6-Bromopurine Nucleosides as Reagents for Nucleoside Analogue Synthesis

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Surprisingly facile direct substitution reactions with acetyl-protected 6-bromopurine nucleosides are described. Included in the series of bromonucleosides studied is the guanosine derivative N^2-2′,3′,5′-tetraacetyl-6-bromopurine ribonucleoside, the synthesis of which is reported here for the first time. Brominated nucleosides had not previously been considered optimal substrates for S_NAr reactions given the general reactivity trend for halogenated aromatic systems (i.e. F > Cl > Br > I). However, even weakly nucleophilic aromatic amines give high yields of the substitution products in polar solvents with these 6-bromopurine nucleosides. For primary aromatic amines, secondary aliphatic amines, and imidazole, reaction takes place only at C6, with no effect on the acetyl-protected ribose. In addition, we report the first synthesis of 3′,5′-di-*O*-acetyl-6-bromopurine-2′-deoxyribonucleoside and its reaction with an arylamine in MeOH in the absence of added metal catalyst. Thus, C6-arylamine derivatives of both adenosine and 2′-deoxyadenosine can be prepared via simple S_NAr reactions with the corresponding 6-bromo precursor. We also describe high yielding and C6-selective substitution reactions with 6-bromonucleosides using alcohol and thiol nucleophiles in the presence of added base (DBU). Finally, C6-bromonucleosides are shown to be readily hydrogenated to give purine or 2-aminopurine products in good yield. This work increases the arsenal of reactions and strategies available for the synthesis of nucleoside analogues as potential biochemical tools or new therapeutics.

Introduction

The development of new methods for the generation of nucleoside analogues continues to be an intensively studied research topic. Nucleoside analogues have found use in a number of areas, including the study of the effects of DNA-damaging reagents[1] and in mechanistic analysis of nucleoside metabolizing and nucleic acid modifying enzymes.[2,3] In addition, these compounds have the potential to be developed into new antibacterial, antiviral or cancer chemotherapeutic agents.[4] Due to these important applications, modern synthetic methods are being applied to nucleoside analogue synthesis to create simple, versatile and efficient procedures for their generation. Purine derivatives with various substituents at C6 have received considerable attention, at least in part, due to their structural similarity to DNA damage products arising from modification of *N*6 of 2′-deoxyadenosine or *O*6 of 2′-deoxyguanosine.[5,6] Recent advances in the synthesis of C6 modified purines include use of such reactions as Stille coupling,[7,8] Suzuki-Miyaura coupling,[9,10] Pd-mediated arylaminations,[5] organocuprate cross couplings,[11,12] and reactions that involve 6-oxyphosphonium intermediates.[6] Generally, *N*6-substituted purine derivatives have been prepared by direct aromatic nucleophilic displacement (S_NAr) of halogens with amine nucleophiles in the presence of a base in alcohol at reflux.[13] Following the general trend of reactivity of halogenated aromatic systems, most syntheses employed the 6-fluoro or 6-chloro derivative; the latter being favored for ease of preparation. Later, other procedures were developed to synthesize *N*6-substituted purine derivatives. For instance, *N*6-substituted purine 2′-deoxyribonucleosides have been synthesized via S_NAr displacement of *O*6-arylsulfonyl purine derivatives with amines in DME at 50 °C.[14] More recently, Robins and Lin[6] described the synthesis of *N*6-substituted purine derivatives by displacing a presumed 6-oxyphosphonium intermediate with cyclic secondary amines and imidazole. These procedures are efficient with good nucleophiles, such as aliphatic amines. However, less reactive nucleophiles (e.g., aromatic amines) rarely succeed in these

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(14) Lakshman, M. K.; Ngassa, F. N.; Keeler, J. C.; Dinh, Y. Q. V.; Hilmer, J. H.; Russon, L. M. *Org. Lett.* **2000**, *2*, 927−930.

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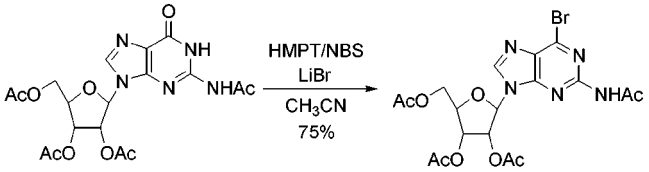
procedures. Indeed, more elaborate alternative methods have been developed to synthesize *N*6-aryl substituted purine derivatives. Lakshman and co-workers[5] described a Pd-mediated coupling of arylamines with a 6-bromopurine derivative. Robins and Lin[6] were successful in synthesizing these types of compounds by allowing aniline to react with C6-sulfonylpurine derivatives, which, in turn, were synthesized from their corresponding inosine nucleosides. Because of the expected general reactivity trend of halogenated aromatic systems, the reactivity of 6-bromopurine nucleosides has been underexplored in S_NAr reactions. Given our recent development of a simple, efficient procedure to prepare 6-bromopurine ribonucleoside[15] and its application in the synthesis of the tetraacetyl-protected 2-amino-6-bromopurine derivative, we wished to ascertain the general efficacy and scope of simple substitution reactions with these compounds and their reactivity with aromatic amines in particular.

Herein we report that direct substitution at C6 of acetyl-protected 6-bromopurine nucleosides occurs in high yield under mild conditions in polar solvents with various amines, including arylamines, in the absence of added base or metal catalyst. These reactions are typically more efficient than those of the analogous 6-chloropurine ribonucleoside, in contrast to the predicted relative reactivity for S_NAr reactions. Moreover, other nucleophiles, such as phenol and thiophenol, react selectively at C6 in the presence of DBU as added base. The observed reactivity at the 6-position is maintained with a 2-amino-6-bromopurine nucleoside giving substituted derivatives of guanosine or 2,6-diaminopurine ribonucleoside. To further expand the use of this reaction to 2′-deoxyribonucleosides, 3′,5′-di-*O*-acetyl-6-bromopurine-2′-deoxyribonucleoside was synthesized using Nair's protocol.[16] Importantly, it also reacts with an arylamine in MeOH in the absence of added metal catalyst. Thus, C6-arylamine derivatives of both adenosine and 2′-deoxyadenosine can be prepared via simple S_NAr reactions with the corresponding C6-bromo precursor and do not require the use of metal catalyst, in contrast to a previous report.[5]

Results and Discussion

Bromination of Guanosine Using HMPT/NBS/LiBr. We recently reported a simple, high yielding procedure for the generation of 2′,3′,5′-tri-*O*-acetyl-6-bromopurine ribonucleoside (**1a**) using triacetylinosine and HMPT/NBS/LiBr in acetonitrile.[15] To determine if this approach could be applied to other nucleosides, we carried out a similar transformation using guanosine protected at the ribose hydroxyls and at the 2-amino position with acetyl groups.[17] This reaction proceeded in high yield to give N^2-2′,3′,5′-tetraacetyl-6-bromopurine ribonucleoside **1b** (Scheme 1). This constitutes the first reported synthesis of this versatile compound. Direct reaction of **1b** with various nucleophiles in polar solvents allows ready access to a variety of 2-amino-substituted purine derivatives (vide infra). Unfortunately, application of our bromination conditions to protected 2′-deoxyinosine failed due to depurination. Also, 2′,3′,5′-tri-*O*-acetyluridine reacts under these conditions to give C5 bromination instead of the desired C4 bromo-product.

Scheme 1



(**1b**)

S_NAr Reactions with 6-Bromopurine Nucleosides and Amine Nucleophiles. A search of the literature found that N^2-aryl-2-aminopurine derivatives had been synthesized by the reaction of 2-bromopurines with the appropriate aromatic amine in alcohol at reflux.[18,19] This result indicated that direct displacement of bromide from the purine C2 could be accomplished with weak nucleophiles, such as aromatic amines. In addition, it was found that 2-halo-6-bromopurine derivatives underwent substitution at the C6 position under mild conditions (25 °C),[20−22] whereas, the subsequent reaction at the C2 position required more forcing conditions (120 °C).[22] Little was known, however, regarding the efficiency of direct displacement of bromide from the 6-position of 6-bromopurine nucleosides. Lakshman and co-workers[5] reported that 6-chloro-9-(2-deoxy-β-D-*erythro*-pentafuranosyl)purine does not react with arylamines, and therefore, the 6-bromo derivative should be even less reactive. They also reported a Pd-catalyzed substitution reaction of bis-*O*-silylated 6-bromopurine 2′-deoxyribonucleoside with aromatic amines and found that no reaction occurred in the absence of the Pd catalyst. This latter observation seemed to suggest that direct displacement of bromide from the purine C6 would fail with weak nucleophiles. However, initial studies in our laboratory indicated that the 6-bromopurine ribonucleoside was quite reactive and underwent a displacement reaction under very mild conditions (5 equiv of K_2CO_3, MeOH/rt/1 h) to give 6-*O*-methyl inosine in 89% yield.[3] Under the same conditions and time, the 6-chloro precursor reacts to give the substituted product in significantly lower yield.[23] This was an unexpected result given the reactivity trend for halogenated aromatic systems in S_NAr reactions (i.e., F > Cl > Br > I). These observations prompted us to explore further the reactivity of 6-bromopurine nucleosides in S_NAr reactions.

Primary aliphatic amines react with acetyl-protected 6-bromopurine ribonucleoside at room temperature to give high yields of the substitution products (Table 1, entries 1−3). For instance, 4-methylbenzylamine reacts with **1a** in DME in a 3 h period to give an 87% yield of adenosine derivative **2a**. This reaction is selective for substitution at C6 with no loss of the acetate-protecting groups. When this reaction is carried out in THF, it takes place at a lower rate and gives an overall lower yield (Table 1, entry 2). The more reactive methylamine reacts at C6 in DME to give a high yield of the substitution

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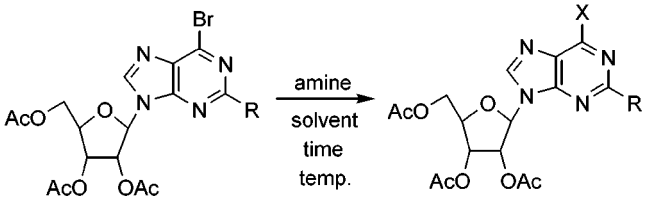
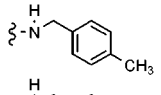
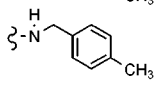
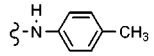
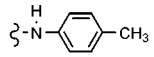
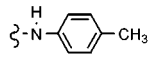
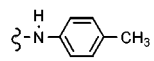
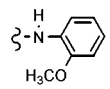
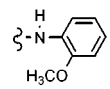
(23) Véliz, E. A.; Beal, P. A. Unpublished results.

Table 1. Substitution Reactions with 6-Bromopurine Ribonucleosides and Amines[a]



1a: R = H
1b: R = NHAc

2a-10a: R = H
4b-10b: R = NHAc

Entry	Product	X	Solvent	Temp.	Time	Yield
1	**2a**		DME	rt	3 h	87%
2	**2a**		THF	rt	14 h	55%
3	**3a**		DME[1]	rt	3 h	94%[2]
4	**4a**		DME	rt	8 h	94%
5	**4b**		DME	rt	8 h	90%
6	**5a**		DME	rt	3 h	87%
7	**5b**		DME	rt	3 h	90%
8	**6a**		DME	rt	12 h	NR[3]
9	**7a**		DME	rt	3 h	99%
10	**7b**		DME	rt	3 h	91%
11	**8a**		DMF	65 °C	8 h	92%
12	**8b**		DMF	65 °C	8 h	65%
13	**9a**		MeOH	65 °C	5 h	85%
14	**9a**		DMF	65 °C	5 h	65%
15	**9b**		MeOH	65 °C	5 h	90%
16	**9a**		EtOH	65 °C	5 h	82%
17	**10a**		MeOH	65 °C	5 h	91%
18	**10b**		MeOH	65 °C	5 h	95%

[a] (1) Trace H_2O from addition of 40% $MeNH_2$ in H_2O. (2) Yield of deprotected nucleoside. (3) NR = no reaction.

product, but under these conditions, ribose deprotection also occurs (Table 1, entry 3). The efficacy of this reaction is noteworthy given the extremely mild conditions employed. The transformation occurs at room temperature, whereas the 6-chloro derivative requires both high pressure (Parr bomb) and temperature (80 °C) and longer period of time (16 h).[24] This specific example demonstrates the increased reactivity of the 6-bromo derivative in comparison with its 6-chloro counterpart. Secondary aliphatic amines react selectively at C6 in DME at room temperature with either inosine derivative **1a** or guanosine derivative **1b** (Table 1, entries 4−10). Given the selectivity of this substitution reaction, an alcohol functional group differentiated from those on ribose can be easily introduced into the structure using the appropriate amino alcohol (Table 1, entries 6 and 7). The substitution reaction with secondary amines does have limitations as no reaction was observed with the bulky diisopropylamine in DME. Substitution with imidazole occurs in DMF at 65 °C taking place in 8 h in 92% yield with **1a** and 65% yield for **1b**. However, no reaction was observed with imidazole in DME.

Importantly, aromatic amines react with both **1a** and **1b** in DMF, MeOH, or EtOH at 65 °C in 5 h to give substitution products in good to excellent yields (Table 1, entries 13−18). Ortho-substitution on the arylamine does not inhibit this reaction (Table 1, entries 17−18). This procedure is the simplest, most efficient reported to prepare arylamine derivatives of adenosine modified at *N*6. The synthesis consists of three high yielding steps from commercially available inosine (acetyl protection, bromination, and substitution) and requires no metal for catalysis of the substitution reaction. Interestingly, no arylamine substitution product was observed when the 6-chloro substrate was used under the same reaction conditions. Furthermore, less polar solvents, such as DME or acetonitrile, do not support the substitution reaction with arylamines.

The efficiency of S_NAr reactions with the 6-bromopurine ribonucleosides and arylamines was surprising given the observation of Lakshman and co-workers.[5] As described above, they reported that no substitution product was observed in a reaction with a 6-bromopurine 2′-deoxyribonucleoside and arylamines in DME even after 24 h at 80 °C. There are several possible explanations for the observed reactivity differences. First, their reaction was carried out in DME and we have shown that a more polar solvent like DMF, MeOH, or EtOH is necessary for substitution with weakly nucleophilic amines. Second, their substrate was protected as a bis-*tert*-butyldimethylsilyl-derivative, whereas we used acetyl-protected substrates. Finally, their reaction was carried out with a 2′-deoxyribonucleoside as opposed to the ribonucleosides discussed above. To determine if the difference in sugar structure was important in defining the different reactivities observed, we prepared 3′,5′-diacetyl-6-bromopurine-2′-deoxyribonucleoside (**11**) as a substrate for substitution reactions with an arylamine (Scheme 2). To do this, we used Nair's diazotization/bromination procedure[16] with *tert*-butylnitrite and bromoform to convert 3′,5′-diacetyl-2′-deoxyadenosine to **11** in 57% yield. This constitutes the first reported synthesis of this derivative which we anticipate could be prepared on a multigram scale. Interestingly, compound **11** reacted in MeOH at 65 °C with *p*-toluidine to give the 2′-deoxyadenosine derivative **12** in 91% in 12 h. Therefore, simple, efficient substitution reactions with arylamines observed for 6-bromopurine ribonucleosides can also take place with 2′-deoxyribonucleosides. Thus, the use of more

(24) Johnson, J. A., Jr.; Thomas, H. J.; Schaeffer, H. J. *J. Am. Chem. Soc.* **1958**, *80*, 699−702.

Scheme 2

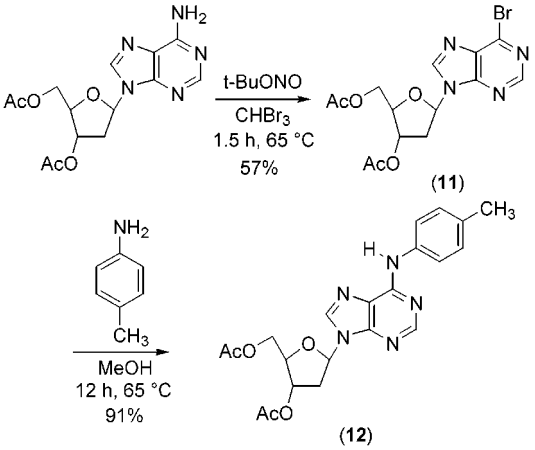
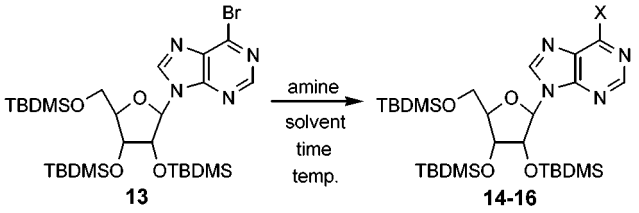
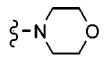
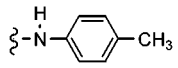


Table 2. Substitution of Reactions with Silyl-Protected 6-Bromopurine Ribonucleoside



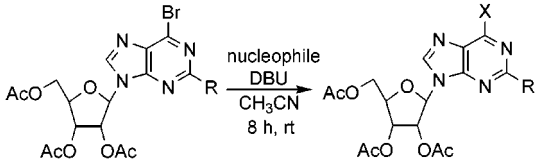
13 **14-16**

Entry	Product	X	solvent	temp.	time	yield
1	**14**		DME	rt	9 h	87%
2	**15**		DME	85 °C	12 h	NR
3	**15**		DMF	65 °C	14 h	93%
4	**16**		DMF	65 °C	12 h	NR

complex procedures, such as Pd-mediated arylaminations, to generate C6 arylamine derivatives of 2′-deoxyadenosine may not be necessary as these compounds can likely be obtained from simpler direct substitution reactions of the acetyl-protected 6-bromo substrate in MeOH.

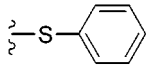
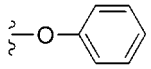
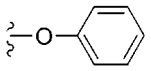
To determine if the ribose-protecting group played a role in determining the reactivity of the brominated nucleosides in substitution reactions, we generated tris-*O*-(*tert*-butyldimethylsilyl)-6-bromopurine ribonucleoside **13** by deprotection of **1a** with NH_3/MeOH at room temperature and silylating the resulting riboside (Table 2). Morpholine reacts readily with **13** in DME at room temperature to give the substitution product **14** in 87% yield (Table 2, entry 1). However, the reaction is slower than that of **1a** (9 h to reach completion compared to 3 h for **1a**), suggesting that the silyl-protecting groups may be adversely affecting the substitution reaction. Weak nucleophiles such as imidazole can also displace bromide from **13** in DMF at 65 °C to give **15** in 93% yield (Table 2, entry 3). Again, no reaction with imidazole was observed in DME (Table 2, entry 2). When the arylamine *p*-toluidine was used with **13**, no substitution product was observed in DMF up to 12 h at 65 °C, whereas the *p*-toluidine substitution product was obtained in 65% yield in 5 h in DMF when **1a** is used as the substrate (Table 2, entry 4; Table 1, entry 14). Thus, direct

Table 3. Substitution Reactions with 6-Bromopurine Ribonucleosides and Oxygen and Sulfur Nucleophiles



1a: R = H
1b: R = NHAc

17a-18a: R = H
18b: R = NHAc

Entry	Product	X	yield
1	**17a**		92%
2	**18a**		82%
3	**18b**		80%

substitution reactions occur more readily when the nucleoside is acetyl-protected as opposed to *tert*-butyldimethylsilyl-protected. How the ribose-protecting group affects the reactivity of the remote C6 position is unknown at this time. The low solubility of **13** in MeOH prevented a test of this solvent for the arylamine substitution reaction with this compound.

S_NAr Reactions of 6-Bromopurine Nucleosides with Oxygen and Sulfur Nucleophiles. To study further the ability of 6-bromo derivatives **1a** and **1b** to undergo nucleophilic displacement, *O*- and *S*-containing nucleophiles were allowed to react with these compounds (Table 3). Thiophenol reacts with **1a** in the presence of DBU in acetonitrile to give **17a** in 92% yield in 8 h at room temperature (Table 3, entry 1). The reaction is selective for C6 with no loss of the acetyl protecting groups. DBU was included in these reactions as a proton acceptor and does not react directly with **1a** or **1b** under these conditions. Phenol also reacts under these conditions with **1a** and **1b** to give **18a** and **18b**, respectively, in high yield. Thus, bromopurine nucleosides **1a** and **1b** are useful precursors to C6-*O* and C6-*S* substituted purines via simple substitution reactions.

Reduction of 6-Bromopurine Nucleosides by Catalytic Hydrogenation. Purine and 2-aminopurine ribonucleosides are important nucleoside analogues with unique enzyme inhibitory and fluorescent properties.[25,26] These compounds have been synthesized previously via the hydrogenolysis of the corresponding 6-chloro derivative,[27,28] as well as via other procedures.[29,16,30] Although the hydrogenolysis of the 6-chloro precursor is typically high yielding, these reactions often require extended reaction times (>24 h) to reach completion. We recently

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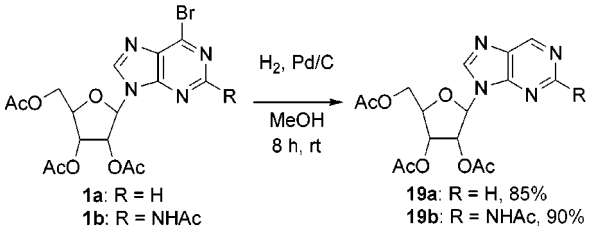
Scheme 3



reported that a copper-mediated coupling reaction to form a 6-trifluoromethylpurine derivative occurred much more readily with the 6-bromo precursor[12] than with the 6-chloro compound.[31] Given this observation, we wished to ascertain the efficacy of Pd-catalyzed hydrogenolysis of **1a** and **1b**. Indeed, we found that excellent yields of purine derivatives **19a** and **19b** were obtained in 8 h in MeOH at room temperature with 2.5 atm of H_2 (Scheme 3).

These results indicate that 6-bromopurine nucleosides are excellent substrates for substitution reactions with *N*-, *O*-, and *S*-containing nucleophiles in polar solvents and are good candidates for transition metal catalyzed reactions, often superior to the 6-chloro alternatives.

Experimental Section

General. Glassware for all reactions was oven dried at 125 °C overnight and cooled in a desiccator prior to use. Reactions were carried out under an atmosphere of dry nitrogen when anhydrous conditions were necessary. All reagents were obtained from commercial sources and were used without further purification unless noted otherwise. Liquid reagents were introduced by oven-dried microsyringes. Tetrahydrofuran was distilled from sodium metal and benzophenone. Thin-layer chromatography (TLC) was performed with Merck silica gel 60 F254 precoated plates, eluting with the solvents indicated. Short- and long-wave visualization was performed with a Mineralight multiband ultraviolet lamp at 254 and 365 nm, respectively. Flash column chromatography was carried out using Mallinckrodt Baker silica gel 150 (60−200 mesh). ^{1}H and ^{13}C nuclear magnetic resonance spectra of pure compounds were acquired at 300 and 75 MHz, respectively. Chemical shifts are reported in parts per million in reference to the solvent peak. The abbreviations s, d, dd, t, td, q, m, and brs stand for singlet, doublet, doublet of doublets, triplet, triplet of doublets, quartet, multiplet, and broad singlet, in that order. High-resolution mass spectra were obtained on a Finnigan Mat 95.

***N*^{2}-2′,3′,5′-Tetraacetyl-2-amino-6-bromonebularine (1b).** The 6-bromo derivative was synthesized according to our modified bromination procedure (NBS 2.1 equiv, HMPT 2.0 equiv, LiBr 2 equiv)[15] with guanosine tetraacetate[17] (540 mg, 1.20 mmol) to afford, after flash column purification (2% MeOH/$CHCl_3$), 461.4 mg (75%) of the product as a pale yellow foam. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.62 (br s, 1H), 8.12 (s, 1H), 6.07 (d, J = 4.5 Hz, 1H), 5.89 (dd, J = 5.7, 4.5 Hz, 1H), 5.78 (t, J = 5.4 Hz, 1H), 4.51−4.35 (m, 3H), 2.40 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.3, 169.5, 169.5, 151.8, 150.5, 143.4, 142.8, 131.0, 87.3, 80.2, 73.3, 70.3, 70.4, 63.1, 25.0, 20.7, 20.4, 20.3. HRFABMS: calcd for $C_{18}H_{21}N_4O_8Br$ $(M + H)^+$ 514.0574, obsd 514.0577.

General Procedure for the Reaction of 6-Bromopurine Derivatives with Aliphatic Amines. The amine was added to a solution of the 6-bromopurine derivative (0.109−0.116 mmol) in the appropriate solvent (5 mL). With the exception of methylamine (40% aqueous solution, 6 equiv), all other amines were present in 2.5 equiv. The reaction mixture was stirred at room temperature until completion by TLC (see Table 1). The reaction mixture was diluted with EtOAc (10 mL) and washed with brine (1 × 15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel using appropriate solvent systems (listed under individual compound headings, vide infra).

2′,3′,5′-Tri-*O*-acetyl-*N*^{6}-(*p*-methylbenzyl)adenosine (2a). Chromatography, 2% MeOH/$CHCl_3$. Yellow syrup (87%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.41 (br s, 1H), 7.87 (s, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 7.8 Hz, 2H), 6.18 (d, J = 5.4 Hz, 1H), 6.08 (br t, J = 4.8 Hz, 1H), 5.92 (t, J = 5.4 Hz, 1H), 5.67 (dd, J = 5.4, 4.5 Hz, 1H), 4.81 (br s, 2H), 4.47−4.41 (m, 2H), 4.36 (dd, J = 12.9, 5.7 Hz, 1H), 2.33 (s, 3H), 2.14 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.4, 169.6, 169.4, 154.7, 153.5, 138.0, 137.2, 135.2, 129.3, 127.7, 86.1, 80.2, 73.1, 70.6, 63.1, 44.3, 21.1, 20.8, 20.5, 20.4. HRFABMS: calcd for $C_{24}H_{28}N_5O_7$ $(M + H)^+$ 498.1989, obsd 498.2007.

***N*-Methyladenosine (3a).** Triturated with EtOAc. White solid (94%). Spectral data agreed with reported values.[32]

2′,3′5′-Tri-*O*-acetyl-*N*^{6},*N*^{6}-(diethyl)adenosine (4a). Chromatography, 2% MeOH/$CHCl_3$. Light yellow syrup (94%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.30 (s, 1H), 7.86 (s, 1H), 6.19 (d, J = 5.7 Hz, 1H), 5.89 (t, J = 5.7 Hz, 1H), 5.63 (dd, J = 5.4, 3.9 Hz, 1H), 4.44−4.39 (m, 2H), 4.34 (dd, J = 12.9, 5.1 Hz, 1H), 3.93 (br s, 4H), 2.12 (s, 6H), 2.05 (s, 3H), 1.26 (t, J = 6.9 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.3, 169.6, 169.4, 153.7, 152.8, 150.3, 136.1, 119.9, 85.6, 80.1, 73.0, 70.4, 63.2, 43.0, 20.8, 20.5, 20.4, 13.4. HRFABMS: calcd for $C_{20}H_{28}N_5O_7$ $(M + H)^+$ 450.1989, obsd 450.1997.

***N*^{2},2′,3′,5′-Tetraacetyl-*N*^{6},*N*^{6}-(diethyl)-2,6-diaminonebularine (4b).** Chromatography, 2% MeOH/$CHCl_3$. Light yellow syrup (90%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.83 (br s, 1H), 7.73 (s, 1H), 6.02 (d, J = 4.8 Hz, 1H), 5.90 (t, J = 5.1 Hz, 1H), 5.69 (t, J = 5.1 Hz, 1H), 4.46−4.37 (m, 2H), 4.35−4.28 (m, 1H), 4.11 (br s, 2H), 3.67 (br s, 2H), 2.54 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 1.24 (t, J = 4.5 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.4, 169.5, 169.3, 153.6, 152.4, 151.0, 135.9, 116.8, 86.2, 79.6, 72.9, 70.4, 63.0, 43.4, 42.6, 24.9, 20.7, 20.5, 20.4, 14.1, 13.0. HREIMS: calcd for $C_{22}H_{30}N_6O_8$ 506.2118, obsd 506.2138.

2′,3′,5′-Tri-*O*-acetyl-*N*^{6}-(methyl)-*N*^{6}-(2-hydroxyethyl)adenosine (5a). Chromatography, 5% MeOH/$CHCl_3$. White foam (87%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.29 (br s, 1H), 7.88 (s, 1H), 6.17 (d, J = 5.7 Hz, 1H), 5.86 (t, J = 5.7 Hz, 1H), 5.61 (dd, J = 5.7, 4.2 Hz, 1H), 4.42−4.37 (m, 2H), 4.33 (dd, J = 12.6, 4.8 Hz, 1H), 4.06 (br s, 2H), 3.92 (t, J = 4.8 Hz, 2H), 3.49 (br s, 3H), 2.11 (s, 3H), 2.10 (s, 3H), 2.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.3, 169.6, 169.3, 155.4, 152.5, 150.3, 136.5, 120.2, 85.8, 80.1, 73.0, 70.6, 63.1, 61.3, 53.5, 29.5 20.7, 20.5, 20.3. HRFABMS: calcd for $C_{19}H_{26}N_5O_8$ $(M + H)^+$ 452.1781, obsd 452.1759.

***N*^{2},2′,3′,5′-Tetraacetyl-*N*^{6}-(methyl)-*N*^{6}-(2-hydroxyethyl)-2,6-diaminonebularine (5b).** Chromatography, 5% MeOH/$CHCl_3$. Light yellow syrup (90%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.08 (br s, 1H), 7.73 (s, 1H), 6.00 (d, J = 4.8 Hz, 1H), 5.89 (t, J = 4.2 Hz, 1H), 5.70 (t, J = 4.2 Hz, 1H), 4.46−4.31 (m, 3H), 4.11 (br s, 2H), 3.90 (br s, 2H), 3.32 (br s, 3H), 2.41 (br s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.5, 169.6, 169.3, 155.4, 152.0, 151.0, 136.3, 117.1, 86.4, 79.7, 72.8, 70.4, 63.0, 61.0, 52.9, 29.6, 25.0, 20.7, 20.5, 20.3. HRFABMS: calcd for $C_{21}H_{29}N_6O_9$ $(M + H)^+$ 509.1996, obsd 509.2002.

2′,3′,5′-Tri-*O*-acetyl-6-(morpholin-4-yl)nebularine (7a). Chromatography, 2% MeOH/$CHCl_3$. Pale yellow foam (99%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.30 (s, 1H), 7.87 (s, 1H), 6.17 (d, J = 5.7 Hz, 1H), 5.87 (t, J = 5.4 Hz, 1H), 5.61 (dd, J = 5.4, 4.5 Hz, 1H), 4.42−4.37 (m, 2H), 4.32 (dd, J = 12.6, 5.1 Hz, 1H), 4.25 (br s, 4H), 3.78 (t, J = 4.8 Hz, 4H), 2.10 (s,

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3H), 2.09 (s, 3H), 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.2, 169.5, 169.3, 153.8, 152.6, 150.6, 136.5, 120.3, 85.8, 80.0, 73.0, 70.6, 66.9, 63.0, 45.4, 20.7, 20.5, 20.3. HREIMS: calcd for $C_{20}H_{25}N_5O_8$ 463.1697, obsd 463.1692.

***N*²,2′,3′,5′-Tetraacetyl-6-(morpholin-4-yl)-2-aminonebularine (7b).** Chromatography, 2% MeOH/$CHCl_3$. Colorless syrup (91%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.91 (s, 1H), 7.75 (s, 1H), 6.02 (d, J = 4.5 Hz, 1H), 5.87 (t, J = 4.8 Hz, 1H), 5.68 (br t, J = 5.1 Hz, 1H), 4.45−4.32 (m, 3H), 4.22 (br s, 4H), 3.78 (br t, J = 4.8 Hz, 4H), 2.46 (br s, 3H), 2.11 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.4, 169.5, 169.3, 153.8, 152.3, 151.4, 136.2, 117.1, 86.4, 79.7, 73.0, 70.4, 66.8, 63.0, 29.6, 25.1, 20.7, 20.5, 20.3. HRFABMS: calcd for $C_{22}H_{29}N_6O_9$ $(M + H)^+$ 521.1996, obsd 521.1988.

General Procedure for the Reaction of 6-Bromopurine Derivatives with Aromatic Amines. The aromatic amine (6 equiv) was added to a solution of the 6-bromopurine derivative (0.109−0.116 mmol) in the appropriate solvent (5 mL). The reaction mixture was heated at 65 °C for 5 h or until completion by TLC (see Table 1). The mixture was concentrated under reduced pressure, the resulting residue dissolved in EtOAc, and the solution was successively washed with 10% aqueous citric acid (1 × 25 mL) and brine (1 × 25 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel using appropriate solvent systems (listed under individual compound headings, vide infra). A different workup procedure was employed when DMF was used as the solvent. The reaction mixture was diluted with EtOAc/hexanes (7:3, 25 mL) and washed successively with water (1 × 15 mL) and brine (1 × 15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel using appropriate solvent systems (listed under individual compound headings, vide infra).

2′,3′,5′-Tri-*O*-acetyl-6-(imidazol-1-yl)nebularine (8a). Chromatography, 2% MeOH/$CHCl_3$. Yellow foam (92%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 9.41 (br s, 1H), 8.78 (s, 1H), 8.36 (br s, 1H), 8.27 (s, 1H), 7.24 (br s, 1H), 6.26 (d, J = 5.1 Hz, 1H), 5.97 (t, J = 5.4 Hz, 1H), 5.66 (t, J = 5.1 Hz, 1H), 4.51−4.46 (m, 1H), 4.39 (dd, J = 12.3, 4.8 Hz, 2H), 2.15 (s, 3H), 2.13 (s, 3H), 2.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.2, 169.5, 169.3, 153.0, 152.5, 145.9, 142.7, 137.6, 130.7, 122.9, 117.3, 86.6, 80.4, 73.1, 70.5, 62.9, 20.7, 20.5, 20.3. HRCIMS: calcd for $C_{19}H_{21}N_6O_7$ $(M + H)^+$ 445.1468, obsd 445.1462.

***N*²-2′,3′,5′-Tetraacetyl-6-(imidazol-1-yl)-2-aminonebularine (8b).** Chromatography, 5% MeOH/$CHCl_3$. Yellow foam (65%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 9.04 (br s, 1H), 8.66 (br s, 1H), 8.28 (br s, 1H), 8.07 (s, 1H), 7.22 (br s, 1H), 6.11 (d, J = 4.5 Hz, 1H), 5.93 (t, J = 4.5 Hz, 1H), 5.80 (br t, J = 5.1 Hz, 1H), 4.53−4.42 (m, 3H), 2.51 (s, 3), 2.15 (s, 3H), 2.10 (s, 3H), 2.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.4, 169.6, 169.5, 154.0, 152.4, 146.0, 142.2, 137.4, 130.8, 119.5, 117.4, 87.2, 80.2, 73.3, 70.5, 63.2, 25.2, 20.8, 20.5, 20.4. HRCIMS: calcd for $C_{21}H_{24}N_7O_8$ $(M + H)^+$ 502.1681, obsd 502.1679.

2′,3′,5′-Tri-*O*-acetyl-*N*⁶-(*p*-tolyl)adenosine (9a). Chromatography, 5% MeOH/$CHCl_3$. Light yellow foam (85%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.49 (s, 1H), 7.98 (s, 1H), 7.81 (br s, 1H), 7.61 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.20 (d, J = 5.4 Hz, 1H), 5.94 (t, J = 5.4 Hz, 1H), 5.68 (t, J = 5.7 Hz, 1H), 4.47−4.42 (m, 2H), 4.37 (dd, J = 12.9, 5.4 Hz, 1H), 2.33 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.3, 169.6, 169.4, 153.3, 152.5, 149.2, 138.7, 135.6, 133.6, 129.5, 120.9, 120.6, 86.1, 80.2, 73.1, 70.6, 63.1, 20.8, 20.7, 20.5, 20.4. HRFABMS: calcd for $C_{23}H_{26}N_5O_7$ $(M + H)^+$ 484.1832, obsd 484.1837.

***N*²-2′,3′,5′-Tetraacetyl-*N*⁶-(*p*-tolyl)-2,6-diaminonebularine (9b).** Chromatography, 2% MeOH/$CHCl_3$. Light yellow syrup (90%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.18 (s, 1H), 7.83 (br s, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 6.02 (d, J = 4.5 Hz, 1H), 5.96 (t, J = 5.1 Hz, 1H), 5.74 (br t, J = 4.8 Hz, 1H), 4.46−4.35 (m, 3H), 2.43 (br s, 3H), 2.33 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.4, 169.5, 169.4, 152.8, 152.4, 149.7, 138.4, 135.4, 133.7, 129.4, 121.0, 117.4, 86.7, 79.8, 73.1, 70.4, 63.1, 25.1, 20.8, 20.7, 20.5, 20.4. HREIMS: calcd for $C_{25}H_{28}N_6O_8$ 540.1969, obsd 540.1948.

2′,3′,5′-Tri-*O*-acetyl-*N*⁶-(*o*-anisyl)adenosine (10a). Chromatography, 2% MeOH/$CHCl_3$. Light yellow foam (91%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.73−8.70 (m, 1H), 8.53 (s, 1H), 8.22 (br s, 1H), 7.99 (s, 1H), 7.04−7.00 (m, 2H), 6.93−6.87 (m, 1H), 6.20 (d, J = 5.4 Hz, 1H), 5.95 (t, J = 5.4 Hz, 1H), 5.68 (dd, J = 5.7, 4.2 Hz, 1H), 4.47−4.41 (m, 2H), 4.36 (dd, J = 13.2, 5.4 Hz, 1H), 3.92 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.3, 169.5, 169.3, 153.0, 152.1, 149.1, 148.4, 138.8, 128.0, 122.9, 121.2, 120.8, 119.9, 109.9, 86.0, 80.2, 73.0, 70.6, 63.0, 55.6, 20.7, 20.5, 20.3. HREIMS: calcd for $C_{23}H_{25}N_5O_8$ 499.1702, obsd 499.1691.

***N*²-2′,3′5′-Tetraacetyl-*N*⁶-(*o*-anisyl)-2,6-diaminonebularine (10b).** Chromatography, 2% MeOH/$CHCl_3$. Light tan foam (95%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.65 (br d, J = 7.8 Hz, 1H), 8.21 (br s, 2H), 7.85 (s, 1H), 7.04−6.97 (m, 2H), 6.90 (dd, J = 7.5, 2.1 Hz, 1H), 6.05 (d, J = 4.8 Hz, 1H), 5.97 (dd, J = 11.7, 4.8 Hz, 1H), 5.74 (t, J = 5.1 Hz, 1H), 4.51−4.36 (m, 3H), 3.90 (s, 3H), 2.42 (s, 3H), 2.13 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.4, 169.5, 169.3, 152.6, 152.1, 149.5, 148.5, 138.3, 127.6, 123.3, 120.7, 120.2, 118.0, 109.9, 86.6, 79.8, 73.0, 70.4, 63.0, 55.6, 25.1, 20.7, 20.5, 20.4. HREIMS: calcd for $C_{25}H_{28}N_6O_9$ 556.1914, obsd 556.1911.

3′,5′-Di-*O*-acetyl-6-bromo-2′-deoxynebularine (11). A purged solution of 3′,5′-di-*O*-acetyl-2′-deoxyadenosine[33] (367 mg, 1.09 mmol), in $CHBr_3$ (10 mL) was heated at 65 °C. To this hot solution was added *t*-BuONO (2.26 g, 21.9 mmol, 20 equiv) and the mixture was stirred at this temperature for 1.5 h. The mixture was purified by flash column chromatography. The column was first eluted with $CHCl_3$ and then with 2% MeOH/$CHCl_3$ to afford 249 mg (57%) of the product as a thick yellow syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.65 (s, 1H), 8.31 (s, 1H), 6.44 (dd, J = 8.1, 6.6 Hz, 1H), 5.41−5.39 (m, 1H), 4.37−4.29 (m, 3H), 2.96 (ddd, J = 14.1, 7.5, 6.3 Hz, 1H), 2.64 (ddd, J = 14.1, 6.0, 2.7 Hz, 1H), 2.09 (s, 3H), 2.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.2, 170.1, 151.8, 149.7, 143.3, 143.2, 134.7, 85.0, 82.7, 74.1, 63.4, 37.4, 20.8, 20.6. HRCIMS: calcd for $C_{14}H_{16}N_4O_5Br$ $(M + H)^+$ 399.0304, obsd 399.0272.

3′,5′-Di-*O*-acetyl-*N*⁶-(*p*-tolyl)-2′-deoxyadenosine (12). Chromatography, 1−2% MeOH/$CHCl_3$. Light yellow syrup (91%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.48 (s, 1H), 7.99 (s, 1H), 7.85 (br s, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.43 (dd, J = 7.8, 6.0 Hz, 1H), 5.44−5.42 (m, 1H), 4.41−4.32 (m, 3H), 2.96 (ddd, J = 14.4, 7.8, 6.6 Hz, 1H), 2.62 (ddd, J = 14.1, 6.0, 2.4 Hz, 1H), 2.33 (s, 3H), 2.12 (s, 3H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.4, 170.2, 153.0, 152.4, 149.0, 138.5, 135.7, 133.5, 129.5, 120.9, 120.7, 84.5, 82.5, 74.5, 63.7, 37.5, 20.8, 20.8, 20.7. HRCIMS: calcd for $C_{21}H_{24}N_5O_5$ $(M + H)^+$ 426.1784, obsd 426.1758.

2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)-6-bromonebularine (13). To a solution of 6-bromopurine ribonucleoside (90 mg, 0.272 mmol) in freshly distilled anhydrous THF (3 mL) was added sequentially imidazole (92.5 mg, 1.36 mmol) and TBDMSCl (135.2 mg, 0.897 mmol) and stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (25 mL) and washed successively with 5% $NaHCO_3$-(aq) (1 × 30 mL) and brine (1 × 30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (30% EtOAc/hexanes) afforded 128.2 mg (70%) of the product as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.68 (s, 1H), 8.54 (s, 1H), 6.11 (d, J = 5.1 Hz, 1H), 4.58 (t, J = 4.8 Hz, 1H), 4.29 (t, J = 3.9 Hz, 1H), 4.15 (q, J = 2.7 Hz, 1H), 4.01 (dd, J = 11.7, 3.6 Hz, 1H), 3.79 (dd, J = 11.4, 2.4 Hz, 1H), 0.95 (s,

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9H), 0.92 (s, 9H), 0.77 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), −0.05 (s, 3H), −0.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 151.8, 150.2, 143.9, 143.0, 134.6, 88.5, 85.7, 76.3, 71.8, 62.4, 26.1, 25.8, 25.6, 18.5, 18.0, 17.8, −4.4, −4.7, −4.8, −5.1, −5.3, −5.4. HRFABMS: calcd for $C_{28}H_{54}N_4O_4BrSi_3$ $(M + H)^+$ 673.2636, obsd 673.2644.

2′,3′,5′,-Tris-*O*-(*t*-butyldimethylsilyl)-6-(morpholin-4-yl)nebularine (14). Chromatography, 2% MeOH/$CHCl_3$. Thick syrup (87%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.32 (s, 1H), 8.02 (s, 1H), 6.02 (d, J = 5.4 Hz, 1H), 4.71 (t, J = 5.1 Hz, 1H), 4.30 (t, J = 3.6 Hz, 4H), 4.10 (q, J = 3.3 Hz, 1H), 4.01 (dd, J = 11.1, 4.2 Hz, 1H), 3.82 (t, J = 4.5 Hz, 4H), 3.76 (dd, J = 11.4, 3.0 Hz, 1H), 0.94 (s, 9H), 0.92 (s, 9H), 0.79 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), −0.06 (s, 3H), −0.23 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 153.9, 152.2, 150.9, 137.7, 120.5, 88.1, 85.4, 75.4, 72.1, 67.0, 62.6, 45.6, 26.1, 25.8, 25.7, 18.5, 18.1, 17.8, −4.4, −4.7, −4.7, −5.0, −5.4, −5.4. HRCIMS: calcd for $C_{32}H_{62}N_5O_5Si_3$ $(M + H)^+$ 680.4043, obsd 680.4081.

2′,3′,5′-Tris-*O*-(*t*-butyldimethylsilyl)-6-(imidazol-1-yl)-nebularine (15). Chromatography, 1% MeOH/$CHCl_3$. Light yellow syrup (93%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 9.19 (br s, 1H), 8.77 (s, 1H), 8.54 (s, 1H), 8.41 (br s, 1H), 7.25 (br s, 1H), 6.15 (d, J = 4.8 Hz, 1H), 4.62 (t, J = 4.8 Hz, 1H), 4.33 (t, J = 4.2 Hz, 1H), 4.17 (dd, J = 6.3, 3.6 Hz, 1H), 4.04 (dd, J = 11.4, 3.6 Hz, 1H), 3.81 (dd, J = 11.4, 2.4 Hz, 1H), 0.97 (s, 9H), 0.93 (s, 9H), 0.81 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H), 0.10 (s, 3H), 0.10 (s, 3H), −0.02 (s, 3H), −0.21 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 153.3, 152.1, 145.6, 143.4, 137.7, 130.6, 122.9, 117.4, 88.5, 85.5, 76.2, 71.7, 62.3, 26.1, 25.8, 25.6, 18.5, 18.0, 17.8, −4.4, −4.7, −4.7, −5.0, −5.4, −5.4. HRCIMS: calcd for $C_{31}H_{57}N_6O_4Si_3$ $(M + H)^+$ 661.3735, obsd 661.3785.

General Procedure for the Reaction of 6-Bromopurine Derivatives with *O*- and *S*-Nucleophiles. To a solution of the 6-bromopurine derivative (0.164−0.109 mmol) in anhydrous acetonitrile (7 mL) was added sequentially DBU (1.5 equiv) and the nucleophile (5 equiv, see Table 3). The reaction mixture was stirred at room temperature for 8 h. It was then concentrated and the resulting residue dissolved in EtOAc (20 mL). The organic layer in each case was successively washed with 5% NaOH(aq) (1 × 25 mL) and brine (1 × 25 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel using appropriate solvent systems (listed under individual compound headings, vide infra).

2′,3′,5′-Tri-*O*-acetyl-*S*^{6}-(phenyl)thioinosine (17a). Chromatography, 2% MeOH/$CHCl_3$. Pale yellow foam (92%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.61 (s, 1H), 8.16 (s, 1H), 7.66−7.63 (m, 2H), 7.48−7.45 (m, 3H), 6.21 (d, J = 5.4 Hz, 1H), 5.95 (t, J = 5.4 Hz, 1H), 5.65 (t, J = 5.4 Hz, 1H), 4.47−4.42 (m, 2H), 4.36 (dd, J = 12.9, 5.1 Hz, 1H), 2.13 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.2, 169.5, 169.3, 161.4, 152.5, 148.4, 141.3, 135.6, 131.2, 129.6, 129.3, 126.8, 86.4, 80.3, 73.0, 70.5, 62.9, 20.7, 20.5, 20.3. HRFABMS: calcd for $C_{22}H_{23}N_4O_7S$ $(M + H)^+$ 487.12875, obsd 487.13064.

2′,3′,5′-Tri-*O*-acetyl-*O*^{6}-(phenyl)inosine (18a). Chromatography, 2% MeOH/$CHCl_3$. White foam (82%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.51 (s, 1H), 8.18 (s, 1H), 7.48−7.43 (m, 2H), 7.32−7.25 (m, 3H), 6.24 (d, J = 5.1 Hz, 1H), 5.98 (t, J = 5.4 Hz, 1H), 5.67 (t, J = 5.1 Hz, 1H), 4.49−4.44 (m, 2H), 4.37 (dd, J = 12.6, 5.1 Hz, 1H), 2.15 (s, 3H), 2.13 (s, 3H), 2.09 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.3, 169.5, 169.3, 160.4, 152.5, 152.4, 152.2, 141.4, 129.6, 125.9, 122.3, 121.8, 86.6, 80.3, 73.1, 70.5, 62.9, 20.7, 20.5, 20.4. HR-FABMS: calcd for $C_{22}H_{23}N_4O_8$ $(M + H)^+$ 471.1516, obsd 471.1499.

***N*^{2}-2′,3′,5′-Tetraacetyl-*O*^{6}-(phenyl)guanosine (18b).** Chromatography, 2% MeOH/$CHCl_3$. White foam (80%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.97 (br s, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.28 (t, J = 7.2 Hz, 1H), 7.21 (t, J = 7.5 Hz, 2H), 6.87 (dd, J = 14.7, 7.5 Hz, 1H), 6.10 (d, J = 4.2 Hz, 1H), 5.92 (t, J = 5.1 Hz, 1H), 5.72 (t, J = 5.1 Hz, 1H), 4.51−4.44 (m, 2H), 4.38 (dd, J = 13.2, 6.0 Hz, 1H), 2.14 (s, 3H), 2.12 (s, 3H), 2.10 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.4, 169.5, 169.4, 156.0, 152.2, 152.1, 129.5, 125.9, 121.9, 120.2, 115.3, 87.0, 80.0, 73.2, 70.4, 63.0, 24.8, 20.7, 20.5, 20.4. HRCIMS: calcd for $C_{24}H_{25}N_5O_9$ 527.1652, obsd 527.1667.

General Procedure for the Catalytic Dehalogenation of 6-Bromopurine Derivatives. The 6-bromopurine derivative (1.94−2.19 mmol) was dissolved in MeOH (30 mL), and 10% Pd-C (0.050 g) and anhydrous NaOAc (2 equiv) were added to the mixture. The flask was evacuated and refilled with hydrogen gas. The mixture was shaken in a Parr apparatus for 8 h and under 2.5 atm of pressure. The mixture was filtered through Celite, and the residue was washed with MeOH. The filtrate was concentrated under reduced pressure. The residue was redissolved in EtOAc (15 mL) and washed with brine (1 × 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel using appropriate solvent systems (listed under individual compound headings, vide infra).

2′,3′,5′-Tri-*O*-acetyl-nebularine (19a). Chromatography, 2% MeOH/$CHCl_3$. Pale yellow foam (85%). Spectral data agreed with reported values.[16]

***N*^{2}-2′,3′,5′-Tetraacetyl-2-aminonebularine (19b).** Chromatography, 5% MeOH/$CHCl_3$. Pale yellow syrup (96%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 9.10 (br s, 1H), 8.92 (s, 1H), 8.09 (s, 1H), 6.09 (d, J = 3.9 Hz, 1H), 5.96 (t, J = 4.5 Hz, 1H), 5.83 (br s, 1H), 4.54−4.37 (m, 3H), 2.43 (s, 3H), 2.14 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.4, 169.6, 169.5, 152.9, 151.5, 149.9, 143.0, 131.1, 86.9, 80.1, 73.3, 70.5, 63.2, 25.0, 20.7, 20.5, 20.4. HRFABMS: calcd for $C_{18}H_{22}N_5O_8$ $(M + H)^+$ 436.1468, obsd 436.1477.

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Supporting Information Available: ^{1}H NMR spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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