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The Synthesis of N^2,N^6-Substituted Diaminopurine Ribosides

N. A. Golubeva[1] and A. V. Shipitsyn

Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, ul. Vavilova 32, Moscow, 119991 Russia

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Abstract—A series of new 2,6-substituted diaminopurine riboside derivatives were synthesized by activation of protected xantosine with sulfonyl chlorides followed by treatment with various amines. The relationship between the reactivity of intermediates and the nature of the activating agents was studied.

Key words: 2,6-diaminopurine riboside derivatives, modified purine nucleosides

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INTRODUCTION

The search for new antiviral drugs is one of the vital tasks of modern medicinal chemistry. Many antiviral medicines approved for world usage in clinical practice belong to the class of purine nucleoside analogues [1].[2] In particular, acyclovir, ganciclovir, and their valine derivatives are successfully used as antiherpetic drugs [2]. It is noteworthy that 9-[2-(phosphonomethoxy)ethyl]purines modified at position N^6 display a wide range of antiviral activities, including antiherpetic and antiretroviral activities [3, 4]. Adenosine N^6-substituted analogues are also of interest as potential antiherpetic and antiretroviral agents [5–7].

In addition to antiviral properties, N^2,N^6-diaminopurine riboside derivatives also manifest affinity to adenosine receptors. These receptors are divided into four major types, namely, A_1, A_{2A}, A_{2B}, and A_3 [8]. Agonists of recently identified A_3 receptors display wide spectrum of pharmacological activities ranging from the cardioprotective effect to treatment of asthma [9].

Thus, adenosine and its analogues are involved in the regulation of numerous processes of cell metabolism, and this allows a considerable expansion of therapeutic targets in search for new drugs with the purinergic mechanism of action [10]. To date, 2,6-disubstituted diaminopurine riboside derivatives are regarded as potential agents with antiviral activity and agonists of adenosine receptors.

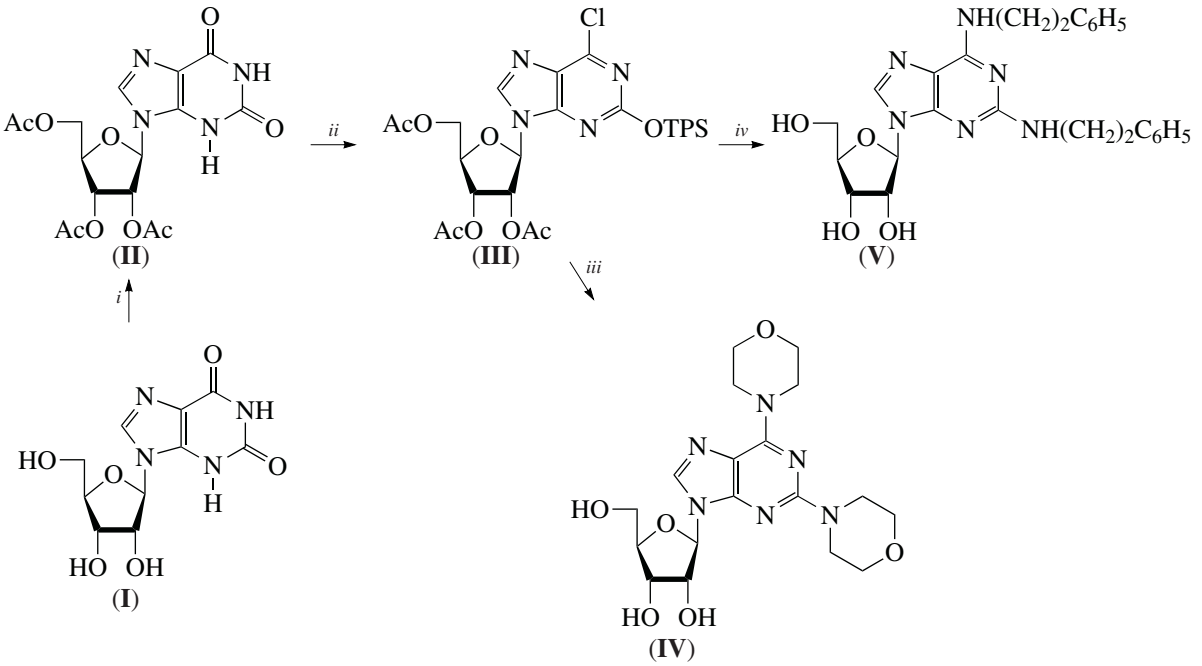
[1] Corresponding author; phone: +7 (495) 135-6065; e-mail: golubeva.na@mail.ru.

[2] Abbreviations: DMAP, 4-dimethylaminopyridine; EDIP, *N*-ethyldiisopropylamine; Ms-Cl, methanesulfonyl chloride; TPS-Cl, 2,4,6-triisopropylbenzenesulfonyl chloride; Tos-Cl, *p*-toluenesulfonyl chloride.

RESULTS AND DISCUSSION

We describe here the synthesis of a new group of 2,6-disubstituted diaminopurine riboside derivatives. 2,6-Dichloropurine riboside is most commonly used for the preparation of compounds of this type [5, 10]. However, its laboratory synthesis is rather laborious. Therefore, we studied the method of preparation of adenosine analogues via sulfonic acid derivatives. Robins et al. suggested to transform 6-oxo group of protected deoxyguanosine into 6-amino group of 2-chloro-2'-deoxyadenosine (cladribine) by activation of the oxo group with TPS-Cl or Tos-Cl, followed by treatment with ammonia. The authors noticed that the ammonolysis of the tosyloxy group proceeded less stereospecifically than that of the TPSO group, which is associated with the attack of the intermediate sulfonate of both sulfur and purine C6 atoms [11].

First of all, we tried to use TPS-Cl as an activating agent in the synthesis of diaminopurine riboside analogues (Scheme 1). This approach requires the protection of hydroxy groups of the riboside residue before the reaction, and the starting xantosine (**I**) was acetylated to 2',3',5'-tri-*O*-acetylxantosine (**II**) by the standard procedure [12]. The next reaction was carried out as described in [11], but we used 1,2-dichloroethane as a solvent and EDIP instead of triethylamine as a more effective proton binder [13]. The reaction was completed after 18 h (TLC monitoring). Disappearance of the starting 2',3',5'-*O*-triacetylxantosine (**II**) and prevalence of a single product was considered to be as the signal of the end of the reaction. Column chromatography on silica gel resulted in isolation of (**III**), which had one TPS group according to the NMR spectral data. However, the reaction of this intermediate with a large excess of morpholine in aqueous dioxane by method A yielded 2,6-bismorpholinopurine riboside (**IV**), whose structure was confirmed by ^{1}H NMR and UV spectros-



Reagents: (*i*) Ac_2O, Py, 50°C; (*ii*) TPS-Cl, DMAP, EDIP, 1,2-dichloroethane; (*iii*) morpholine, dioxane–water, 37°C; (*iv*) 2-phenylethylamine, dioxane–water, 37°C.

Scheme 1. The synthesis of substituted N^2,N^6-diaminopurine ribosides via a TPS derivative (**III**) (method A).

copy. Based on these facts, we assumed that the obtained intermediate (**III**) bears a TPSO group in position 2, whereas the TPSO group in position 6 due to its increased reactivity was substituted by a Cl atom; i.e., compound (**III**) is 2-TPSO-6-Cl-purine 2',3',5'-*O*-triacetylriboside.

After a similar reaction of TPS intermediate (**III**) with 2-phenylethylamine by method A, 2,6-bis(2-phenylethylamino)purine riboside (**V**) was obtained, which supports a suggestion on the presence of the second leaving group in (**III**).

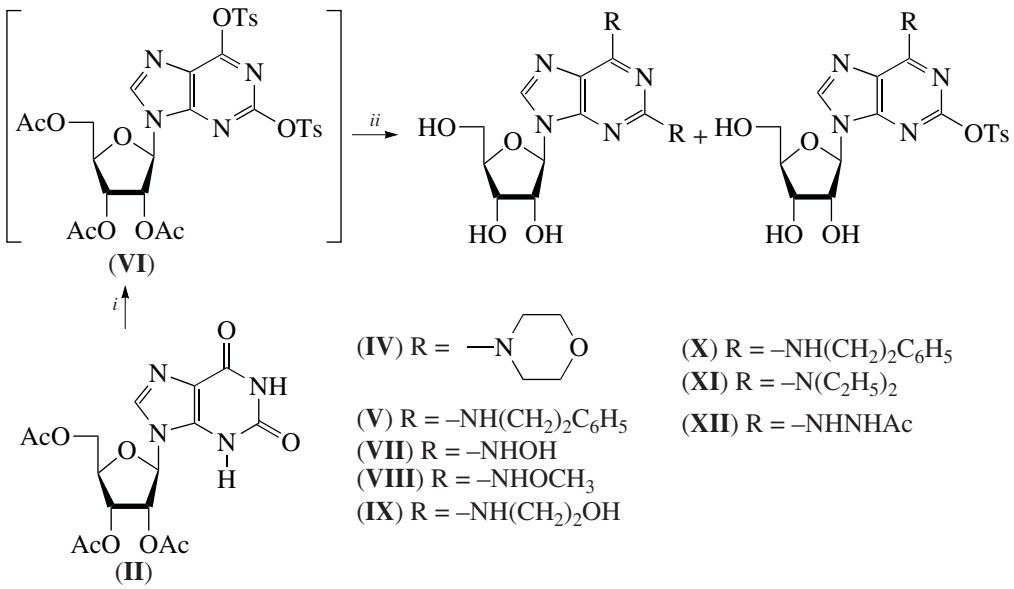
The yields of (**IV**) and (**V**) were 25 and 37%, respectively, or 12 and 18% from 2',3',5'-*O*-triacetylxantosine (**II**). Therefore, in the activation reaction, we chose to use Tos-Cl, which was also applied by Robins et al. (Scheme 2) [11].

The activation was achieved similarly to that for TPS-Cl; the synthesis of disulfonyl derivative (**VI**) was completed for an hour in this case (TLC monitoring). Because of (**VI**) instability during silica gel column chromatography, a considerable loss of the compound occurred and its yield decreased to 25%. ^{1}H NMR spectra demonstrated that, unlike intermediate (**III**), compound (**VI**) had two Tos groups.

We excluded chromatographic purification of intermediate 2,6-bis(*p*-toluenesulfonyloxy)-2',3',5'-*O*-triacetylxantosine (**VI**) to increase the total yield (method B). After the activation, the chloroform extraction from water was carried out, the organic layer was evaporated, the residue was dissolved in aqueous dioxane, and (**VI**) was subjected to reactions with excess of various amines: morpholine, 2-phenylethylamine, acethydrazide, diethylamine, hydroxylamine, *O*-methylhydroxylamine, aminoethanol, and β-alanine (Scheme 2). Note that interactions with morpholine, hydroxylamine, *O*-methylhydroxylamine, and aminoethanol led to disubstituted derivatives (**IV**), (**VII**)–(**IX**), whereas acethydrazide and diethylamine gave only monosubstituted products retaining one tosyloxy group, which was confirmed by NMR spectroscopy. In the case of 2-phenylethylamine, we isolated both mono- (**X**) and disubstituted (**V**) products. The reaction product of β-alanine was not isolated even after addition of 10 eqiv of EDIP.

We believe that the formation of this product set can be explained by the initial attack at C6 of the purine base, because the substituent reactivity at this position is higher than that at position C2 [10] and the substitution at C2 not always occurs due to different nucleophilic strengths of the amines.

Substituted amino derivatives of apolar compounds (**V**), (**X**), and (**XI**) were isolated by column chromatography on silica gel, whereas a reversed-phase chromatography was used for isolation of polar (**IV**), (**VII**)–(**IX**), and (**XII**). The yields of (**IV**)–(**XII**) varied from 20% for 2-2-hydroxyethylamino)purine riboside (**VII**) to 60% for 2,6-bis(*p*-toluenesulfonyloxy-6-(diethylamino)purine riboside (**XI**): the more bulky the substituent, the higher the yield. We presume that it can be related to large isolation losses, because TLC patterns



Reagents: (*i*) Tos-Cl, DMAP, EDIP, 1,2-dichloroethane; (*ii*) RH, dioxane–water, 37°C.

Scheme 2. The synthesis of substituted N^2,N^6-diaminopurine ribosides via a Tos derivative (**VI**) (method B).

of the reaction mixtures did not imply such large differences. In all the cases a simultaneous deblocking of acetyl groups took place, which agree with the published data [10].

The resulting compounds were subjected to acidic hydrolysis with to estimate the stability of glycoside bonds. The products were analyzed by NMR spectroscopy. Derivative (**IV**) was found to be completely hydrolyzed overnight at room temperature with 0.05 M HCl to give dimorpholinopurine. The other derivatives were hydrolyzed less than by 10% under the same conditions.

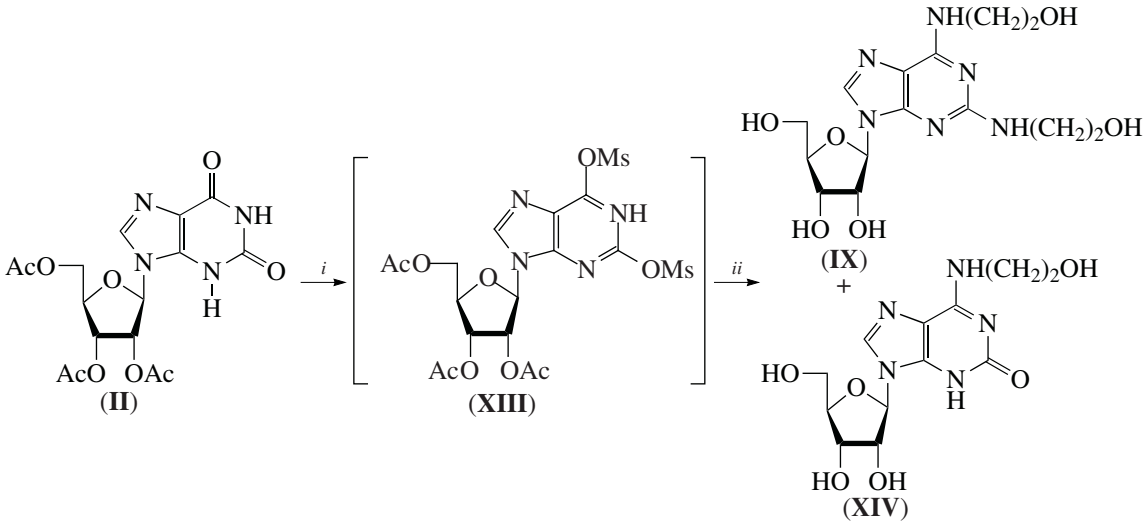
Thus, we found that, unlike in the published results [11], the activation of a xantosine base with Tos-Cl is more effective than with TPS-Cl in amination reactions. For example, the yields of dimorpholine derivative (**IV**) relative to 2',3',5'-*O*-triacetylxantosine (**II**) were 50 and 12% for Tos-Cl and TPS-Cl activations, respectively. In addition, the tosyl activation enables the preparation of monosubstituted derivatives, which can be further modified by substituting the retaining tosyl group with other nucleophiles.

These facts led us to the conclusion: the less the steric hindrances of the activating group, the smoother the activation and the higher the yield of the final amino product. Therefore, we carried out a similar reaction with Ms-Cl (Scheme 3). Taking into account instability of Ms-derivative (**XIII**) under isolation conditions, we excluded the stage of chromatography, like in the case of Tos-derivative (**VI**), and used chloroform extraction of (**XIII**) with its subsequent interaction with aminoethanol excess. As a result, we isolated two products, one of which was 2,6-bis(2-hydroxyethylamino) purine riboside (**IX**). The second derivative contained one hydroxyethyl group and lacked an NMR signal of methanesulfonyl group. We concluded that, like in some cases of tosyl activation, only one mesyloxy group was substituted, but, unlike more stable tosylamines (**X**)–(**XII**), the compound bearing a 2-OMs group was not isolated. We presumed that, in this manner, the isoguanosine analogue (**XIV**) was obtained after hydrolysis of 2-OMs group, which was supported by UV spectroscopy. We think that the results obtained with Ms-Cl support the advantage of tosyl activation, as the synthon (**VI**) has optimal stability and reactivity.

To conclude, we obtained a series of 2,6-disubstituted diaminopurine riboside derivatives using activation of substituted xantosine with several sulfonyl chlorides followed by substitution by various amino residues.

EXPERIMENTAL

N-Ethyldiisopropylamine, 2-phenylethylamine, morpholine, diethylamine, and methanesulfonyl chloride were from Fluka; DMAP, *p*-toluenesulfonyl chloride, ethanolamine, 2,4,6-triisopropylbenzenesulfonyl chloride, xantosine, and acethydrazide were from Aldrich; hydroxylamine hydrochloride, *O*-methylhydroxylamine hydrochloride, and acetic anhydride were from Reakhim (Russia). The solvents used in the work were purified by standard procedures. TLC was carried out on Kieselgel 60 F_{254} plates (Merck) in (A) 19 : 1 $CHCl_3$–MeOH, (B) 9 : 1 $CHCl_3$–MeOH, (C) 4 : 1 $CHCl_3$–MeOH, and (D) 1 : 1 $CHCl_3$–MeOH. Column chromatography was executee on Kieselgel (40–63 μm,



Reagents: (*i*) Ms-Cl, DMAP, EDIP, 1,2-dichloroethane; (*ii*) $NH_2CH_2CH_2OH$, dioxane–water, 37°C.

Scheme 3. The synthesis of substituted N^2,N^6-diaminopurine ribosides via a Ms derivative (**XIII**).

Merck) and reversed-phase silica gel LiChroprep RP-8 and LiChroprep RP-18 (40–63 μm, Merck); elution systems are indicated in the text.

UV spectra were registered on a Shimadzu UV-2401 PC (United States) spectrometer in water (pH 7) and methanol in the range of 200 to 300 nm. ^{1}H NMR spectra were registered on a Bruker AMXIII-400 spectrometer (United States) (δ, ppm, *J*, Hz) with the working frequency of 400 MHz; Me_4Si ($CDCl_3$ and CD_3OD) and sodium 3-trimethylsilyl-1-propanesulfonic acid (D_2O) were internal standards.

2',3',5'-*O*-Triacetylxantosine (II). Acetic anhydride (2.6 ml, 27 mmol) was added to a solution of xantosine (**I**) (750 mg, 2.7 mmol) in pyridine (5 ml), and the mixture was kept for 12 h at +50°C. The reaction mixture was evaporated to dryness in a vacuum, and the residue was dissolved in $CHCl_3$ (25 ml) and washed with H_2O and saturated $NaHCO_3$. The organic layer was dried with anhydrous Na_2SO_4, the solvent was evaporated in a vacuum, and the residue was dissolved in $CHCl_3$ (3 ml) and purified by chromatography on a silica gel column eluted in a gradient of methanol concentration in chloroform (0⟶20%). The fractions containing the product were pooled, evaporated, and dried in a vacuum to give (**II**); yield 873 mg (81%); R_f 0.4 (C); UV (CH_3OH): λ_{max} 240 nm (ε 8800), 261 nm (ε 8900). ^{1}H NMR: ($CDCl_3$): 7.71 (1 H, s, H8), 6.17 (1 H, d, *J* 3.8, H1'), 5.44 (1 H, *t*, *J* 4.8, H2'), 5.32 (1 H, t, *J* 5.8, H3'), 4.54–4.49 (1 H, m, H4'), 4.45 (1 H, dd, *J* 2.5, $H5'_a$); 4.40 (1 H, dd, *J* 1.9, $H5'_b$), and 2.14 (9 H, s, CH_3CO).

2,6-Bismorpholinopurine riboside (IV). Method A. DMAP (4 mg, 0.03 mmol), EDIP (125 μl, 0.73 mmol), and TPS-Cl (222 mg, 0.73 mmol) were successively added to a solution of 2',3',5'-*O*-triacetylxantosine (**II**) (100 mg, 0.24 mmol) in 1,2-dichloroethane (5 ml), and the mixture was kept for 18 h at room temperature. The reaction mixture was evaporated to dryness in a vacuum, and the residue was dissolved in $CHCl_3$ (10 ml) and washed with H_2O. The organic layer was dried with anhydrous $NaSO_4$, the solvent was evaporated, and the residue was dissolved in $CHCl_3$ (3 ml) and purified by chromatography on a silica gel column eluted in a gradient of methanol concentration in chloroform (0⟶10%). The fractions containing the product were pooled, evaporated, and dried in a vacuum to give acetylated intermediate (**III**); R_f 0.6 (A); ^{1}H NMR ($CDCl_3$): 8.16 (1 H, s, H8), 7.15 (1 H, d, *J* 8.1, Ph), 6.12 (1 H, d, *J* 5.9, H1'), 5.66 (1 H, t, *J* 5.9, H2'), 5.54 (1 H, dd, *J* 3.7 and 5.6, H3'), 4.43–4.39 (3 H, m, H4'+H5'), 4.24–4.10 (3 H, m, C<u>H</u>$(CH_3)_2$), 2.16, 2.12 and 2.05 (9 H, 3 s, CH_3CO), and 1.25–1.14 (18 H, m, CH_3).

Morpholine (85 μl, 1.4 mmol) was added to a solution of acetylated intermediate (**III**) (80 mg, 0.14 mmol) in dioxane (32 ml), and the mixture was kept for 120 h at 37°C. The mixture was evaporated in a vacuum, and the residue was dissolved in chloroform (1 ml) and purified by chromatography on a silica gel column eluted with a gradient of methanol concentration in chloroform (0⟶20%). The fractions containing product (**IV**) were pooled, evaporated, and dried in a vacuum. The residue was repurified on a LiChroprep RP-8 column (20 × 200 mm) in a gradient of methanol concentration (0⟶50%, volume 400 ml) and lyophilized from water to give (**IV**) (15 mg, 12%).

Method B. DMAP (4 mg, 0.03 mmol), EDIP (129 μl, 0.75 mmol), and Tos-Cl (143 mg, 0.75 mmol)

^{1}H NMR spectra of substituted N^2,N^6-diaminopurine ribosides (**IV**), (**V**), and (**VII**)–(**IX**)

Compound, solvent	H1'	H2'	H3'	H4'	H5'	H8	Other
(**IV**), CD_3OD	5.92 d, *J* 5.3	4.72 ~t, *J* 5.3	4.34 ~t, *J* 4.8	4.05 ~q, *J* 3.8	3.85–3.81 m	7.97 s	4.14 (4 H, t, *J* 4.4, CH_2N^2); 3.77 (4 H, t, *J* 4.8, CH_2N^6); 3.72 (8 H, c, OCH_2)
(**V**), $CDCl_3$	5.61 d, *J* 7.2	5.00 ~t, *J* 5.3	4.35 br. d, *J* 4.7	4.27 br. s	3.89–3.84 m	7.32 s	7.28–7.16 (10 H, m, Ph); 3.73–3.66 (4 H, m, CH_2N); 2.93, 2.84 (4 H, 2t, *J* 7.3, CH_2Ph)
(**VII**), D_2O	5.82 d, *J* 6.2	~4.8*	4.35 dd, *J* 3.1, 5.0	4.21 ~q, *J* 2.8	3.85 dd, *J* 2.3, 12.9 and 3.76 dd, *J* 3.4	7.85 s	–
(**VIII**), D_2O	5.73 d, *J* 7.5	~4.8*	4.36–4.33 m	4.21 ~q, *J* 1.9	4.36–4.33 m and 4.26 dd, *J* 1.9, 11.3	7.69 s	3.85 and 3.82 (6 H, 2c, OCH_3)
(**IX**), D_2O	5.86 d, *J* 5.9	4.78 ~t, *J* 3.5	4.38 ~t, *J* 4.4	4.17 ~q, *J* 3.5	3.84 dd, *J* 3.9, 12.6 and 3.70–3.75 m	7.88 s	3.70–3.75 (m, CH_2N^2); 3.72 (2 H, t, *J* 5.6, CH_2N^6); 3.65 (2 H, t, $N^6CH_2C\underline{H}_2$); 3.48 (2 H, t, *J* 5.5, $N^2CH_2C\underline{H}_2$)

* H2' resonance is partially overlapped with HOD resonance.

~t is dd with close *J*, a triplet in appearance; a pseudoconstant is given.

~q is dt or ddd with close *J*, a quartet in appearance; a pseudoconstant is given.

were successively added to a solution of 2',3',5'-tri-*O*-acetylxantosine (**II**) (100 mg, 0.25 mmol) in 1,2-dichloroethane (5 ml), and the mixture was kept for 1 h at room temperature. The reaction mixture was evaporated to dryness in a vacuum, and the residue was dissolved in $CHCl_3$ (10 ml) and washed with H_2O. The organic layer was evaporated to dryness in a vacuum, and the residue was dissolved in aqueous dioxane (1 ml). Morpholine (218 μl, 2.5 mmol) was added, and the mixture was kept for 120 h at +37°C, evaporated in a vacuum, and purified by chromatography as described above. The pooled fractions were lyophilized from water to give (**IV**) (53 mg, 50%); R_f 0.5 (B); UV ((H$_2$O): λ_{max}, nm (ε): 295 (4500), 249 (9700); for ^{1}H NMR (CD_3OD), see the table.

2,6-Bis(2-phenylethylamino)purine riboside (V) was obtained by method A as described for (**IV**) from acetylated intermediate (**III**) (166 mg, 0.14 mmol) and 2-phenylethylamine (176 μl, 1.4 mmol) in dioxane (2 ml). The reaction mixture was evaporated in a vacuum and purified by gel chromatography on a column eluted in a gradient of methanol concentration in chloroform (0⟶5%). The fractions containing the product were pooled, evaporated, and dried in a vacuum to give (**V**) (25 mg, 18%); R_f 0.45 (A); UV (CH_3OH): λ_{max}, nm (ε): 289 (9400), 263 (9600); for ^{1}H NMR ($CDCl_3$), see the table.

2,6-Bis(*p*-toluenesulfonyloxy)-2',3',5'-tri-*O*-acetylxantosine (VI). DMAP (11 mg, 0.09 mmol), EDIP (375 μl, 2.16 mmol), and Tos-Cl (418 mg, 2.19 mmol) were successively added to a solution of 2',3',5'-tri-*O*-acetylxantosine (**II**) (300 mg, 0.73 mmol) in 1,2-dichlorethane (5 ml), and the mixture was kept for 1 h at room temperature and evaporated to dryness in a vacuum. The residue was dissolved in $CHCl_3$ (10 ml) and washed with H_2O. The solvent was evaporated in a vacuum, and the residue was dissolved in $CHCl_3$ (1 ml) and purified by chromatography on a silica gel column eluted with chloroform. The fractions containing the product were pooled, evaporated, and dried in a vacuum to give (**VI**) (103 mg, 25%); R_f 0.7 (A); ^{1}H NMR: ($CDCl_3$): 8.17 (1 H, s, H8), 8.04–7.99 (4 H, m, *o*-Tos), 7.38–7.33 (4 H, m, *m*-Tos), 6.13 (1 H, d, *J* 5.6, H1'), 5.69 (1 H, t, *J* 5.6, H2'), 5.51 (1 H, dd, *J* 4.0 and 5.6, H3'), 4.42 (1 H, q, *J* 3.7, H4'), 4.36 (1 H, br. s, $H5'_a$), 4.35 (1 H, br. s, $H5'_b$), 2.45 and 2.44 (6 H, 2 s, CH_3-Ph), 2.15, 2.10, and 2.05 (9 H, 3 s, CH_3CO).

2,6-Bis(hydroxylamino)purine riboside (VII). The reaction was carried out by method B using 2',3',5'-tri-*O*-acetylxantosine (**II**) (200 mg, 0.49 mmol), DMAP (8 mg, 0.06 mmol), EDIP (250 μl, 1.46 mmol), Tos-Cl (278 mg, 1.46 mmol), and hydroxylamine hydrochloride (341 mg, 4.9 mmol) and EDIP (839 μl, 4.9 mmol). After amination, the reaction mixture was evaporated in a vacuum. The residue was dissolved in chloroform (1 ml) and chromatographed on a silica gel column eluted with a gradient of methanol concentration in chloroform (0⟶30%). The fractions containing the product were pooled, evaporated, and dried in a vacuum. The residue was repurified on a LiChroprep RP-18 column (20 × 200 mm) in a gradient of methanol concentration (0⟶20%, volume 400 ml) and lyophilized from water to give (**VII**) (48 mg, 31%); R_f 0.3 (D); UV

((H_2O): λ_{max}, nm (ε): 275 (8600), 248 (10100); for ^1H NMR (D_2O), see the table.

2,6-Bis(methoxyamino)purine riboside (VIII). The reaction was carried out by method B using 2',3',5'-tri-*O*-acetylxantosine (**II**) (200 mg, 0.49 mmol), DMAP (8 mg, 0.06 mmol), EDIP (250 μl, 1.46 mmol), Tos-Cl (278 mg, 1.46 mmol), and *O*-methylhydroxylamine hydrochloride (409 mg, 4.9 mmol) and EDIP (839 μl, 4.9 mmol). The reaction mixture was evaporated in a vacuum, the residue was dissolved in chloroform (10 ml), and the product was extracted with water. The aqueous layer was evaporated in a vacuum to dryness and purified on a LiChroprep RP-18 column (20 × 200 mm) in a gradient of methanol concentration (0⟶50%, volume 300 ml). The fractions containing the product were pooled, evaporated, and dried in a vacuum. The residue was lyophilized from water to give (**VIII**) (39 mg, 23%); R_f 0.4 (D); UV (H_2O): λ_{max}, nm (ε): 266 (9300); for ^1H NMR (D_2O), see the table.

2,6-Bis(2-hydroxyethylamino)purine riboside (IX). The reaction was carried out by method B using 2',3',5'-tri-*O*-acetylxantosine (**II**) (150 mg, 0.37 mmol), DMAP (6 mg, 0.05 mmol), EDIP (190 μl, 1.11 mmol), Tos-Cl (212 mg, 1.11 mmol), and ethanolamine (225 μl, 3.7 mmol). After amination, the reaction mixture was evaporated in a vacuum. The residue was dissolved in chloroform (1 ml) and chromatographed on silica gel column eluted with a gradient of methanol concentration in chloroform (0⟶30%). The fractions containing the product were pooled, evaporated, and dried in a vacuum. The residue was repurified on a LiChroprep RP-18 column (20 × 140 mm) in a gradient of methanol concentration (0⟶35%, volume 400 ml) and lyophilized from water to give (**IX**) (27 mg, 20%); R_f 0.29 (C); UV ((H_2O): λ_{max}, nm (ε)): 277 (4200), 223 (9500); for ^1H NMR (D_2O), see the table.

2,6-Bis(2-phenylethylamino)purine riboside (V) and 2-*p*-toluenesulfonyloxy-6-(2-phenylethylamino)purine riboside (X). The reaction was carried out by method B using 2',3',5'-tri-*O*-acetylxantosine (**II**) (100 mg, 0.25 mmol), DMAP (4 mg, 0.03 mmol), EDIP (129 μl, 0.75 mmol), Tos-Cl (143 mg, 0.75 mmol), and 2-phenylethylamine (315 μl, 2.5 mmol). After amination, the reaction mixture was evaporated in a vacuum. The residue was dissolved in chloroform (1 ml) and chromatographed on a silica gel column eluted with a gradient of methanol concentration in chloroform (0⟶5%) to give (in the order of elution) compounds (**V**) (27 mg, 40%) and (**X**) (23 mg, 30%); R_f 0.45 (A); UV ((CH_3OH): λ_{max}, nm (ε)): 265 (9600), 230 (9800); ^1H NMR ($CDCl_3$): 7.88 (2 H, d, *J* 8.1, *o*-Tos), 7.76 (1 H, s, H8), 7.30–7.13 (7 H, m, *m*-Tos, Ph), 5.75 (1 H, d, *J* 6.6, H1'), 4.81 (1 H, *t, J* 5.8, H2'), 4.43 (1 H, br. d, *J* 4.0, H3'), 4.37 (1 H, br. s, H4'), 3.88 (1 H, br. d, *J* 11.0, $H5'_a$), 3.72 (1 H, br. d, $H5'_b$), 3.61–3.44 (2 H, m, CH_2N), 2.79 (2 H, t, *J* 6.52, $C\underline{H}_2Ph$), 2.33 (3 H, s, CH_3).

2-(*p*-Toluenesulfonyloxy)-6-(diethylamino)purine riboside (XI). The reaction was carried out by method B using 2',3',5'-tri-*O*-acetylxantosine (**II**) (144 mg, 0.35 mmol), DMAP (5 mg, 0.04 mmol), EDIP (180 μl, 1.05 mmol), Tos-Cl (200 mg, 1.05 mmol), and diethylamine (362 μl, 3.5 mmol). After amination, the reaction mixture was evaporated in a vacuum. The residue was dissolved in chloroform (1 ml) and chromatographed on a silica gel column eluted with chloroform. The fractions containing the product were pooled, evaporated, and dried in a vacuum to give (**XI**) (104 mg, 60%); R_f 0.7 (A); UV ((CH_3OH): λ_{max}, nm (ε)): 266 (9300), 232 (9300); ^1H NMR ($CDCl_3$): 7.90 (2 H, d, *J* 8.1, *o*-Tos); 7.86 (1 H, s, H8); 7.33 (2 H, d, *m*-Tos); 5.90 (1 H, d, *J* 4.7, H1'), 4.51 (1 H, t, *J* 4.5, H2'), 4.43 (2 H, br. s, H3'+H4'), 4.37 (1 H, dd, *J* 2.8 and 12.4, $H5'_a$), 4.26 (1 H, dd, *J* 5.3, $H5'_b$), 4.10 and 3.44 (4 H, 2 br. s, NCH_2), 2.43 (3 H, s, CH_3-Ph); 1.24 (6 H, s, $C\underline{H}_3CH_2$).

2-(*p*-Toluenesulfonyloxy)-6-(2-acethydrazino)purine riboside (XII). The reaction was carried out by method B using 2',3',5'-tri-*O*-acetylxantosine (**II**) (200 mg, 0.49 mmol), DMAP (8 mg, 0.06 mmol), EDIP (250 μl, 1.46 mmol), Tos-Cl (278 mg, 1.46 mmol), and acethydrazide (363 mg, 4.9 mmol). After amination, the reaction mixture was evaporated in a vacuum. The residue was dissolved in chloroform (1 ml) and purified by chromatography on a silica gel column eluted with a gradient of methanol concentration in chloroform (0⟶20%). The fractions containing the product were pooled, evaporated, and dried in a vacuum. The residue was repurified on a LiChroprep RP-18 column (20 × 200 mm) in a linear gradient of methanol concentration (0⟶50%, volume 300 ml). The fractions containing the product were pooled, evaporated, and dried in a vacuum to give (**XII**) (80 mg, 33%); R_f 0.4 (C); UV ((CH_3OH): λ_{max}, nm (ε)): 265 (8900), 227 (9800); ^1H NMR ($CDCl_3$): 7.96 (1 H, s, H8); 7.93 (2 H, d, *J* 8.2, *m*-Ph); 7.32 (2 H, d, *o*-Ph); 6.04 (1 H, d, *J* 5.6,H1'); 5.72 (1H, t, *J* 5.6, H2'); 5.51 (1 H, t, *J* 4.8, H3'); 4.37 (1 H, d, *J* 3.7,$H5'_a$); 4.32 (2 H, br. d, H4' + $H5'_b$); 2.42 (3 H, s, CH_3-Ph); 2.14 (3 I, s, $C\underline{H}_3CO$).

2,6-Bis(2-hydroxyethylamino)purine riboside (IX) and 6-(2-hydroxyethyl)isoguanosine (XIV). DMAP (6 mg, 0.05 mmol), EDIP (190 μl, 1.11 mmol), and Ms-Cl (86 μl, 1.11 mmol) were successively added to a solution of 2',3',5'-tri-*O*-acetylxantosine (**II**) (150 mg, 0.37 mmol), and the mixture was kept for 3 h at room temperature. The reaction mixture was evaporated to dryness in a vacuum, and the residue was dissolved in $CHCl_3$ (10 ml) and washed with H_2O. The organic layer was evaporated to dryness in a vacuum, and the residue was dissolved in aqueous dioxane (1 ml). Ethanolamine (225 μl, 3.7 mmol) was added, and the mixture was kept for 120 h at +37°C. The reaction mixture was evaporated in a vacuum. The residue was dissolved in chloroform (1 ml) and purified by

chromatography on a silica gel column eluted with a gradient of methanol concentration in chloroform (0⟶30%) to give two fractions. Fraction 1 eluted with 20% methanol in chloroform was dried in a vacuum, and the residue was repurified on a LiChroprep RP-18 column (20 × 140 mm) in a linear gradient of methanol concentration (0⟶35%, volume 400 ml). The product was lyophilized from water to give compound (**IX**) (27 mg, 30%); R_f and UV and ^{1}H NMR spectra were identical to those described above. Fraction 2 eluted with 30% methanol in chloroform was dried in a vacuum, and the residue was repurified on a LiChroprep RP-18 column (20 × 140 mm) in a linear gradient of methanol concentration (0⟶25%, volume 400 ml). The product was lyophilized from water to give (**XIV**) (21 mg, 17%); R_f 0.25 (C); UV ((H_2O): $\lambda_{max,}$ nm (ε)): 286 (9900), 249 (12200); ^{1}H NMR: (D_2O): 7.92 (1 H, s, H8); 5.89 (1 H, d, *J* 5.9, H1'); 4.83 (1 H, *t*, *J* 5.6, H2'); 4.41 (1 H, *t*, *J* 5.0, H3'); 4.19 (1 H, q, *J* 3.7, H4'); 3.86 (1 H, dd, *J* 3.3, 12.6, $H5'_a$); 3.78 (1 H, dd, *J* 4.4, $H5'_b$); 3.74 (2 H, t, *J* 5.4, CH_2N); 3.47 (2 H, t, $C\underline{H}_2OH$).

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