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Design and Divergent Synthesis of Aza Nucleosides from a Chiral Imino Sugar

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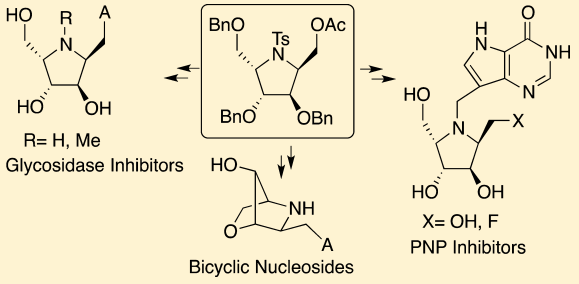
Supporting Information

ABSTRACT: Several novel nucleoside analogues as potential inhibitors of glycosidases and purine nucleoside phosphorylase (PNP) have been synthesized via selective coupling of an appropriate nucleobase at different positions of an orthogonally protected imino sugar as a common precursor. This synthetic strategy offers a straightforward protocol for the assembly of imino sugar containing nucleosides, establishing a new repertoire of molecules as potential therapeutics.



INTRODUCTION

The synthesis and development of glycosidase inhibitors have been the focus of attention, due to their vital role played by carbohydrates in a variety of biological processes. The glycosidases are responsible for catalyzing the cleavage of the glycosidic bonds in oligosaccharides and glycoconjugates. Thus, these enzymes are involved in a wide range of biochemical process such as intestinal digestion, post-translational processing of glycoproteins, and the lysosomal catabolism of glycoconjugates.[1] Consequently, compounds that are able to inhibit or modulate the activity of glycosidases have proven to be promising anticancer, antidiabetes, and antiviral agents.[2]

One of the most potent glycosidase inhibitors belongs to the class of imino sugars (or aza sugars), with a demonstrated ability to mimic the carbohydrates or their transition states during hydrolysis as the primary mechanism of their action.[2a,3] As an example, Miglitol (**1**, Figure 1) is an FDA approved drug for the treatment of diabetes.[2a] Yet another important class of imino sugars are the polyhydroxypyrrolidines, which are known to interact with glycosidases and glycotransferases. Radicamine A (**2**) and B (**3**) are representative examples[4] together with naturally occurring 3,4-dihydroxy-2,5-bis(hydroxymethyl)-pyrrolidine (DMDP, **4**) and its corresponding analogues **5** and **6** exhibiting potent glycosidase inhibition.[5]

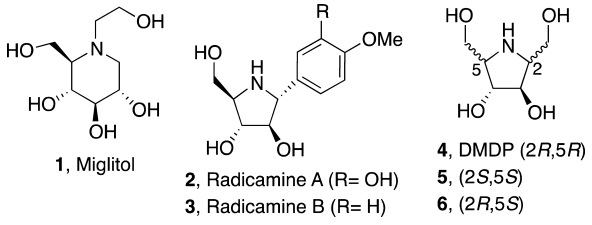


Figure 1. Structures of selected potent glycosidase inhibitors.

Additionally, the therapeutic potential of aza sugars has been further exploited by Schramm and co-workers in the design of purine nucleoside phosphorylase (PNP, E.C. 2.4.2.1) inhibitors. PNP is a ubiquitous nucleoside processing enzyme essential for DNA and RNA synthesis and energy metabolism. It is involved in the reversible phosphorolysis of purine nucleosides to their respective bases and ribose(deoxyribose)-α-1-phosphate. Inhibition of PNP leads to an accumulation of 2′-deoxyguanosine triphosphate (dGTP) in T-cells that are not able to metabolize dGTP because of their low nucleotidase activity, causing high concentrations of this compound and ultimately leading to cellular apoptosis. Therefore, PNP is a key target for the control of T-cell proliferative disorders and consequently, for the treatment of leukemia and autoimmune related diseases.[6]

The seminal work by Schramm in understanding the transition state for the natural PNP-catalyzed hydrolysis of inosine has resulted in the rational design and synthesis of a series of PNP inhibitors.[7] A variety of imino sugar containing nucleoside analogues have been identified to mimic the oxocarbenium ion character at the transition state. Some of

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them have shown to exhibit high PNP inhibitory activity.[8] In fact, two nucleoside analogues are currently in human clinical trials for the treatment of T- and B-cell cancers and other autoimmune disorders. These are first-generation Immucillin-H (**7**, Figure 2) and second-generation DADMe-immucillin-H (**8**) analogues. Use of an imino sugar and 9-deazapurine base was a central feature in the design of these two nucleoside analogues.

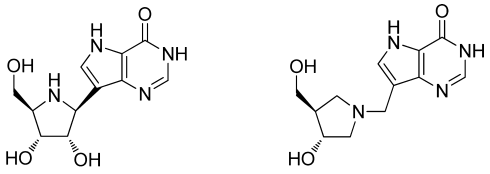


Figure 2. Structures of the two PNP inhibitors currently in clinical trials.

The overall biological importance of polyhydroxypyrrolidines has sparked significant efforts in their synthesis.[9] As a result, further studies on the synthesis and biological evaluation of polyhydroxypyrrolidines and related compounds are of broad interest. Additionally, one of the key objectives of modern drug discovery is to increase the diversity and number of small molecules available for biological screening.[10] Diversity-oriented synthesis (DOS) is already playing a major role in medicinal chemistry. Although DOS is usually directed toward a single biological target, it can also be used to identify new ligands for different targets, usually enzymes. To achieve this goal, one approach involves generation of inhibitors of different enzymes from a common synthetic precursor.[11]

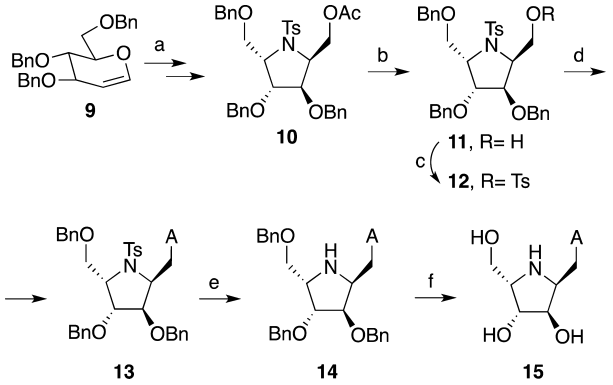
Given the central role of the polyhydroxypyrrolidine moiety in the design of glycosidase, PNP type inhibitors and our ongoing efforts for discovering biologically active nucleosides,[12] we embarked on the synthesis of novel structures. The focus of this study is to use a common and versatile polyhydroxypyrrolidine precursor and introduce a suitable nitrogenated base at different positions of the imino sugar to generate potential enzyme inhibitors. Herein, we describe a practical synthetic strategy leading to a fast and efficient preparation of structurally diverse nucleoside analogues from a single imino sugar precursor.[13]

RESULTS AND DISCUSSION

An efficient synthesis of imino sugar **5** has been described by Kumar and Ramesh as a strong α-fucosidase inhibitor[14] from commercially available tri-*O*-benzyl-D-glucal **9** (Scheme 1).[15] The synthesis of **5** was accomplished in a few steps from the protected imino sugar **10**. We noted that chiral imino sugar **10** is perfectly set up with three orthogonal protecting groups that could be cleaved or manipulated selectively to expose a single functionality at a time. Also, we were inspired by the fact that five-membered imino sugars have shown glycosidase inhibitory activity.[16] Therefore, it was of interest to expand the study to construct nucleosides containing imino sugars. Herein, we describe the utility of **10** as an ideal starting material for building novel nucleoside analogues (Figure 3).

We envisioned synthesizing two types of nucleoside analogues starting from imino sugar **10**. The first set of C-linked nucleosides was built via attachment of a natural adenine base to the C2 position of **10**, resulting in compounds **15**, **20**, and **25**. In the second set of N-linked nucleosides, we utilized the unnatural 9-deazapurine base and connected it to the ring nitrogen to furnish compounds **28** and **31**.

Scheme 1. Synthesis of Aza Sugar Nucleoside 15[a]



[a]Reaction conditions: (a) ref 15; (b) Na_2CO_3/MeOH (99%); (c) TsCl, pyridine, 50 °C (90%); (d) adenine, 18-crown-6, DMF, 90 °C (81%); (e) Mg/MeOH, reflux (90%); (f) concentrated HCl, reflux (82%).

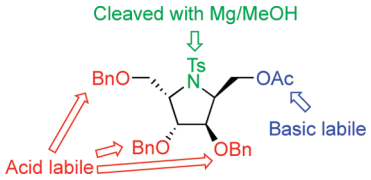


Figure 3. Three classes of orthogonal protecting groups of imino sugar **10**.

Synthesis of C-Linked Nucleosides. The synthesis of imino sugar containing nucleoside **15** was accomplished in five steps, starting with **10**. First, selective hydrolysis of the acetyl group with Na_2CO_3 in MeOH furnished **11** in quantitative yield. The deprotection of N-Ts was not observed under the mild conditions used for the hydrolysis of an acetyl group. Second, the primary hydroxyl group in **11** was tosylated under standard conditions to furnish **12** in excellent yield. In the third step, glycosylation of protected **12** with adenine base[17] afforded protected nucleoside **13** in good yield (ca. 81%) after silica gel chromatography. It is noteworthy that N9-substituted product was isolated as the major product upon glycosylation. The deprotection of **13** into **15** was achieved in a two-step process. First, detosylation with Mg/MeOH and then debenzylation with an acid offered unprotected nucleoside **15** in good yield (Scheme 1). The structure of nucleoside **15** was established by ^1H and ^{13}C NMR data.

Wong et al. reported that the introduction of a methyl group into the N1 position of the imino sugars resulted in improved biological properties.[16a,18] Therefore, we also became interested in developing a method to synthesize the N-methylated analogue of **15**. As shown in Scheme 2, the reaction of compound **10** with Mg in MeOH removed the tosyl group with concomitant cleavage of the acetyl protecting group to afford **16** in high yield (ca. 89%). Interestingly, when we tried the N-detosylation of **10** using Mg turnings activated with iodine, we observed the formation of **17** in moderate yield (46%). We postulate that in situ iodine mediated oxidation of MeOH to formaldehyde may have contributed to the formation of bicyclic structure **17**.[19]

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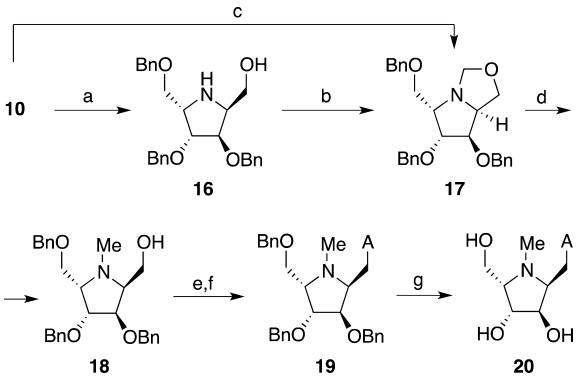
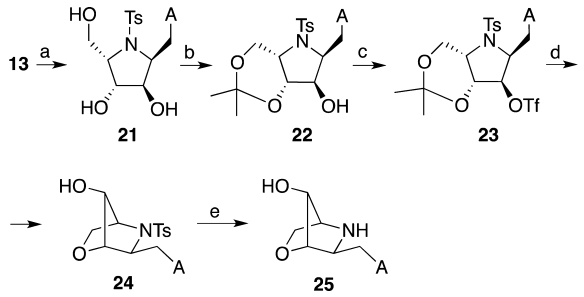
Scheme 2. Synthesis of Aza Sugar Nucleoside 20[a]



[a]Reaction conditions: (a) Mg/MeOH, reflux (89%); (b) HCHO, dioxane, AcOH, 60 °C (94%); (c) Mg/MeOH/I_2, room temperature (46%); (d) H_2/Pd/C, MeOH (68%); (e) MsCl, Py, room temperature; (f) adenine, 18-crown-6, K_2CO_3, DMF, 90 °C (36%, two steps); (g) concentrated HCl, reflux (81%).

Scheme 3. Synthesis of Bicyclic Locked Nucleoside 25[a]



[a]Reaction conditions: (a) concentrated HCl, reflux (66%); (b) CH_2=C(OMe)CH_3, THF, DMF, *p*-TSOH, room temperature (98%); (c) TfCl, DMAP, Py, room temperature (53%); (d) TFA, CH_2Cl_2, room temperature (91%); (e) Mg/MeOH, reflux (79%).

However, the synthesis of **17** was unequivocally established by treatment of **16** with aqueous formaldehyde in the presence of acid, giving 94% of the desired product. Next, selective hydrogenolysis of the hemiaminal afforded N-methylated aza sugar **18** without cleaving the benzyl groups. Subsequent tosylation of **18** under conditions identical with those described for **11** furnished a mixture of products. The ^{1}H NMR spectra of the mixture failed to show the presence of the tosyl signals. Gratifyingly, mesylation of **18** followed by nucleophilic substitution by adenine yielded the fully protected compound **19**. Debenzylation of **19** with concentrated HCl furnished N-methylated nucleoside **20**, and the structure was corroborated by ^{1}H and ^{13}C NMR data. Moreover, the NOESY spectrum of **20** did not show correlations between H2 and H5, either between H3 and H4 hydrogen atoms, which is in agreement with a relative trans configuration, indicating retention of the stereochemistry of the aza sugar after several transformations.

The expeditious synthesis of nucleoside **15** and the C3-hydroxyl group configuration suitable for an elimination followed by ring closure encouraged us to assemble locked nucleic acid structures that are key building blocks for antisense oligonucleotides as therapeutic agents.[20] Additionally, examples of natural and synthetic bicycle imino sugars with glycosidase inhibitory activity prompted us to undertake the synthesis of a locked aza nucleoside.[9b,21] Therefore, installation of a leaving group on the C3 hydroxyl group may allow ring closure onto the hydroxymethyl group, furnishing the novel bicyclic locked nucleoside analogue **25** (Scheme 3).

The synthesis of nucleoside **25** was accomplished in five steps starting with **13**. First, acid treatment of **13** successfully cleaved the three benzyl groups simultaneously to furnish **21** in good yield. The resulting 1,3-diol system in **21** was selectively protected with 2,2-dimethoxypropane to afford ketal **22** in almost quantitative yield. Next, the hydroxyl group in **22** was transformed into triflate by treatment with TfCl in the presence of DMAP, furnishing **23** in a modest 53% yield. We were pleased to note that the treatment of **23** with a TFA−CH_2Cl_2 mixture not only deblocked the acetal but also triggered an in situ cyclization, resulting in the formation of bicyclic homoaza nucleoside **24** in excellent yield. Removal of the tosyl group from **24** following the same protocol as before yielded the final compound **25**. To the best of our knowledge, this is the first example of a locked bicyclic homoaza nucleoside synthesized in a straightforward manner.

The structures of **24** and **25** were confirmed by extensive analysis of 1D and 2D NMR spectroscopy. After cyclization, HMBC spectra of compound **24** clearly showed a three-bond correlation between *C*3 and *CH*$_2$O hydrogen atoms of the new five-membered ring together with other expected cross-peaks. The structure was further confirmed on the basis of the NOESY spectrum of the final compound **25**, which showed a correlation between H3 and H4 hydrogen atoms, supporting the change in the previous trans relative configuration between them. These data supported the inversion at the C3 position (Figure 4).

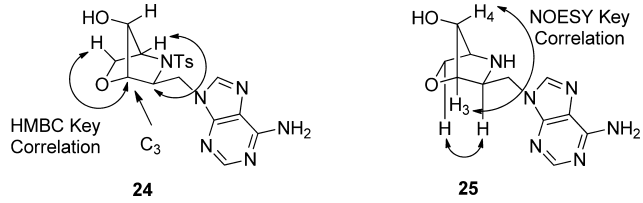


Figure 4. Key HMBC and NOESY correlations in **24** and **25**.

Synthesis of N-Linked Nucleosides. The first and second generations of PNP inhibitors containing an imino sugar moiety have already demonstrated their potential in the design of drug molecules, where Immucillin-H was granted orphan drug status in the United States for the treatment of various leukemia. Subsequently, Schramm and co-workers described a new class of inhibitors (**8**, Figure 2) for PNP in which the 9-deazapurine moiety is directly attached to the N atom of the aza sugar via a methylene bridge.[22] Currently, DADMe-Immunillin-H is under phase II clinical development for the treatment of gout. The promising PNP inhibitory activity of N-linked nucleosides prompted us to undertake the synthesis of the two aza sugar nucleoside analogues **28** and **31** (Schemes 4 and 5, respectively).

Orthogonally protected aza sugar **10** also serves as an attractive starting material for the synthesis of proposed PNP inhibitors, increasing the molecular diversity that can be created from a single imino sugar structure. The aza sugar **10** was conveniently transformed into **16** (Scheme 2) with the unprotected imino group ready for coupling with the base. Schramm et al. have utilized the Mannich reaction for the assembly of immucillin analogues starting with imino sugars.[23] Surprisingly, the reaction of **16**, 9-deazapurine, and form-

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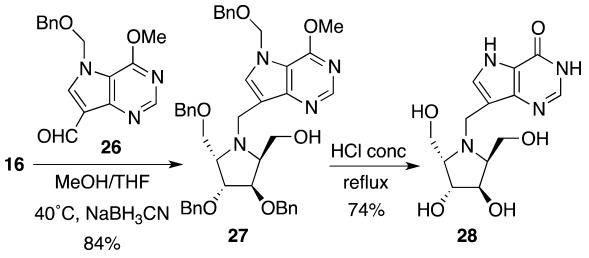
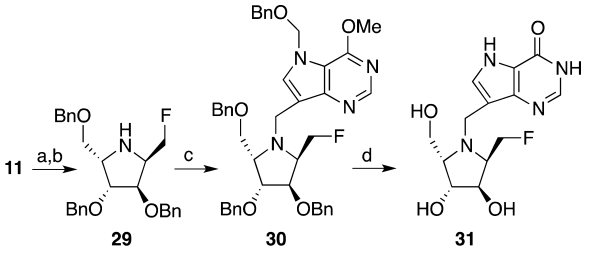
Scheme 4. Synthesis of N-Linked Nucleoside 28



Scheme 5. Synthesis of Fluoro Aza Sugar Nucleoside 31[a]



[a]Reaction conditions: (a) DAST, CH_2Cl_2, 0 °C; (b) Mg/MeOH, reflux (56%, two steps); (c) **26**, MeOH/THF, 40 °C, $NaBH_3CN$ (85%); (d) concentrated HCl, reflux (84%)

aldehyde under Mannich conditions led to the formation of the bicycle **17** (Scheme 2) as a major product instead of the desired nucleoside. We believe that the iminium intermediate formed after the reaction of **16** with formaldehyde underwent concomitant intramolecular attack of the free hydroxyl group to furnish **17**. Therefore, an alternative approach was conceived, starting with the previously reported 9-deazapurine **26**[8g] prefunctionalized with an aldehyde group that will be easier to link with imino sugar **16** using reductive amination conditions. As expected, the coupling of **16** with aldehyde **26** in the presence of $NaBH_3CN$ furnished the desired nucleoside **27** in 84% isolated yield after chromatography (Scheme 4).

Next, the treatment of **27** with acid cleanly removed all five protecting groups in 2.5 h under reflux to furnish the N-linked nucleoside **28** as a hydrochloride salt. The structure of **28** was established by extensive NMR and MS data. ^{1}H NMR spectrum of compound **28** shows only half of the expected signals, confirming the C_2 axis of symmetry that was further supported by NOESY experiments. It is striking to note that the synthesis of a complex nucleoside such as **28** was accomplished in three simple steps starting with **10** in high yield.

In recent years, use of the fluorine atom has proven to be an indispensable tool for drug discovery efforts.[24] For this reason, Schramm et al. have described the synthesis and biological evaluation of an inhibitor of human PNP where one of the hydroxyl groups of the pyrrolidine moiety has been replaced by a fluorine atom.[25] In a similar way, we wished to synthesize the fluoro nucleoside **31** as a structural analogue of nucleoside **28**, expanding the repertoire of aza nucleosides accessible for drug discovery efforts. The prior success of the synthesis of **28** prompted us to install the fluorine substituent first and then carry out the coupling with the formyl-functionalized **26**. Therefore, treatment of **11** with DAST at a low temperature followed by N-detosylation of the crude product furnished **29** in moderate yield (ca. 55%) over two steps (Scheme 5).

Fluoro aza sugar **29** was then reductively alkylated with aldehyde **26** in the presence of $NaBH_3CN$ in a MeOH/THF mixture to afford the protected product **30** in excellent yield. Next, the acid-mediated deprotection of **30** gave the fluoro nucleoside **31** in 84% yield, isolated as the hydrochloride salt.

■ CONCLUSIONS

In summary, we have synthesized a series of five nucleoside analogues using divergent and high-yielding protocols. We started from the common chiral imino sugar **10** by selective removal of the protecting groups followed by glycosylation with appropriate bases. The homoaza nucleoside **15** and its bicyclic analogue **25** were assembled by starting from **10**, where the *O*-acetyl group was deblocked selectively. A serendipitous reaction led to the formation of the bicyclic structure **17**, which was further transformed into the N-methyl derivative **20**. On the other hand, concomitant deprotection of *N*-tosylate and *O*-acetyl groups from **10** offered a short synthesis of potential PNP inhibitors **28** and its fluorine analogue **31** via reductive amination. This study illustrates the successful utility and applications of the easily accessible aza sugar **10** for the preparation of novel N- and C-linked nucleoside analogues with potential for interesting biological activity. Clearly, aza sugar **10** is a desirable scaffold containing orthogonal protecting groups that will enable the discovery of divergent reaction pathways and synthesis of structurally diverse compounds needed for modern day drug discovery and synthetic organic chemistry applications. Full exploitation of this unique class of nucleosides as potential therapeutics and their biological screening is currently in progress.

■ EXPERIMENTAL SECTION

General Considerations. All reagents were the highest commercial quality and were used without further purification. All nonaqueous reactions were carried out under anhydrous conditions in dry, freshly distilled solvents. Reactions were monitored by TLC carried out using UV light as visualizing agent and/or acidic aqueous permanganate or 7% ethanolic phosphomolybdic acid. Flash chromatography was performed using silica gel 60 (230−400 mesh). ^{1}H, ^{13}C NMR, and DEPT were obtained using 300.13, 400.13, and 600.13 MHz instruments for ^{1}H and 75.5, 90.61, and 150.90 MHz for ^{13}C. The same spectrometers were used for the acquisition of ^{1}H−^{1}H homonuclear (COSY and NOESY) and ^{1}H−^{13}C heteronuclear (HSQC and HMBC) correlations. Optical rotations were recorded on a polarimeter, and values are reported as follows: $[\alpha]_\lambda^T$ (c (g/100 mL), solvent). High-resolution mass spectra (HRMS) were recorded on a mass spectrometer under electron spray ionization (ESI) conditions.

Procedures and Experimental Data. *(2S,3R,4R,5R)-3,4-Bis-(benzyloxy)-5-(benzyloxymethyl)-2-(hydroxymethyl)-N-(p-toluenesulfonamido)pyrrolidine (11).* A suspension of **10** (400 mg, 0.635 mmol) and Na_2CO_3 (508 mg, 4.8 mmol) in MeOH (8 mL) was stirred at reflux for 1.5 h. After completion of the reaction, the mixture was filtered over Celite and washed with MeOH and CH_2Cl_2. Solvents were evaporated to give **11**[15] as a colorless viscous liquid (372 mg, 99%) without purification.

(2S,3R,4R,5S)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-2-[(4-methylphenyl)sulfonyl]oxy-N-(p-toluenesulfonamido)pyrrolidine (12). A solution of **11** (373 mg, 0.635 mmol) and *p*-TsCl (607 mg, 3.2 mmol) in dry pyridine (6.5 mL) was stirred overnight at 50 °C. Pyridine was evaporated under high vacuum, and the resulting residue was subjected to flash chromatography (20% EtOAc/hexane) to yield **12** (424 mg, 90%) as a colorless viscous liquid. R_f (50% EtOAc/hexanes): 0.69. IR (KBr): ν 3.063, 3034, 2924, 2871, 1736, 1598, 1496 cm^{-1}. $[\alpha]_D^{20}$ = −14° (c 0.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 2.34, (s, 3H), 2.38 (s, 3H), 3.58 (d, 1H, J_{HH} 10.0 Hz), 3.80 (dd, 1H, J_{HH} 10.0 Hz, J_{HH} 3.1 Hz), 3.98 (m, 2H), 4.23 (m, 5H), 4.63 (m, 6H), 7.03 (m, 2H), 7.24 (m, 16H), 7.70 (d, 2H, J_{HH} 8.4 Hz), 7.77

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(d, 2H, J_{HH} 6.9 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 21.3, 21.4, 56.9, 58.2, 65.8, 67.2, 72.5, 73.0, 73.3, 80.0, 80.2, 126.8−129.4 (23 C), 132.8, 137.2, 137.8, 138.0, 138.2, 143.4, 144.6. MS (ESI$^+$, m/z) 742 [(M + H)$^+$ 10%], 764 [(M + Na)$^+$ 60%]. HRMS (ESI$^+$): calcd for $C_{41}H_{43}NNaO_8S_2$ [M + Na]$^+$ 764.2322, found 764.2299.

*(2S,3R,4R,5S)-2-(9-Adeninylmethyl)-3,4-bis(benzyloxy)-5-(benzyloxymethyl)-N-(p-toluenesulfonamido)pyrrolidine (**13**).* A mixture of compound **12** (300 mg, 0.426 mmol), adenine (86 mg, 0.639 mmol), K_2CO_3 (118 mg, 0.852 mmol), and 18-crown-6 (168 mg, 0.639 mmol) in DMF (4.3 mL) was heated to 90 °C overnight. DMF was evaporated under vacuum, and flash column chromatography (2% MeOH/CH_2Cl_2) of the residue gave pure **13** (239 mg, 81%) as a white foam. R_f (10% MeOH/90% CH_2Cl_2): 0.48. $[\alpha]_D^{20}$ = +20° (*c* 0.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300.13 MHz), 2.32 (s, 3H), 3.57 (d, 1H, J_{HH} 9.0 Hz), 3.97−4.17 (m, 4H), 4.25−4.70 (m, 7H), 4.96 (dd, 1H, J_{HH} 2.2 Hz, J_{HH} 13.8 Hz), 6.26 (br s, 2H), 6.88 (m, 2H), 6.90−7.32 (m, 16H), 7.93 (d, 2H, J_{HH} 9.0 Hz), 7.97 (s, 1H), 8.39 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 21.5, 44.3, 57.2, 59.0, 65.3, 72.6, 73.2, 80.1, 80.5, 119.3, 126.8−129.4 (20C), 136.9, 137.3, 137.5, 137.8, 142.1, 143.4, 150.5, 152.7, 155.6. MS (ESI$^+$, m/z): 705 [(M + H)$^+$ 100%]; 727 [(M + Na)$^+$ 50%]. HRMS (ESI$^+$): calcd for $C_{39}H_{41}N_6O_5S$ [M + H]$^+$ 705.2854, found 705.2809.

*(2S,3R,4R,5S)-2-(9-Adeninylmethyl)-3,4-bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidine (**14**).* Mg (turnings) was added (68 mg, 2.8 mmol) to a solution of compound **13** (200 mg, 0.28 mmol) in dry MeOH (2.8 mL), and the mixture was refluxed for 2 h. MeOH was evaporated, and purification by flash chromatography (10% MeOH/90% CH_2Cl_2) afforded **14** (141 mg, 90%) as a white foam. R_f (10% MeOH/CH_2Cl_2): 0.32. $[\alpha]_D^{20}$ = +19° (*c* 0.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 2.33 (br s, 1H), 3.53 (dd, 1H, $^3J_{HH}$ 9.0 Hz, $^3J_{HH}$ 9.0 Hz), 3.61 (dd, 1H, J_{HH} 6.4 Hz, J_{HH} 9.2 Hz), 3.69 (q, 1H, J_{HH} 6.4 Hz), 3.94 (m, 1H), 4.00 (m, 1H), 4.04 (m, 1H), 4.18 (dd, 1H, J_{HH} 8.0 Hz, J_{HH} 14.0 Hz), 4.21−4.59 (m, 7H), 5.86 (br s, 2H), 7.22−7.39 (m, 15H), 7.81 (s, 1H), 8.33 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 45.1, 58.0, 59.0, 68.8, 72.3, 73.4, 82.1, 82.2, 84.0, 127.5−128.5 (15 C), 138.0, 137.9, 138.1, 141.8, 150.1, 152.7, 156.4. HRMS (ESI$^+$): calcd for $C_{32}H_{35}N_6O_3$ [M + H]$^+$ 551.2765, found 551.2802.

*(2S,3R,4R,5S)-2-(9-Adeninylmethyl)-3,4-dihydroxy-5-(hydroxymethyl)pyrrolidine (**15**).* A mixture of **14** (100 mg, 0.18 mmol) and concentrated aqueous HCl (38%; 1.8 mL) was refluxed for 2 h. Water was evaporated, and aqueous NH_3 (32%; 1 mL) was added to the residue. After the aqueous phase was evaporated, the resulting solid was purified by column chromatography (CH_2Cl_2/MeOH/NH_4OH, 88/10/2) to afford **15** (41 mg, 82%) as a white solid. R_f (CH_2Cl_2/MeOH/NH_4OH, 6:3:1): 0.32. $[\alpha]_D^{20}$ = −21° (*c* 0.5, MeOH). ^{1}H NMR (D_2O, 400.13 MHz): δ 3.80 (dd, 1H, $^3J_{HH}$ 8.8 Hz, $^3J_{HH}$ 12.4 Hz), 3.93 (dd, 1H, $^3J_{HH}$ 4.4 Hz, $^3J_{HH}$ 12.0 Hz), 4.07 (q, 1H, J_{HH} 4.4 Hz), 4.25 (dd, 1H, J_{HH} 1.6 Hz, J_{HH} 3.2 Hz), 4.31 (m, 1H), 4.36 (dd, 1H, J_{HH} 1.6 Hz, J_{HH} 4.0 Hz), 4.62 (dd, 1H, J_{HH} 7.6 Hz, J_{HH} 15.2 Hz), 4.70 (dd, 1H, J_{HH} 6.5 Hz, J_{HH} 15.2 Hz), 8.18 (s, 2H). ^{13}C NMR (D_2O, 100.6 MHz): δ 40.7, 57.5, 60.3, 63.9, 74.3, 74.6, 118.4, 142.3, 150.0, 152.3, 155.3. MS (ESI$^+$, m/z): 281 [(M + H)$^+$ 100%], 303 [(M + Na)$^+$ 80%]. HRMS (ESI$^+$): calcd for $C_{11}H_{17}N_6O_3$ [M + H]$^+$ 281.1357, found 281.1378.

*(2S,3R,4R,5S)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-2-(hydroxymethyl)pyrrolidine (**16**).* Mg (turnings) was added (115 mg, 4.8 mmol) to a solution of compound **10** (600 mg, 0.96 mmol) in dry MeOH (4.8 mL), and the mixture was refluxed for 2 h. MeOH was evaporated, and purification by flash chromatography (10% MeOH/CH_2Cl_2) afforded **16**[15] (367 mg, 89%) as a colorless gummy liquid.

*(8S,6R,7R,5S)-(8-Benzyloxymethyl)-6,7-bis(benzyloxy)-3-oxa-1-azabicyclo[3.3.0]octane (**17**).* A solution of **16** (280 mg, 0.65 mmol), 37% aqueous formaldehyde (146 μL, 1.95 mmol), and acetic acid (186 μL, 3.25 mmol) in dioxane (6.5 mL) was stirred at 60 °C for 30 min. After it was cooled, the solution was concentrated under vacuum and the residue purified by flash column chromatography (50% EtOAc/hexane) to give **17** (270 mg, 94%) as a colorless viscous oil. R_f (30% EtOAc/hexanes): 0.16. $[\alpha]_D^{20}$ = +8° (*c* 0.8, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 3.31 (q, 1H, J_{HH} 6.3 Hz), 3.48 (t, 1H, J_{HH} 8.3 Hz), 3.62 (dd, 1H, J_{HH} 6.6 Hz, J_{HH} 9.1 Hz), 3.82 (dd, 1H, J_{HH} 6.0 Hz, J_{HH} 9.3 Hz), 3.90 (q, 1H, J_{HH} 4.4 Hz), 4.09 (m, 2H), 4.20 (m, 2H), 4.45 (d, 1H, J_{HH} 12.0 Hz), 4.69−4.52 (m, 6 H), 7.29−7.43 (m, 15H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 65.0, 65.5, 65.7, 71.1, 72.9, 73.1, 74.1, 81.9, 83.4, 87.5, 128.2−129.2 (15C), 138.5, 138.7, 139.1. MS (ESI$^+$, m/z): 446 [(M + H)$^+$ 100%]. HRMS (ESI$^+$): calcd for $C_{28}H_{32}NO_4$ [M + H]$^+$ 446.2326, found 446.2350.

*(2S,3R,4R,5S)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-2-(hydroxymethyl)-N-methylpyrrolidine (**18**).* To compound **17** (220 mg, 0.49 mmol) in MeOH (3 mL) was added 10% Pd−90% C (70 mg), and the mixture was stirred at room temperature under an atmosphere of hydrogen overnight. The solution was filtered through Celite and the filtrate concentrated in vacuo. The resulting residue was purified by chromatography (60% EtOAc/40% hexane) to afford **18** (150 mg, 68%) as a colorless viscous oil. R_f (5% MeOH/CH_2Cl_2): 0.44. $[\alpha]_D^{20}$ = −56° (*c* 0.8, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 2.51 (s, 3H), 2.75 (br s, 1H), 3.15 (m, 1H), 3.46 (m, 1H), 3.58 (dd, 1H, J_{HH} 3.0 Hz, J_{HH} 9.9 Hz), 3.72 (m, 3H), 4.25 (t, 1H, J_{HH} 6.9 Hz), 4.42−4.66 (m, 6H), 4.78 (d, 1H, J_{HH} 11.7 Hz), 7.20−7.45 (m, 15H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 35.8, 59.7, 62.1, 64.8, 66.3, 72.7, 72.9, 73.5, 84.0, 84.7, 127.4−128.5 (15C), 138.1, 138.3, 138.5. MS (ESI$^+$, m/z): 448 [(M + H)$^+$ 100%]. HRMS (ESI$^+$): calcd for $C_{28}H_{34}NO_4$ [M + H]$^+$ 448.2482, found 448.2492.

*(2S,3R,4R,5S)-2-(9-Adeninylmethyl)-3,4-bis(benzyloxy)-5-(benzyloxymethyl)-N-methylpyrrolidine (**19**).* To a solution of compound **18** (130 mg, 0.29 mmol) in CH_2Cl_2 (3.6 mL) was added pyridine (88 μL, 1.1 mmol) and MsCl (79 μL, 1.0 mmol). The mixture was stirred at 0 °C for 20 min. The solvent was removed under vacuum. Without purification, the residue was dissolved in DMF (3 mL). Adenine (58 mg, 0.435 mmol), K_2CO_3 (80 mg, 0.58 mmol), and 18-crown-6 (115 mg, 0.435 mmol) were added to the solution, and the mixture was stirred at 90 °C for 2.5 h. After the solvent was evaporated under high vacuum, the residue was purified by flash column chromatography (2% MeOH, CH_2Cl_2) to give **20** (60 mg, 81%) as a white foam. R_f (10% MeOH/CH_2Cl_2): 0.38. $[\alpha]_D^{20}$ = −7° (*c* 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 2.41 (s, 3H), 3.35 (br s, 1H), 3.53 (m, 2H), 3.68 (dd, 1H, J_{HH} 2.8 Hz, J_{HH} 10.0 Hz), 4.11 (t, 1H, J_{HH} 6.0 Hz), 4.22 (dd, 1H, J_{HH} 4.0 Hz, J_{HH} 14.0 Hz), 4.34 (m, 2H), 4.50 (m, 5H), 4.71 (d, 1H, J_{HH} 11.6 Hz), 6.16 (s, 2H), 7.32 (m, 15H), 7.85 (s, 1H), 8.35 (s, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 36.5, 42.9, 62.0, 63.5, 66.0, 72.7, 72.8, 73.4, 82.1, 84.0, 119.3, 127.5−128.5 (15 C), 137.9, 138.0, 138.3, 142.1, 150.5, 152.7, 155.1. MS (ESI$^+$, m/z): 565 [(M + H)$^+$ 100%]; 587 [(M + Na)$^+$ 10%]. HRMS (ESI$^+$): calcd for $C_{33}H_{37}N_6O_3$ [M + H]$^+$ 565.2922, found 565.2928.

*(2S,3R,4R,5S)-2-(9-Adeninylmethyl)-3,4-dihydroxy-5-(hydroxymethyl)-N-methylpyrrolidine (**20**).* A mixture of **19** (60 mg, 0.11 mmol) and concentrated aqueous HCl (38%, 1.8 mL) was refluxed for 2 h. Water was evaporated, and aqueous NH_3 (32%, 1 mL) was added to the residue. After the aqueous phase was evaporated, the resulting solid was purified by column chromatography (CH_2Cl_2/MeOH/NH_4OH, 88/10/2) to afford **15** (25 mg, 81%) as a white solid. R_f (CH_2Cl_2/MeOH/NH_4OH, 7.5:2:0.5): 0.24. $[\alpha]_D^{20}$ = +9° (*c* 0.5, MeOH). ^{1}H NMR (MeOH-d_4, 300.13 MHz): δ 2.55 (s, 3H), 3.26 (q, 1H, H-5, J_{HH} 2.8 Hz), 3.55 (q, 1H, H-2, J_{HH} 5.1 Hz), 3.80 (dd, 1H, CH_2O, J_{HH} 5.1 Hz, J_{HH} 11.7 Hz), 3.87 (dd, 1H, CH_2O, J_{HH} 4.8 Hz, J_{HH} 12.0 Hz), 4.10 (m, 2H, H-3 + H-4), 4.39 (dd, 1H, CH_2N, J_{HH} 5.1 Hz, J_{HH} 14.0 Hz), 4.47 (dd, 1H, CH_2N, J_{HH} 7.8 Hz, J_{HH} 15.0 Hz), 8.21 (s, 1H, H-2 or H-8), 8.22 (s, 1H, H-8 or H-2). ^{13}C NMR (MeOH-d_4, 75.5 MHz): δ 36.2 (CH_3), 41.4 (CH_2N), 57.6 (CH_2O), 65.8 (C-5 + C-2), 75.6 (C-3), 76.8 (C-4B), 118.5 (C-5B), 142.3 (C-8B), 149.4 (C-4B), 152.1 (C-2B), 155.9 (C-6B). MS (ESI$^+$, m/z): 295 [(M + H)$^+$ 60%], 317 [(M + Na)$^+$ 20%]. HRMS (ESI$^+$): calcd for $C_{12}H_{19}N_6O_3$ [M + H]$^+$ 295.1513, found 295.1511.

*(2S,3R,4R,5S)-2-(9-Adeninylmethyl)-3,4-dihydroxy-5-(hydroxymethyl)-N-(p-toluenesulfonamido)pyrrolidine (**21**).* Compound **13** (220 mg, 0.31 mmol) was refluxed in concentrated aqueous HCl (38%, 2.0 mL) for 2 h. Water was evaporated, and aqueous NH_3 (32%, 1 mL) was added to the residue. After the aqueous phase was evaporated, the resulting solid was purified by column chromatography (10% MeOH/90% CH_2Cl_2) to give **21** (89 mg, 66%) as a white solid. R_f (10% MeOH/CH_2Cl_2): 0.39. ^{1}H NMR (DMSO-d_6, 300.13 MHz):

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δ 2.38 (s, 3H), 3.17 (m, 1H), 3.60 (br s, 1H), 3.78 (m, 3H), 4.16 (m, 1H), 4.30 (br s, 1H), 4.45 (dd, 1H, J_{HH} 9.6 Hz, J_{HH} 13.4 Hz), 4.85 (dd, 1H, J_{HH} 2.9 Hz, J_{HH} 13.3 Hz), 5.16 (br s, 1H), 5.68 (br s, 1H), 7.23 (br s, 2H), 7.36 (d, 2H, J_{HH} 8.1 Hz), 7.90 (d, 2H, J_{HH} 8.1 Hz), 8.01 (s, 1H), 8.22 (s, 1H). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ 20.9, 42.3, 56.7, 59.9, 63.9, 72.8, 73.1, 118.5, 127.2 (2C), 129.4 (2C), 137.5, 141.8, 142.8, 149.6, 152.4, 155.9. MS (ESI$^+$, m/z): 435 [(M + H)$^+$ 100%], 457 [(M + Na)$^+$ 10%]. HRMS (ESI$^+$): calcd for $C_{18}H_{23}N_6O_5S$ [M + H]$^+$ 435.1445, found 435.1452.

*(4aS,6S,7R,7aR)-6-((6-Amino-9H-purin-9-yl)methyl)-2,2-dimethyl-5-tosylhexahydro[1,3]dioxino[5,4-b]pyrrol-7-ol (**22**).* To a solution of **21** (89 mg, 0.205 mmol) in anhydrous THF (4.0 mL) and DMF (0.4 mL) were added 2-methoxypropene (57 μL, 0.60 mmol) and *p*-TsOH (0.41 mmol, 72 mg) under a nitrogen atmosphere. The solution was stirred at room temperature. After 30 min, additional 2-methoxypropene (97 μL, 1.02 mmol) was added and the solution was allowed to react for an additional 30 min. Solvents were evaporated under vacuum, and the residue was purified by flash chromatography (2% MeOH/CH_2Cl_2) to afford pure **22** (95 mg, 98%). R_f (10% MeOH/CH_2Cl_2): 0.56. $[\alpha]_D^{20}$ = −15° (*c* 0.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.09 (s, 3H), 1.31 (s, 3H), 2.39 (s, 3H), 3.68 (s, 1H), 4.02 (tt, 1H, J_{HH} 3.9, J_{HH} 11.2), 4.13−4.30 (m, 4H), 4.47 (dd, 1H, J_{HH} 11.2 Hz, J_{HH} 13.6 Hz), 5.09 (dd, 1H, J_{HH} 1.5 Hz, J_{HH} 14.0 Hz), 6.53 (br s, 2H), 6.93 (br s, 1H), 7.30 (d, 2H, J_{HH} 7.9 Hz), 7.82 (d, 2H, J_{HH} 7.9 Hz), 8.00 (s, 1H), 8.25 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 20.7, 21.4, 25.9, 41.1, 59.9, 60.0, 64.5, 73.0, 73.5, 98.4, 119.5, 127.0 (2C), 130.0 (2C), 138.7, 141.2, 143.7, 149.3, 152.5, 156.1. MS (ESI$^+$, m/z): 475 [(M + H)$^+$ 100%], 497 [(M + Na)$^+$ 25%]. HRMS (ESI$^+$): calcd for $C_{21}H_{27}N_6O_5S$ [M + H]$^+$ 475.1758, found 475.1782.

*(4aS,6S,7R,7aR)-6-((6-Amino-9H-purin-9-yl)methyl)-2,2-dimethyl-5-tosylhexahydro[1,3]dioxino[5,4-b]pyrrol-7-yl Trifluoromethanesulfonate (**23**).* Protected compound **22** (95 mg, 0.20 mmol) was dissolved in dry CH_2Cl_2, and DMAP (73 mg, 0.6 mmol) and TfCl (32 μL, 0.24 mmol) were added. The solution was stirred for 2.5 h at 0 °C. Solvent was concentrated, and the residue was subjected to flash chromatography (1% MeOH/99% CH_2Cl_2) to give **23** (64 mg, 53%). R_f (10% MeOH/CH_2Cl_2): 0.53. $[\alpha]_D^{20}$ = +41° (*c* 0.48, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.16 (s, 3H), 1.37 (s, 3H), 2.38 (s, 3H), 4.07 (dd, 1H, J_{HH} 4.4 Hz, J_{HH} 12.8 Hz), 4.17 (q, 1H, J_{HH} 4.4 Hz), 4.26 (dd, 1H, J_{HH} 4.8 Hz, J_{HH} 12.8 Hz), 4.45 (m, 2H), 5.12 (m, 3H), 5.95 (br s, 2H), 7.21 (d, 2H, J_{HH} 8.0 Hz), 7.70 (d, 2H, J_{HH} 8.0 Hz), 7.87 (s, 1H), 8.28 (s, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 20.9, 21.4, 26.6, 42.1, 57.3, 59.2, 60.0, 70.8, 87.3, 99.4, 119.4, 126.6 (2C), 129.6 (2C), 136.9, 141.1, 143.9, 150.2, 152.9, 155.5. MS (ESI$^+$, m/z): 607 [(M + H)$^+$ 100%], 629 [(M + Na)$^+$ 20%]. HRMS (ESI$^+$): calcd for $C_{22}H_{26}F_3N_6O_7S_2$ [M + H]$^+$ 607.1251, found 607.1277.

*(2S,3S,4R,5S)-2-(9-Adenylmethyl)-(3-O,5-C-methylene)-N-(p-toluenesulfonamido)pyrrolidine (**24**).* A solution of compound **23** (64 mg, 0.106 mmol) in a 1:1 mixture of TFA and CH_2Cl_2 (3 mL) was stirred at room temperature for 1 h. After the solvents were evaporated, the resulting residue was purified by chromatography (5% MeOH/95% CH_2Cl_2) to afford **24** as a white solid (40 mg, 91%). R_f (10% MeOH/CH_2Cl_2): 0.39. $[\alpha]_D^{20}$ = +89° (*c* 0.52, MeOH). ^{1}H NMR (DMSO-d_6, 400.13 MHz): δ 2.41 (s, 3H, CH_3), 3.28 (d, 1H, CH_2O, J_{HH} 8.4 Hz), 3.59 (d, 1H, CH_2O, J_{HH} 8.0 Hz), 3.78 (dd, 1H, H-2, J_{HH} 3.6 Hz, J_{HH} 8.4 Hz), 3.87 (s, 1H, H-5), 3.97 (s, 1H, H-4), 3.99 (s, 1H, H-3), 4.33 (dd, 1H, CH_2N, J_{HH} 8.8 Hz, J_{HH} 14.4 Hz), 4.48 (dd, 1H, CH_2N, J_{HH} 3.4 Hz, J_{HH} 14.5 Hz), 5.67 (br s, 1H, OH), 7.30 (s, 2H, NH_2), 7.47 (d, 2H, Ts-m, J_{HH} 8.1 Hz), 7.91 (d, 2H, Ts-o, J_{HH} 8.2 Hz), 8.09 (s, 1H, H-8), 8.24 (s, 1H, H-2). ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 21.5 (CH_3, Ts), 44.6 (CH_2N), 62.3 (C-3), 65.3 (C-2), 67.6 (CH_2O), 71.1 (C-4), 79.5 (C-5), 119.1 (C-5B), 128.1 (Ts-m), 144.1 (Ts-o), 136.1 (Ts), 141.3 (C-8B), 144.7 (Ts), 150.1 (C-4B), 153.3 (C-2B), 156.5 (C-6B);. MS (ESI$^+$, m/z): 417 [(M + H)$^+$ 100%], 439 [(M + Na)$^+$ 60%]. HRMS (ESI$^+$): calcd for $C_{18}H_{21}N_6O_4S$ [M + H]$^+$ 417.1340, found 417.1349.

*(2S,3S,4R,5S)-2-(9-Adenylmethyl)-(3-O,5-C-methylene)pyrrolidine (**25**).* A mixture of compound **24** (40 mg, 0.096 mmol) and Mg (turnings) was refluxed in dry MeOH (2 mL) for 2 h. MeOH was evaporated, and purification by flash chromatography (10% MeOH/90% CH_2Cl_2) afforded **25** (19 mg, 79%) as a white solid. R_f (10% MeOH/CH_2Cl_2): 0.16. $[\alpha]_D^{20}$ = −85° (*c* 0.5, MeOH). ^{1}H NMR (D_2O, 600.13 MHz): δ 3.38 (s, 1H, H-5), 3.52 (t, 1H, H-2, J_{HH} 8.2 Hz), 3.76 (d, 1H, CH_2O, J_{HH} 8.4 Hz), 3.98 (m, 2H, CH_2O + CH_2N), 4.03 (s, 1H, H-3), 4.10 (dd, 1H, CH_2N, J_{HH} 7.4 Hz, J_{HH} 12.6 Hz), 4.28 (s, 1H, H-4), 7.98 (s, 1H, H-8), 8.04 (s, 1H, H-2). ^{13}C NMR (D_2O, 100.6 MHz): 46.0 (CH_2N), 55.7 (C-5), 60.5 (C2), 71.2 (C4), 71.9 (CH_2O), 78.8 (C-3), 118.0 (C-5B), 141.9 (C-8B), 148.6 (C-4B), 152.4 (C-2B), 155.2 (C-6B). MS (ESI$^+$, m/z): 263 [(M + H)$^+$ 100%], 285 [(M + Na)$^+$ 25%]. HRMS (ESI$^+$): calcd for $C_{11}H_{15}N_6O_2$ [M + H]$^+$ 263.1251, found 263.1244.

*(2S,3R,4R,5S)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-2-(hydroxymethyl)-N-(7-(benzyloxymethyl)-6-methoxy-9-deazapurin-9-yl)-methylpyrrolidine (**27**).* Imino sugar **16** (90 mg, 0.21 mmol), sodium cyanoborohydride (0.36 mmol, 22 mg), and compound **26** (56 mg, 0.19 mmol) were dissolved in a 4/1 mixture of MeOH and THF (4 mL). Three drops of acetic acid were added, and the solution was stirred at 40 °C overnight. Solvents were evaporated in vacuo, and the residue was purified by flash chromatography (3% MeOH/97% CH_2Cl_2) to give the coupled product **27** (113 mg, 84%). R_f (5% MeOH/CH_2Cl_2): 0.44. $[\alpha]_D^{20}$ = −30° (*c* 0.50, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 3.25 (m, 1H), 3.46 (tt, 1H, J_{HH} 3.7 Hz), 3.57 (dd, 1H, J_{HH} 3.7 Hz, J_{HH} 10.1 Hz), 3.79 (m, 2H), 3.87 (dd, 1H, J_{HH} 3.5 Hz, J_{HH} 11.8 Hz), 4.10 (s, 3H), 4.19 (m, 3H), 4.38−4.77 (m, 7H), 4.68 (d, 1H, J_{HH} 12.3 Hz), 4.73 (d, 1H, J_{HH} 12.3 Hz), 5.60 (d, 1H, J_{HH} 10.5 Hz), 5.66 (d, 1H, J_{HH} 10.5 Hz), 7.17 (s, 1H), 7.21−7.38 (m, 20H), 8.55 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 41.8, 53.4, 57.3, 60.7, 62.6, 66.6, 69.9, 72.4, 72.8, 73.3, 82.3, 83.7, 115.3, 116.0, 127.2−128.3 (22C), 131.5, 136.8, 138.4, 138.6, 149.6, 150.0, 156.1. MS (ESI$^+$, m/z): 715 [(M + H)$^+$ 100%], 737 [(M + Na)$^+$ 10%]. HRMS (ESI$^+$): calcd for $C_{43}H_{47}N_4O_6$ [M + H]$^+$ 715.3490, found 715.3526.

*(2S,3R,4R,5S)-3,4-Dihydroxy-2,5-bis(hydroxymethyl)-N-(9-deazahypoxanthin-9-yl)methylpyrrolidine (Hydrochloride Salt) (**28**·HCl).* Compound **27** (112 mg, 0.16 mmol) was heated under reflux in concentrated HCl (38%, 2 mL) for 2.5 h. After it was cooled, the solution was concentrated in vacuo and aqueous NH_3 (32%, 1 mL) was added to the residue. Water was evaporated, and the resulting solid was purified by column chromatography (CH_2Cl_2/MeOH/NH_4OH, 88/10/2) to afford **28** (36 mg, 74%), which was then converted with 10% aqueous HCl to **28**·HCl. R_f (CH_2Cl_2/MeOH/NH_4OH, 6/3/1): 0.19. $[\alpha]_D^{20}$ = +2° (*c* 0.50, MeOH). ^{1}H NMR (D_2O, 600.13 MHz, 373 K): δ 3.80 (br s, 4H, CH_2O), 4.58 (s, 2H, H-2 + H-5, J_{HH} 5.3 Hz), 4.90 (d, 2H, H-3 + H-4, J_{HH} 3.3 Hz), 5.10 (d, CH_2N, 1H, J_{HH} 13.4 Hz), 5.28 (d, 1H, CH_2N, J_{HH} 13.5 Hz), 8.22 (s, 1H, H-8), 8.54 (s, 1H, H-2). ^{13}C NMR (D_2O, 150.92 MHz): δ 45.9 (CH_2N), 55.9 (CH_2O), 69.0 (C-2 + C-5), 74.6 (C-3 + C-4), 105.6 (C-9B), 117.7 (C-4B), 131.4 (C-8B), 143.1 (C-2B), 144.1 (C-5B), 155.1 (C-6B). MS (APCI$^+$, m/z): 311 [(M + H)$^+$ 20%]. HRMS (ESI$^+$): calcd for $C_{13}H_{19}N_4O_5$ [M + H]$^+$ 311.1350, found 311.1340.

*(2S,3R,4R,5S)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-2-(fluoromethyl)pyrrolidine (**29**).* DAST (33 μL, 0.20 mmol) was added dropwise to a solution of compound **11** (80 mg, 0.14 mmol) in dry CH_2Cl_2 (2 mL) in dry CH_2Cl_2, and the solution was stirred at 0 °C for 1 h. The reaction mixture was concentrated in vacuo, the crude product, without any purification, was dissolved in dry MeOH (2 mL), and Mg (33 mg, 1.4 mmol) was added to the solution. The mixture was refluxed for 2 h, solvents were evaporated, and the residue was purified by flash chromatography (5% MeOH/95% CH_2Cl_2) to give **29** (31 mg, 85%) as a viscous colorless oil. R_f (5% MeOH/CH_2Cl_2): 0.26. $[\alpha]_D^{20}$ = −11° (*c* 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 3.56−3.81 (m, 4H), 4.05 (m, 2H), 4.38−4.71 (m, 8H), 7.28−7.40 (m, 15H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 58.1 (d, J_{CF} 20.4 Hz), 58.6, 71.2 (J_{CF} 322.4 Hz), 72.3 (3C), 82.1, 82.3, 84.3, 127.6−128.5 (18C). HRMS (ESI$^+$): calcd for $C_{27}H_{31}FNO_3$ [M + H]$^+$ 436.2282, found 436.2284.

*(2S,3R,4R,5S)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-2-(fluoromethyl)-N-(7-(benzyloxymethyl)-6-methoxy-9-deazapurin-9-yl)-methylpyrrolidine (**30**).* Sodium cyanoborohydride (8 mg, 0.13 mmol) was added to a stirred solution of **29** (31 mg, 0.07 mmol)

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and **26** (22 mg, 0.07 mmol) in a 4/1 mixture of MeOH and THF (2 mL). The reaction mixture was stirred overnight at 40 °C. Solvents were evaporated in vacuo, and the crude reaction was subjected to flash chromatography (2% MeOH/98% CH_2Cl_2) to afford **30** as a white foam (43 mg, 85%). R_f (5% MeOH/CH_2Cl_2): 0.54. ^{1}H NMR ($CDCl_3$ 300.13 MHz): δ 3.57 (m, 3H), 3.84 (dd, 1H, J_{HH} 3.0 Hz, J_{HH} 7.5 Hz), 4.13 (s, 3H), 4.15−4.64 (m, 13H), 4.75 (ddd, 1H, J_{HH} 3.3 Hz, J_{HH} 7.2 Hz, J_{HF} 35.7 Hz), 5.67 (d, 1H, J_{HH} 7.8 Hz), 5.71 (d, 1H, J_{HH} 7.8 Hz), 7.22−7.40 (m, 21 H), 8.57 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 42.3, 53.51, 60.4, 61.2 (d, J_{CF} 14.3 Hz), 68.0, 70.1, 72.8, 73.4, 77.0, 82.3 (d, J_{CF} 126.8 Hz), 83.1, 83.5, 114.7, 114.8, 126.3−127.5 (22C), 131.2, 136.0, 137.5, 137.6, 148.9, 149.1, 155.2. MS (ESI$^+$, *m*/*z*): 717 [(M + H)$^+$ 100%]. HRMS (ESI$^+$): calcd for $C_{43}H_{46}FN_4O_5$ [M + H]$^+$ 717.3447, found 717.3419.

*(2S,3R,4R,5S)-5-(Fluoromethyl)-3,4-dihydroxy-5-(hydroxymethyl)-N-(9-deazahypoxanthin-9-yl)methylpyrrolidine (Hydrochloride Salt) (**31**·HCl).* Concentrated HCl (2 mL) was added to a flask containing compound **30** (43 mg, 0.06 mmol). The mixture was refluxed for 2 h. After water was evaporated, aqueous NH_3 (32%, 1 mL) was added to the residue and then this mixture was concentrated under vacuum. The resulting residue was purified by column chromatography (CH_2Cl_2/MeOH/NH_4OH, 88/10/2) to afford **31** (16 mg, 84%), which was then converted with 10% aqueous HCl to **31**·HCl. R_f (CH_2Cl_2/MeOH/NH_4OH, 6/3/1): 0.26; Data for **31** are as follows. ^{1}H NMR (MeOH-d_4, 300.13 MHz): δ 3.10 (dtt, J_{HH} 2.4 Hz, J_{HH} 7.0 Hz, J_{HF} 38.1 Hz), 3.28 (m, 1H), 3.68 (dd, 1H, J_{HH} 3.0 Hz, J_{HH} 11.8 Hz), 3.82 (dd, 1H, J_{HH} 4.1 Hz, J_{HH} 11.8 Hz), 4.08−4.27 (m, 4H), 4.57 (ddd, 1H, J_{HH} 2.4 Hz, J_{HH} 7.0 Hz, J_{HF} 46.1 Hz), 4.80 (ddd, 1H, J_{HH} 2.6 Hz, J_{HH} 10.1 Hz, J_{HF} 46.1 Hz), 7.42 (s, 1H), 7.89 (s, 1H). Data for the hydrochloride (**31**·HCl) are as follows. ^{1}H NMR (D_2O 300.13 MHz): δ 3.65 (br s, 4H), 4.05 (q, 1H, J_{HH} 6.0 Hz), 4.24−4.39 (m, 3H), 4.62 (d, 1H, J_{HH} 13.2 Hz), 4.76 (d, 1H, J_{HH} 13.5 Hz), 7.42 (s, 1H), 7.88 (s, 1H). ^{13}C NMR (D_2O, 75.5 MHz): δ 46.3, 56.8, 69.2, 74.3 (2C), 78.4 (d, J_{CF} 182.7 Hz), 104.3, 117.9, 131.8, 141.1, 143.6, 154.3. MS (APCI$^+$, *m*/*z*): 335 [(M + Na)$^+$ 15%], 647 [(2M + Na)$^+$ 15%]. HRMS (ESI$^+$): calcd for $C_{13}H_{18}FN_4O_4$ [M + H]$^+$ 313.1307, found 313.1296.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving ^{1}H, ^{13}C, and DEPT NMR spectral data and 2D NMR experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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