 6′b); ^{13}C NMR (DMSO-d_6): δ 155.9, 152.4, 148.6, 140.1, 117.9, 78.5, 77.2, 71.0, 70.5, 63.6, 61.4: EI MS (*m*/*z*, relative intensity) 297 (M, 5.7), 164 (100), 148 (9.8), 135 (88.7), 119 (6), 108 (18); HRESIMS *m*/*z* calcd for $C_{11}H_{16}N_5O_5$ $[M+H]^+$: 297.2673. Found, 297.2653.

1.18. 9-β-D-Allopyranosyladenine (3)

Compound **3** (26 mg, 87 μmol) was obtained from **16** (50 mg, 94 μmol) in 93% using general procedure (B)

and (C) followed by preparative HPLC (MeOH–H_2O, 7:93) and recrystallization from MeOH. $[\alpha]_D$ +94.1 (*c* 0.017, H_2O); ^1H NMR (DMSO-d_6): δ 8.58 (s, 1H, H-2), 8.31 (s, 1H, H-8), 7.22 (br s, 2H, NH_2), 5.71 (d, 1H, $J_{1',2'}$ 9.6 Hz, H-1′), 5.15, 5.05, and 4.80 (3d, 3H, H-2′, 3′, and 4′), 4.50 (br t, 1H, H-6′), 4.21–3.33 (m, 6H, H-2′, 3′, 4′, 5′, 6′a, and 6′b): ^{13}C NMR (DMSO-d_6): δ 155.9, 152.4, 148.6, 140.1, 117.9, 78.5, 77.2, 71.0, 70.5, 63.6, 61.4: EI MS (*m*/*z*, relative intensity) 297 (M, 3.7), 164 (100), 148 (8.8), 135 (88.7), 119 (6), 108 (17.5); HRESIMS *m*/*z* calcd for $C_{11}H_{16}N_5O_5$ $[M+H]^+$: 297.2673. Found, 297.2645.

1.19. 9-β-D-Idopyranosyladenine (6)

Compound **6** (23 mg, 78 mmol) was obtained from **18** (45 mg, 92 μmol) in 85% using general procedure (B) and (C) followed by preparative HPLC (MeOH–H_2O, 5:95) and recrystallization from MeOH. $[\alpha]_D$ +52.8 (*c* 0.026, H_2O); ^1H NMR (DMSO-d_6): δ 8.26 (s, 1H, H-2), 8.15 (s, 1H, H-8), 5.97 (s, 1H, $J_{1',2'}$ 2.0 Hz, H-1′), 5.40, 5.20, and 4.64 (3d, 3H, OH-2′, OH-3′, OH-4′), 4.49 (t, 1H, OH-6′), 3.90–3.46 (m, 6H, H-2′, 3′, 4′, 5′, 6′a, and 6′b); ^{13}C NMR (DMSO-d_6): δ 155.9, 152.4, 148.6, 140.1, 115.8, 79.5, 77.1, 71.0, 70.5, 63.5, 61.1: EI MS (*m*/*z*, relative intensity) 297 (M, 7.4), 164 (100), 148 (11.0), 135 (78.5), 119 (7), 108 (19.5); HRESIMS *m*/*z* calcd for $C_{11}H_{16}N_5O_5$ $[M+H]^+$: 297.2673. Found, 297.2655.

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