A General Approach to N^6,C5'-Difunctionalization of Adenosine

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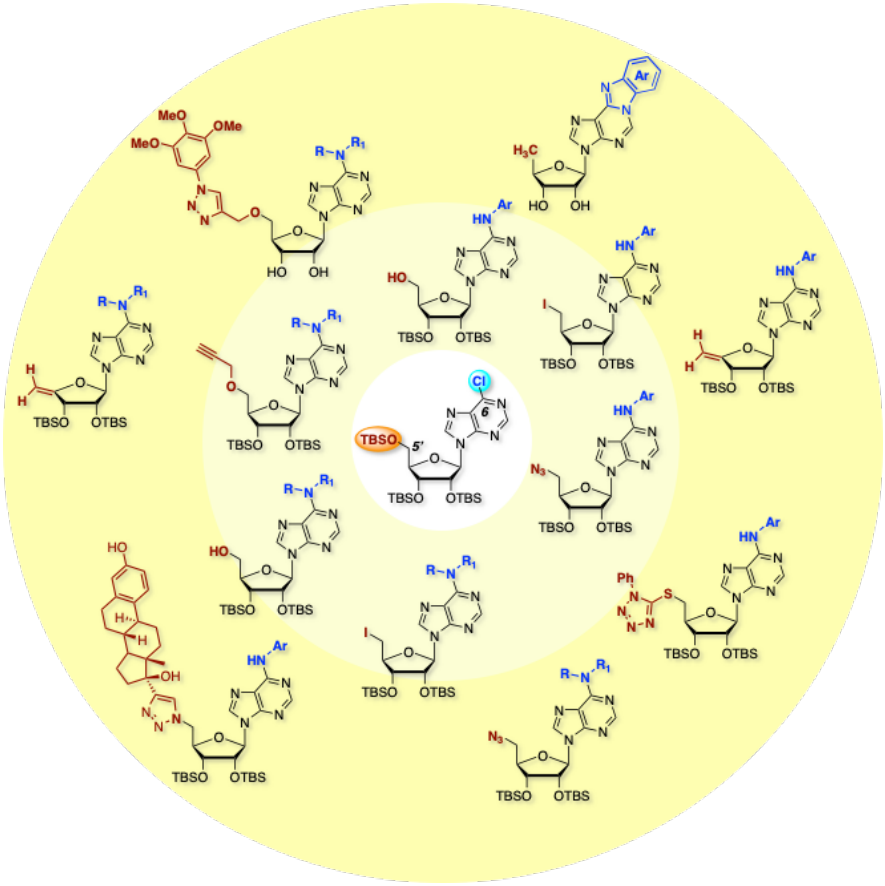


■ **ABSTRACT:** Among the C6-halo purine ribonucleosides, the readily accessible 6-chloro derivative has been known to undergo slow S_NAr reactions with amines, particularly aryl amines. In this work, we show that in 0.1 M AcOH in EtOH, aryl amines react quite efficiently at the C6-position of 2',3',5'-tri-*O*-(*t*-BuMe_2Si)-protected 6-chloropurine riboside (6-ClP-riboside), with concomitant cleavage of the 5'-silyl group. These two-step processes proceeded in generally good yields, and notably, reactions in the absence of AcOH were much slower and/or lower yielding. Corresponding reactions of 2',3',5'-tri-*O*-(*t*-BuMe_2Si)-protected 6-ClP-riboside with alkyl

amines proceeded well but without desilylation at the primary hydroxyl terminus. These differences are likely due to the acidities of the ammonium hydrochlorides formed in these reactions, and the role of AcOH was not desilylation but possibly only purine activation. With 50% aqueous TFA in THF at 0 °C, cleavage of the 5'-silyl group from 2',3',5'-tri-*O*-(*t*-BuMe_2Si)-protected N^6-alkyl adenosine derivatives and from 6-ClP-riboside was readily achieved. Reactions of the 5'-deprotected 6-ClP-riboside with alkyl amines proceeded in high yields and under mild conditions. Because these complementary methodologies yielded N^6-aryl and alkyl adenosine derivatives containing a free 5'-hydroxyl group, a variety of product functionalizations was undertaken to yield N^6,C5'-doubly modified nucleoside analogues.

INTRODUCTION

The biological centrality of ribo and 2'-deoxyribonucleosides in all living systems naturally lends great value to the development of un-natural nucleoside analogues for applications as probes in understanding and modulating cellular function and, in medicine, as anticancer and antiviral agents.[1–4] Among the natural nucleosides, adenosine and its 2'-deoxy analogue offer three positions on the base moiety for modification: the exocyclic N6, C2, and C8. A classical method for introduction of aryl and alkyl groups at the N6 position is via S_NAr reactions of electrophilic nucleoside derivatives with aryl and alkyl amines. Typically, the commercially available and readily accessed 6-chloropurine riboside (6-ClP-riboside)[5–7] serves as a precursor for reactions with a wide range of nucleophiles and, in the context of the present work, for aryl and alkyl amines.[8] Generally, the conditions used for these transformations are variations of those originally described,[9,10] involving reaction of 6-ClP-riboside or the 2',3',5'-tri-*O*-acetyl-protected version with the amine, in an alcohol solvent (e.g. EtOH, MeOH, PrOH) or DMF, either with or without a base (e.g. $CaCO_3$, $BaCO_3$, Et_3N, iPr_2NEt, etc.). More recently, microwave-induced amination in water has also been described.[11]

Use of 6-bromopurine riboside (6-BrP-riboside) for such reactions is rare, but specifically, its 2',3',5'-tri-*O*-acetyl derivative readily reacted with alkyl amines at room temperature in 1,2-DME.[12] On the other hand, reaction with imidazole proceeded in DMF, and those with *p*-toluidine and *o*-anisidine proceeded in MeOH, EtOH, and DMF, at 65 °C. Reactions in an alcohol medium generally gave higher yields than in DMF. Most notably, and relevant to the present work,

reaction of 2',3',5'-tri-*O*-(*t*-BuMe$_2$Si)-protected 6-BrP-riboside with *p*-toluidine in DMF at 65 °C did not proceed, and the reaction between these partners could not be tested in MeOH due to the low solubility of the silyl-protected nucleoside.[12]

In comparison to the reactions of 6-ClP-riboside and alkyl amines, those of 6-iodopurine riboside (6-IP-riboside) are also fewer and again, in these cases the 2',3',5'-*O*-triacetyl derivative has been utilized.[13,14] There are only two examples of reactions of 6-IP-riboside with an aryl amine (aniline); one involved the 2',3',5'-tri-*O*-*p*-toluoyl derivative and the other the 2',3',5'-tri-*O*-(2,4,6-trimethylbenzoyl) equivalent, and both were conducted in MeCN at 70 °C.[15,16]

For completeness, it would be relevant to mention other approaches for the introduction of substituents at the N^6 position of adenosine. Alkylation of N^6,2',3',5'-tetra-*O*-acetyladenosine with alcohols either under Mitsunobu conditions or with alkyl bromides and a base (K_2CO_3 or DBU), followed by deprotection, yielded the *N*^{6}-alkylated products.[17–19] We[20–22] and others[23] have developed a method for amide-group activation in purine nucleosides using (benzotriazolyl-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate, followed by S_NAr reactions with amines (and other nucleophiles). In order to introduce aryl moieties at the N6 position of adenine nucleosides, we have developed Pd-catalyzed reactions of silyl- and acetyl-protected 6-ClP- and 6-BrP-riboside as well as direct *N*-arylation.[21,24,25]

This establishes the background for our efforts described herein, important considerations being: (a) reaction of 6-ClP-riboside with 40% aq. $MeNH_2$ required heating at 80 °C in a Parr bomb for 16 h,[26] (b) displacement of a C6-chloride from 2',3',5'-tri-*O*-(*t*-BuMe$_2$Si)-protected 6-chloro-8-iodopurine riboside required deprotonated indoline and aniline,[27] and (c) the reported failure of the silyl-protected 6-BrP-riboside in a reaction with *p*-toluidine.[12] In this work, we have found that under appropriate conditions, 2',3',5'-tri-*O*-(*t*-BuMe$_2$Si)-protected 6-ClP-riboside undergoes S_NAr reactions with aryl amines with concomitant desilylation at the C5'. Reactions of the alkyl amines were also evaluated under these conditions but desilylation was not observed. We ascertained that removal of the 5'-silyl group from 2',3',5'-tri-*O*-(*t*-BuMe$_2$Si)-protected *N*^{6}-alkyl adenosine analogues as well as 6-ClP-riboside can be readily conducted under a separate set of conditions. The partially desilylated 6-ClP-riboside readily reacts with alkyl amines under relatively mild conditions to give the corresponding adenosine analogues. Because these

complementary approaches provide products with a free 5'-hydroxyl group, ready functionalization at the C5' positions of both N^6-aryl and alkyl adenosine derivatives could be accomplished. Examples of some biologically important N^6,C5'-doubly functionalized adenosine derivatives are shown in Figure 1.[28–31]

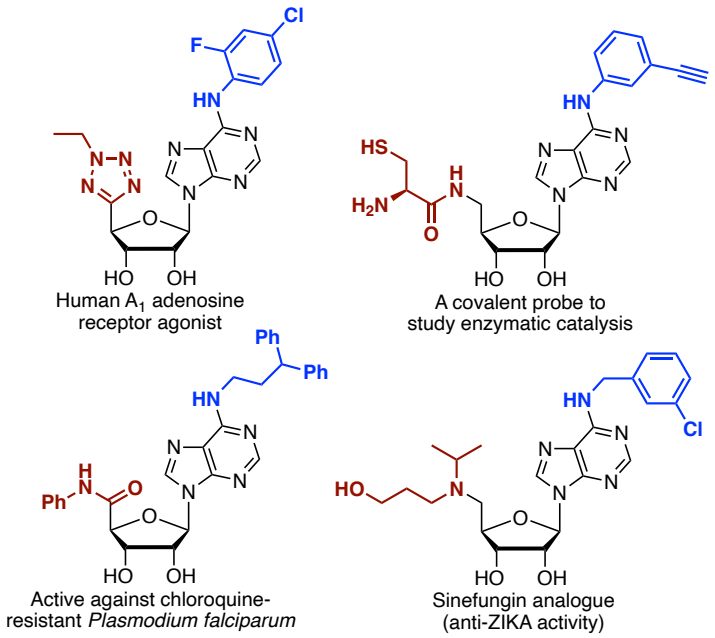


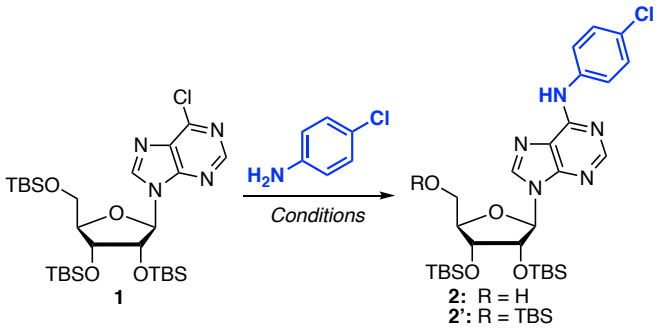
Figure 1. Examples of N^6,C5'-doubly functionalized adenosine derivatives bearing N^6-aryl and -alkyl groups.

■ RESULTS AND DISCUSSION

Prior work has established the order of reactivity of halo purine ribosides with a primary alkyl amine (10 equiv of *n*-butylamine in MeCN, at 25 °C) to be F >> Br > Cl > I, whereas with an aryl amine (5 equiv of aniline in MeCN, at 70 °C) the order is I > Br > Cl >> F.[16] The latter is particularly quite different from the well-established "element effect" in S_NAr reactions of activated systems such as 1-halo 2,4-dinitrobenzenes, where the nucleofuge order is F > Br ≈ Cl > I with piperidine.[32,33]

From these data, it became evident that accomplishing successful S_NAr reactions with the readily accessible 6-ClP-riboside would represent an important milestone. Our investigations commenced with an evaluation of conditions using 2',3',5'-tri-*O*-(*t*-BuMe_2Si)-protected 6-ClP-riboside (**1**) and *p*-chloroaniline (NH pK_a = 29.4 versus aniline pK_a = 30.7[34]). These data are shown in Table 1.

Table 1. Reactions of 2',3',5'-Tri-*O*-(*t*-BuMe$_2$Si)-protected 6-ClP-riboside and *p*-Chloroaniline[a]



entry	solvent	temp	time	result[b]
1	EtOH	65–70 °C	23 h	**2:** 65%
2	MeOH	65–70 °C	19 h	**2:** 66%
3	MeCN	65–70 °C	24 h	**2:** 55%
4	DMF	65–70 °C	47 h	na[c]
5	CF_3CH_2OH	65–70 °C	36 h	**2:** 50%, **2':** 39%
6	$(CF_3)_2CHOH$	65–70 °C	40 h	**2:** 24%,[d] **2':** 32%
7	EtOH	85–90 °C	9 h	**2:** 69%
8	EtOH/AcOH[e]	85–90 °C	4 h	**2:** 68%
9	CF_3CH_2OH/AcOH[e]	85–90 °C	17 h	**2:** 42%

[a] Reactions were conducted with 0.083 mmol of compound **1** and 1.2 equiv of *p*-chloroaniline in 0.83 mL of solvent, at the specified temperature range in a pre-equilibrated sand bath. [b] When reported, yield is of isolated and purified product. [c] Multiple spots were observed by TLC. [d] The product was contaminated with a trace amount of *p*-chloroaniline. By ^{1}H NMR the amount of product **2** was estimated as 21%. [e] AcOH (0.1 M) in EtOH or CF_3CH_2OH was used.

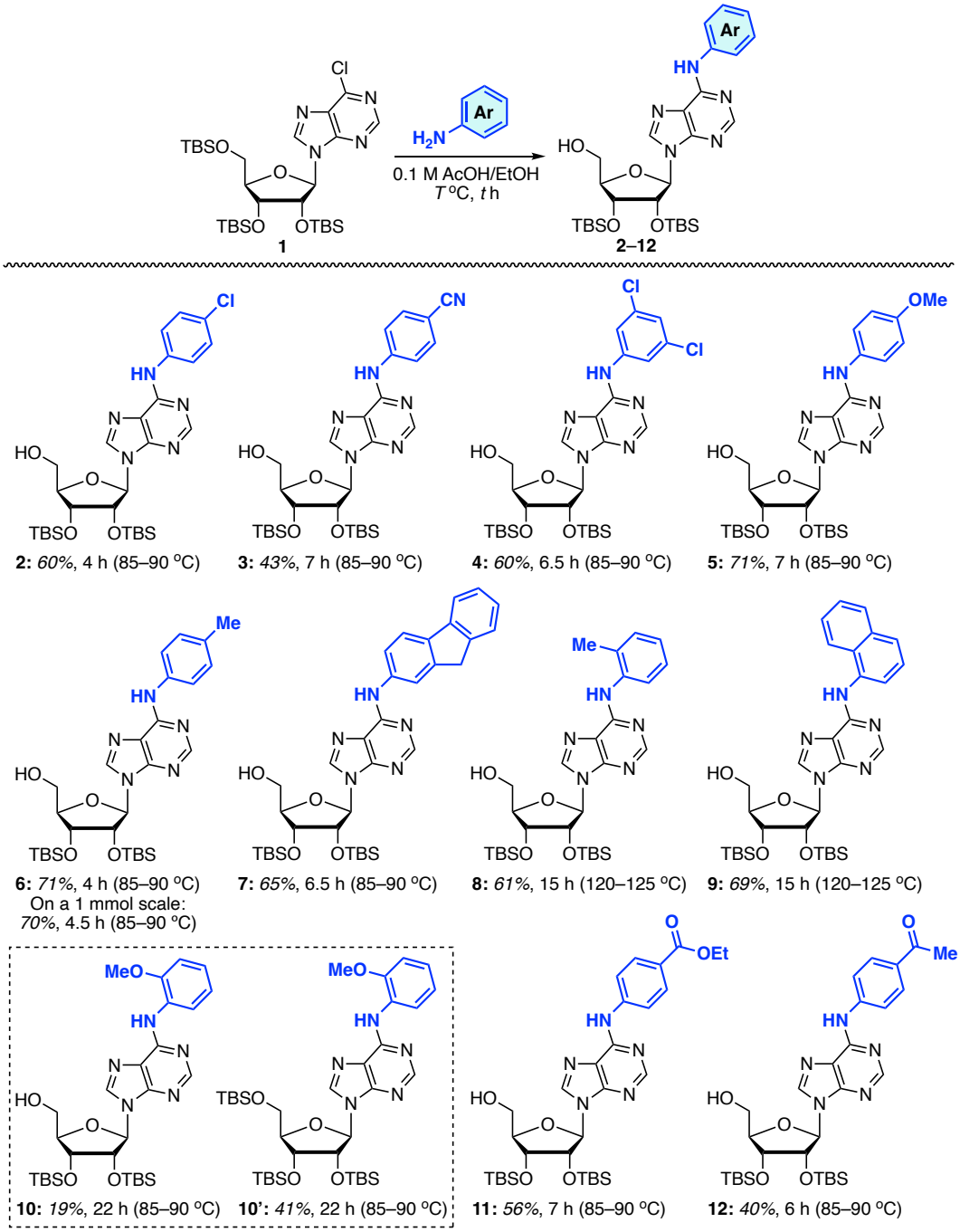
From Table 1, it becomes evident that reactions in EtOH and MeOH gave comparable yields; MeCN was less effective, whereas DMF was ineffective (entries 1–4). However, the successful reactions took between 19 and 24 h to attain completion. Most interestingly, the 5'-silyl group had been cleaved in the product obtained from each successful reaction, a factor that can be leveraged to great utility (*vide infra*). In recent years, the acidity of a fluorinated solvent such as CF_3CH_2OH has been used in combination with a strong acid such as CF_3CO_2H to enhance substitution reactions at the C2-position of purines with aryl amines (see discussion below on the influence of acid on S_NAr reactions with aryl amines).[35,36] Thus, a reaction was attempted in CF_3CH_2OH but this led to the isolation of a significant amount of the trisilyl product **2'** (entry 5). Use of $(CF_3)_2CHOH$ also returned a significant amount of trisilyl **2'** (entry 6). A reaction was then performed in EtOH at an increased temperature of 85–90 °C (entry 7). As anticipated, the reaction

time was reduced from 23 to 9 h, while the yield of the desilylated product remained comparable (compare entry 7 to 1).

For over 70 years it has been known that reaction of 2-chloro-4,6-diamino-*s*-triazine and aniline is abrogated by stoichiometric base, but reaction occurred with a lowered amount of base with an induction period.[37] More interestingly, addition of just 0.01 equiv of HCl doubled the rate as compared to a reaction in water (0.1 equiv quadrupled the rate), and the reactions of certain other halogenated heterocycles in acidic media have also been shown.[37–39] The rationale for these observations is the protonation of the ring nitrogen, thereby increasing the reactivity of the heterocycle in the S_NAr process with aryl amines. These results are connected to the lag times observed in the reactions of 2',3',5'-tri-*O*-(2,4,6-trimethylbenzoyl) 6-halopurine ribosides with aryl amines, and where the lag times disappeared when reactions were conducted in the presence of CF_3CO_2H.[16] *However, even in the presence of CF_3CO_2H, the 6-ClP-ribose derivative was slowest to react with 5 equiv of aniline.*[16] Thus, we conducted a reaction of chloronucleoside **1** and *p*-chloroaniline in 0.1 M AcOH in EtOH and to our surprise the reaction time was reduced from 9 h to 4 h, without loss of yield (compare entry 8 to 7). It should be noted that reactions herein were conducted with just 1.2 equiv of the aniline. We chose AcOH over CF_3CO_2H because compound **1** is protected with silyl and not acyl groups. Acyl groups, in contrast to silyl groups, are electron-withdrawing and generally contribute to nucleoside stability under conditions that can lead to deglycosylation. Finally, we attempted a reaction in 0.1 M AcOH in CF_3CH_2OH (entry 9). However, this led to a lowered yield of aryl product **2** as compared to AcOH in EtOH (entry 8). Having identified a set of conditions for successful S_NAr reaction between chloronucleoside **1** and *p*-chloroaniline that gave N^6-aryl 5'-desilyl adenosine derivative **2**, we next tested the reaction of the highly electron-deficient *p*-cyanoaniline (NH pK_a = 25.3[34]). With 1.2 equiv of this amine in just EtOH at 85–90 °C, no product was observed over 22 h, contrasting with the result obtained using *p*-chloroaniline. At 105 °C, a 22% yield of the N^6-aryl 5'-desilyl adenosine derivative **3** was obtained after a 22 h reaction time. However, in 0.1 M AcOH in EtOH a 43% yield of **3** was obtained in 7 h at a reaction temperature of 85–90 °C. Rather than AcOH, Et_3N•HCl and *p*-TsOH were tested as additives, and the amount of amine was varied from 1.2 to 1.5 equiv, with reaction temperatures of 85–90 to 100–105 °C. The product yields in these experiments were inferior,

ranging from ~5–30%. A reaction using TMSCl in EtOH, to generate HCl *in situ*, did not provide any product (at 65–70 °C, over 7 h). Therefore, using 0.1 M AcOH in EtOH, several N^6-aryl 5'-desilyl adenosine derivatives (**2**–**12**) were prepared (Scheme 1).

Scheme 1. Products from the S_NAr Reaction of Several Aryl amines with 2',3',5'-Tri-*O*-(*t*-$BuMe_2Si$)-protected 6-ClP-riboside (1) on a 0.1 mmol Scale



Results from the reactions in Scheme 1 provide some interesting insight. In comparison to *p*-chloroaniline, reaction with 3,5-dichloroaniline also proceeded quite efficiently. Product yields from reactions of *p*-anisidine and *p*-toluidine were somewhat higher than that obtained with *p*-chloroaniline (a reaction of 1 mmol of nucleoside **1** with 1.3 equiv of *p*-toluidine, at 0.09 M in 0.1 M AcOH/EtOH, gave a high 70% product yield). 2-Aminofluorene, *o*-toluidine, and 1-naphthylamine reacted well, although the latter two required longer reaction times and increased temperature. This may be due to the steric hindrance posed by the *o*-methyl group and the *peri* hydrogen atom, respectively, in the two amines. The reaction of *o*-anisidine proved to be interesting and different from the *para* isomer. Not only did the reaction require a much longer time but also the desilylated product (shown in the dotted box) was the minor component. Although steric hindrance could be a factor in the slow reaction, it is unclear why desilylation was incomplete in this case. As could be anticipated, lower yields (40–60%) were obtained with the highly electron-deficient anilines (*p*-CN $\sigma_p = 0.66$, *p*-CO_2Et $\sigma_p = 0.45$, *p*-COMe $\sigma_p = 0.50$[40]). On the other hand, with anilines that bore modestly electron-withdrawing and electron-donating groups (*p*-Cl $\sigma_p = 0.23$, *p*-OMe $\sigma_p = -0.27$, *p*-Me $\sigma_p = -0.17$[40]) the yields were superior (60–70%).

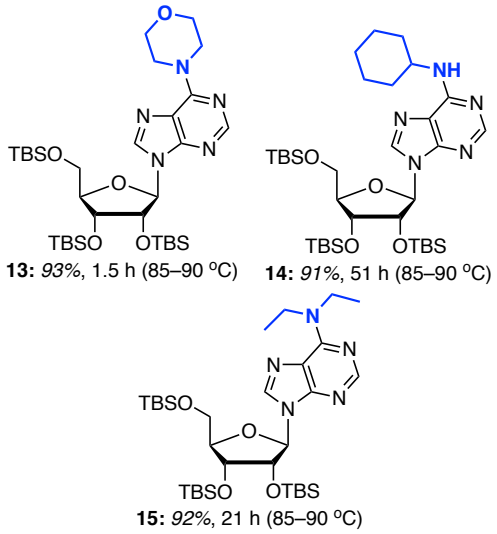


Figure 2. Products from reactions of 2',3',5'-tri-*O*-(*t*-BuMe_2Si)-protected 6-ClP-riboside (**1**) with three alkyl amines.

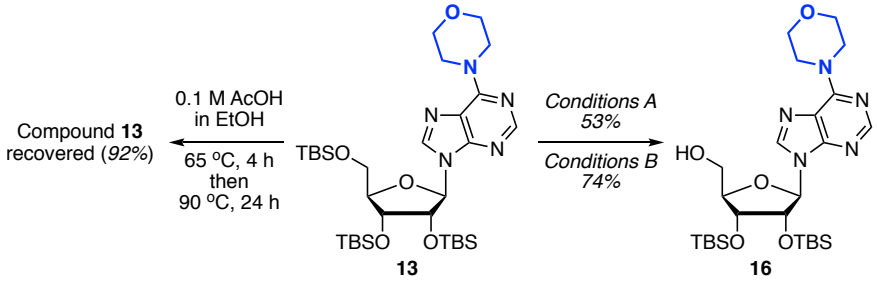
Having completed reactions with aryl amines, we then focused on analogous transformations, i.e., N^6-modification and 5'-desilylation, via reactions involving alkyl amines. In parallel to the reactions of the aryl amines, in an attempt to promote 5'-desilylation along with S_NAr

displacement, initial experiments were conducted in 0.1 M AcOH in EtOH at 85–90 °C. Three reactions were performed with 2 equiv each of morpholine, cyclohexylamine, and diethylamine (we anticipated 1 equiv to be irreversibly consumed in salt formation). All reactions proceeded well, although the reaction of cyclohexylamine took 51 h, and 3% of precursor **1** was reisolated in this case. The products, yields, and reaction times are shown in Figure 2, but notably, the 5'-silyl group remained intact in each case.

The reactions of 2',3',5'-tri-*O*-(2,4,6-trimethylbenzoyl) 6-halopurine ribosides with aniline were autocatalyzed by the HX produced in the reaction.[16] Because aniline is weakly basic, it is anticipated that anilinium salts can liberate free aniline as nucleophile and HX,[38] and the latter can activate the purine for the S_NAr reaction by protonation of a ring nitrogen atom. This also parallels the reaction of 2',3',5'-tri-*O*-acetyl-8-bromoguanosine with aniline/anilinium bromide.[41] In this case, protonation of the imidazolyl N^7-atom is proposed to promote the S_NAr displacement and also a subsequent depurination by the same process.[41]

Thus, in the reactions with aryl amines described above, the HCl released is not only anticipated to activate the purine for the S_NAr process but also likely responsible for 5' desilylation. In contrast, in reactions with the more basic alkyl amines, it is conceivable that HCl does not become available for the desilylation (pK_a of the protonated forms of Et_2NH = 10.98, morpholine = 8.36, and piperidine = 11.22,[42] in comparison to the pK_a value of 5.29 of protonated *p*-anisidine, which was the most basic aniline studied here[43]). To test these, we subjected C6-morpholinyl adenosine derivative **13** to several conditions (Scheme 2).

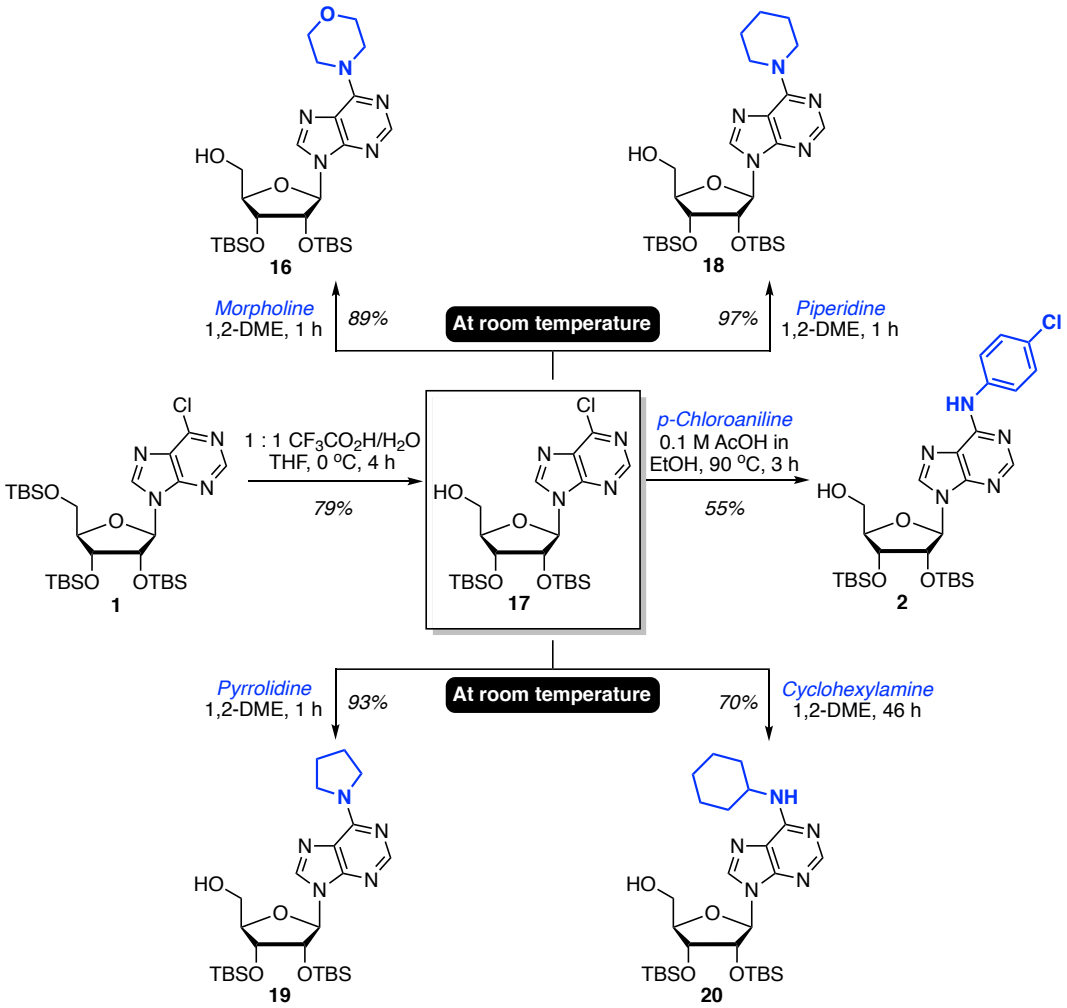
Scheme 2. Evaluations of the 5'-Desilylation of C6-Morpholinyl Purine Nucleoside 13



The first reaction of morpholinyl product **13** in 0.1 M AcOH (pK_a = 4.75) in EtOH did not result in desilylation, either at 65–70 °C (4 h) or at 85–90 °C (an additional 24 h). As we suspected, AcOH was not responsible for the observed desilylations. Next, a reaction of compound **13** and *p*-

chloroanilium chloride (pK_a = 3.98[43]) was conducted in EtOH at 65–70 °C (*Conditions A*). This reaction gave a 53% yield of desilylated product **16** in 30 h, supporting our hypothesis that the anilinium chloride is responsible for cleavage of the silyl group.

Scheme 3. Cleavage of the 5'-*O*-TBS Group from 2',3',5'-Tri-*O*-(*t*-BuMe$_2$Si)-protected 6-ClP-riboside (1) and Reactions with *p*-Chloroaniline, Morpholine, Piperidine, Pyrrolidine, and Cyclohexylamine



There are two reports for desilylation at the 5'-terminus of persilylated nucleosides. One of these methods involves the use of CF_3CO_2H/H_2O in THF at 0 °C, and the other utilizes methanolic phosphomolybdic acid,[44,45] and we decided to evaluate a modification of the first method.[46] Exposure of morpholinyl compound **13** to 1:1 CF_3CO_2H/H_2O in THF at 0 °C for 4 h (*Conditions B*) gave a good 74% yield of the 5'-desilylated product **16**. On the basis of these observations, we considered the direct 5'-desilylation of 2',3',5'-tri-*O*-(*t*-BuMe$_2$Si) 6-ClP-riboside (**1**), followed by

S_NAr displacements (Scheme 3). This would then put us in a position to conduct dual functionalization at the C6- and 5'-positions and product diversification. As shown in Scheme 3, after efficient desilylation of compound **1**, we first evaluated the reaction of product **17** with *p*-chloroaniline. This reaction proceeded to give a 55% yield of the N^6-arylated adenosine derivative **2**. Reactions with 2.5 equiv morpholine, piperidine, and pyrrolidine proceeded very rapidly at room temperature in 1,2-DME, to yield the respective aminated products **16**, **18**, and **19** in high yields (89–97% in 1 h). Although much slower (46 h), even the reaction with cyclohexylamine proceeded at room temperature, resulting in a 70% yield of product **20** (6% of unreacted precursor **17** was reisolated, 74% yield of **20** based upon the recovered precursor).

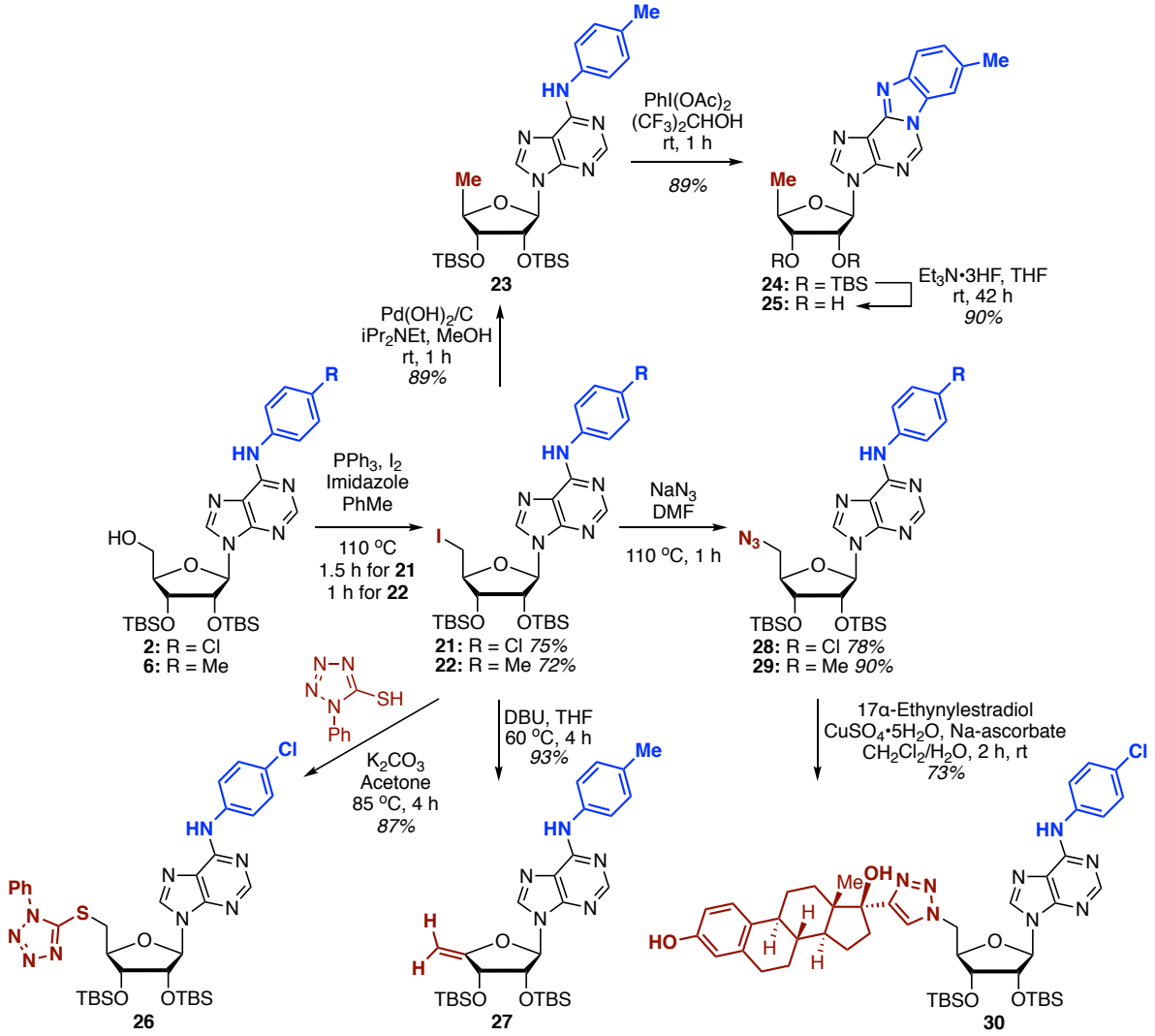
In the context of reactions with nucleophilic alkyl amines, use of Pd catalysis (at room temperature, 4 h),[47a] Cu catalysts (at 30 °C, 22 h),[47b] and protonative heterocycle activation by fluorinated solvents (at 50 °C, 12 h)[48] has been reported for access to fully deprotected versions of **16**, **18**, and **19**. However, such approaches may not be necessary given the high proclivity of compound **17** towards direct S_NAr reactions even in a solvent of a low dielectric constant such as 1,2-DME ($\varepsilon \approx 7$). Some of the previously reported reactivity under catalysis conditions may occur via a direct S_NAr process.

With the N^6-modification and 5'-desilylation studies completed, we turned our focus to utilizing the released 5'-hydroxyl group for diverse modifications at the C5'. The reactions with N^6-aryl adenosine derivatives are shown in Scheme 4. Compounds **2** and **6** were initially converted to the 5'-iodo derivatives **21** and **22** (75 and 72% yield, respectively), by reaction with PPh_3/I_2 and imidazole in PhMe at 110 °C.[49] Compound **22** was reduced to the 4'-methyl derivative **23** in a high 89% yield.[50] Under conditions we have recently reported,[21,51] exposure of N^6-aryl adenosine derivative **23** to $PhI(OAc)_2$ in $(CF_3)_2CHOH$ at room temperature gave the benzimidazopurine nucleoside analogue **24** in 89% yield. This compound was smoothly desilylated with $Et_3N{\bullet}3HF$ in THF to give compound **25** in an excellent 90% yield.

Iodo intermediate **21** was readily converted to the S-adenosylhomocysteine analogue **26** by reaction with 1-phenyl-1*H*-tetrazole-5-thiol. Such S-aryl adenosine derivatives have been studied as inhibitors of cell transformation and viral replication[52] and as substrates of human 5'-deoxy-5'-methylthioadenosine phosphorylase, which is involved in the purine salvage pathway.[53]

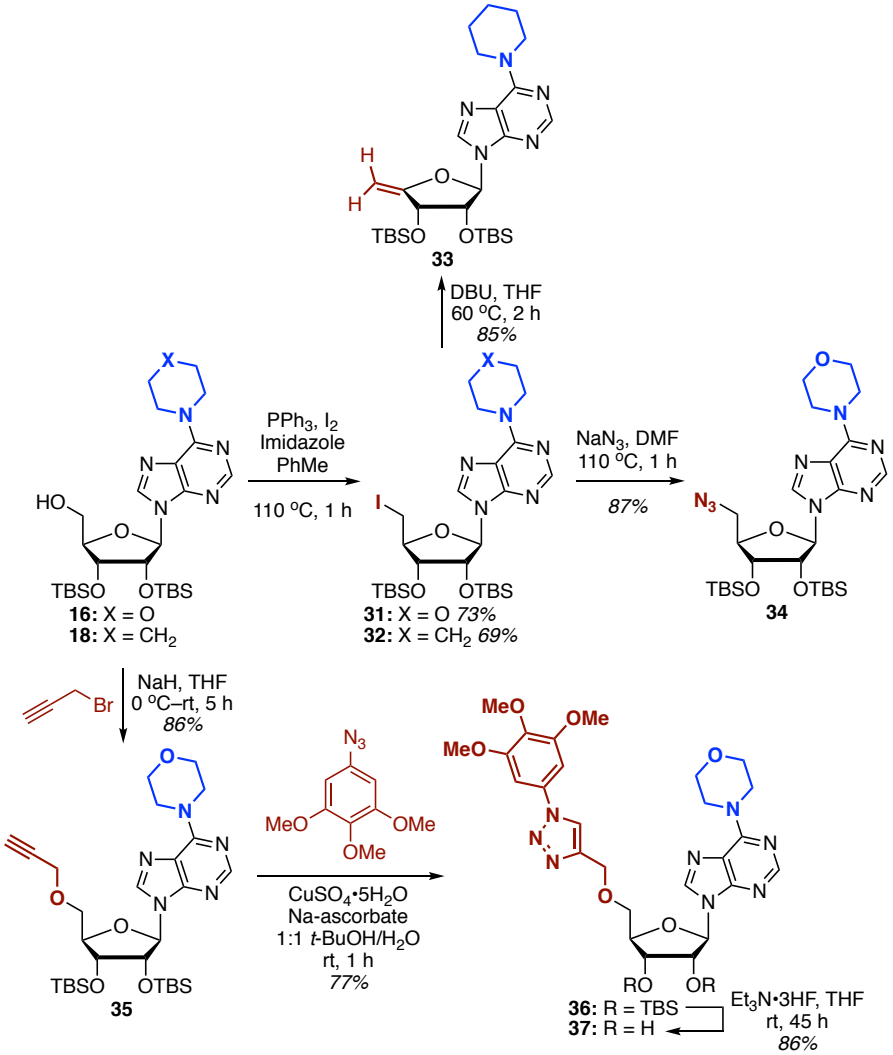
Beyond their medicinal values, *N*-phenyltetrazolylsulfides are potential intermediates in Julia-Kocienski olefination reactions. Subjecting iodo intermediate **22** to elimination conditions, with DBU in THF at 60 °C, yielded the 4'-methylene derivative **27** in a high 93% yield.[54] Iodo intermediates **21** and **22** were converted to the 5' azides **28** (78% yield) and **29** (90% yield), respectively, by reaction with NaN_3 in DMF at 110 °C.[49] CuAAC reaction of azide **28** with 17α-ethynylestradiol using 10 mol % of $CuSO_4 \bullet 5H_2O$/0.20 equiv of Na-ascorbate under biphasic conditions, which we have previously developed for reactions of C6-azido purine nucleosides,[55] furnished nucleoside-steroid conjugate **30** in a good 73% yield, where the 5'-position of the nucleoside was linked to the 17α-position of the steroid via a 1,2,3-triazolyl moiety.

Scheme 4. Diverse 5'-Modifications of N^6-Aryl Adenosine Analogues



We then evaluated 5'-modifications with products obtained from reactions with alkyl amines. First, similar to the conversion of precursors **2** and **6** to the 5'-iodo derivatives in Scheme 4, reaction of morpholinyl and piperidinyl derivatives **16** and **18** with PPh_3/I_2 and imidazole in PhMe at 110 °C,[49] gave products **31** and **32** in 73% and 69% yield, respectively (Scheme 5). The piperidinyl compound **32** was then subject to elimination with DBU in THF, at 60 °C,[54] and gave the 4'-methylene derivative **33** in a high 85% yield. Morpholinyl compound **31** was converted to the 5'-azide **34** in an 87% yield, with NaN_3 in DMF at 110 °C. This derivative is potentially utilizable for CuAAC reactions with a diverse range of alkynes, as exemplified by the reaction of azide **28** in Scheme 4.

Scheme 5. Diverse 5'-Modifications of N^6,N^6-Dialkyl Adenosine Analogues



Finally, propargyl derivative **35** was prepared in an 86% yield, by deprotonation of morpholinyl precursor **16** with NaH in THF and reaction with propargyl bromide (Scheme 5). In contrast to the use of nucleoside azide **28** in a CuAAC reaction (Scheme 4), compound **35** was used as a two-carbon donor in a CuAAC reaction with 5-azido-1,2,3-trimethoxybenzene.[56] For this reaction, *t*-BuOH/H_2O proved to be a suitable solvent mixture. In initial experimentation, use of 10 mol % of the copper salt and 0.10 equiv of Na-ascorbate resulted in incomplete conversion after 24 h. Addition of another 10 mol % of the copper salt and 0.10 equiv of Na-ascorbate led to further conversion, but precursor **35** remained unconsumed after another 21 h (yield of product **36** was 49%). Use of 25 mol % of $CuSO_4$•$5H_2O$ and 0.25 equiv of Na-ascorbate led to complete conversion within 1 h and a 77% yield of product **36**. Desilylation with Et_3N•3HF in THF gave product **37** in 86% yield.

While this manuscript was being finalized, reactions of 5'-*O*-(4,4'-dimethoxytrityl)-2'-deoxyadenosine with electron-deficient aryl fluorides were reported as a route to N^6-aryl 2'-deoxyadenosine derivatives.[57] These reactions, which were performed in DMSO at 110 °C with K_3PO_4 as the base, presumably operate through an S_NAr reaction on the aryl fluoride and are therefore limited to electron-deficient systems. The reactions were unsuccessful with either unprotected or with 2',3'-di-*O*-TBS protected 2'-deoxyadenosine. Comparable reactions for the N^6-modification of adenosine were not reported in this work.

As a final step, we also tested the desilylation of compound **10'** (Scheme 1), which was the major product obtained in the reaction of 2',3',5'-tri-*O*-(*t*-$BuMe_2Si$)-protected 6-ClP-riboside (**1**) and *o*-anisidine. Treatment of **10'** with 1:1 CF_3CO_2H/H_2O in THF at 0 °C over 1 h resulted in a clean removal of the 5'-silyl group, resulting in a 72% (overall 91%) yield of product **10**. This test indicates that in any instances where the 5'-silyl group is only partly cleaved, use of 1:1 CF_3CO_2H/H_2O in THF at 0 °C can lead to complete deprotection at the 5'-position. In every case, 5'-desilylated products with modifications at the N^6-atom are readily accessible, where the liberated hydroxyl group can be used for subsequent functionalization, and diversification.

Some important NMR-based information that was gathered during the course of product characterization are shown in Figure 3. In the NOESY spectrum of the benzimidazole nucleoside **24**, correlations were observed between an aromatic proton (s, δ= 7.72 ppm) and the aryl methyl

resonance (s, δ = 2.54 ppm) as well as the purinyl C2 proton (s, δ = 9.03 ppm). The 5'-methyl group (d, δ = 1.47 ppm) showed correlation with the 3'-proton (dd, δ = 4.00 ppm), and the purinyl C8 proton (s, δ = 8.07 ppm) showed correlation with the 1'-proton (d, δ = 6.00 ppm). In the gHMQC spectrum of olefinic compound **33**, the two olefinic protons (d, δ = 4.50 ppm and d, δ = 4.25 ppm) showed correlations to the ^{13}C resonance at δ = 86.7 ppm. In addition, the two indicated protons were correlated in the gCOSY spectrum (*J* = 1.9 Hz). Through the gHMQC spectrum of the steroid conjugate **30**, correlation of the two 5'-protons (dd, δ = 4.88 ppm and dd, δ = 4.79 ppm) to the ^{13}C resonance at δ = 51.7 ppm and that of the triazolyl proton (s, δ = 7.53 ppm) to the ^{13}C resonance at δ = 123.5 ppm (not shown in Figure 3) was established. The HMBC spectrum showed a correlation between the two 5'-protons to the triazolyl ^{13}C resonance at δ = 123.5 ppm. The NOESY spectrum of this compound showed correlations of the two 5'-protons with the triazolyl as well as purinyl protons. For the triazolyl derivative **36**, NOESY correlations were observed between the methoxy resonances (s, δ = 3.91 ppm) and the aromatic protons (s, δ = 6.92 ppm). The aromatic proton showed an NOE correlation to the triazolyl proton (s, δ = 7.95 ppm). Beyond these observations, in $CDCl_3$ when exchange is slow, the diastereotopic 5'-protons in the 5'-desilylated products generally appear as downfield doublet and an upfield triplet between ~δ = 3.6–4.0 ppm. This is consistent with a *syn*-conformation of the purine and sugar, with an intramolecular hydrogen bond between the 5'-hydroxyl proton and the purinyl N^3-atom.[58,59] In such an event, strong coupling of one H5' to the hydroxyl proton and geminal coupling to the other H5' is observed, whereas the second H5' only displays geminal coupling.

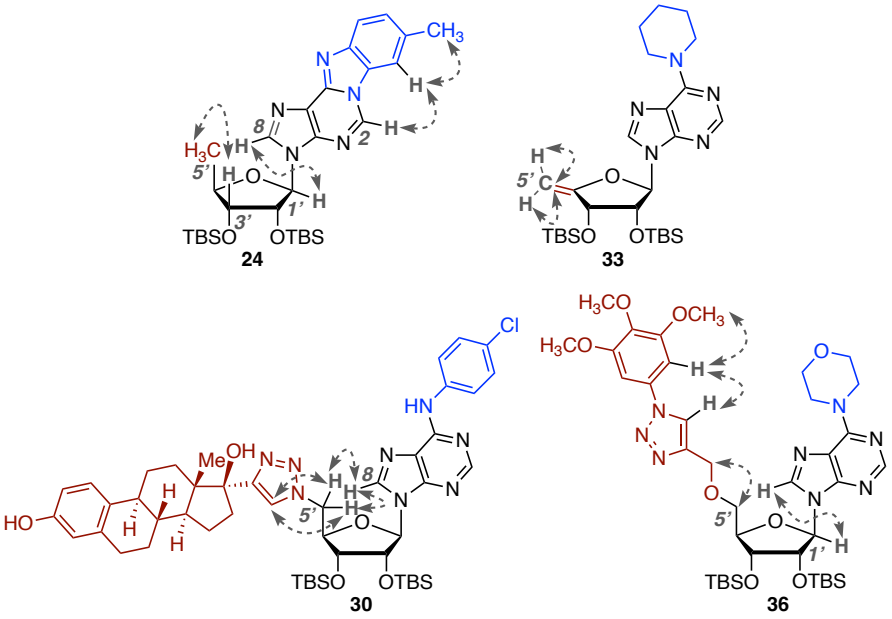


Figure 3. Key NMR-based observations for some of the products synthesized.

■ CONCLUSIONS

In summary, whereas S_NAr reactions of 2',3',5'-tri-*O*-acyl 6-ClP-riboside have been evaluated, we have studied the relatively unknown reactivity of 2',3',5'-tri-*O*-(*t*-BuMe_2Si)-protected 6-ClP-riboside (**1**) with aryl amines. These reactions can be accomplished reasonably well in 0.1 M AcOH in EtOH at elevated temperatures, and selective cleavage of the 5'-silyl group occurs in addition to the substitution at the C6 position. In the one instance, where the major product was fully silylated, subsequent treatment with 1:1 CF_3CO_2H/H_2O in THF at 0 °C led to deprotection at the 5'-position. It is plausible that protonative activation of the purine may be responsible for the S_NAr reactivity towards aryl amines. The formation of HCl and or the anilinium hydrochlorides (which can lead to the presence of HCl in the reaction) is likely responsible for the cleavage of the 5'-silyl group. Comparable reactions of 2',3',5'-tri-*O*-(*t*-BuMe_2Si)-protected 6-ClP-riboside (**1**) with alkyl amines did not result in products containing a free 5'-hydroxyl group, but rather the fully silylated adenosine derivatives were formed in generally high yields. Studies showed that AcOH in the reaction medium was not responsible for the 5'-desilylation but that the anilinium chloride was. In order to prepare adenosine derivatives from reactions with alkyl amines, containing a free 5'-hydroxyl group, 2',3',5'-tri-*O*-(*t*-BuMe_2Si)-protected 6-ClP-riboside (**1**) was treated with 1:1 CF_3CO_2H/H_2O in THF at 0 °C. The ensuing 5'-monodesilylated chloro nucleoside **17** underwent

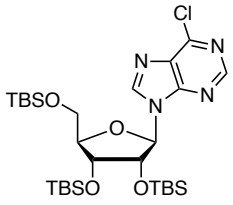
efficient reactions with alkyl amines at room temperature. The presence of a free 5'-hydroxyl moiety in all of these products offers an opportunity for additional modification at the C5'. This was demonstrated by a variety of transformations on aryl amino and alkyl amino adenosine analogues that were available. There are two additional noteworthy aspects to this work. First, neither Pd catalysis nor fluorinated solvents are necessary for reactions of the 6-chloro nucleoside with reactive, alkyl amines. Second, ready access to adenosine analogues with a free 5'-hydroxyl group provides segue to rapid functionalization at the C5'-position as well. Thus, we have shown an approach for dual N^6,C5'-modification of adenosine derivatives, and this can be easily adapted in a variety of other scenarios where such ready accessibility is desired.

■ EXPERIMENTAL SECTION

General Experimental Considerations

CH_2Cl_2, EtOAc, and hexanes were distilled over $CaSO_4$. THF was distilled over $LiAlH_4$ and then over Na prior to use. PhMe was distilled over Na prior to use, acetone was distilled over $CaCl_2$, and iPr_2NEt was distilled over CaH_2. 6-Chloropurine-9-β-D-ribofuranoside (6-ClP-riboside) and other reagents were purchased from commercial sources, and were used without additional purification. For the reaction requiring NaH, a 60% dispersion in mineral oil was used. Where stated, reactions were performed in a round-bottom, screwcap culture tube of ~9 mL capacity, with dimensions of ~950 mm $L \times 9$ mm i.d. For reactions conducted above ambient temperature, a sand bath pre-equilibrated to the desired temperature was used, and the bath temperatures are reported. Thin-layer chromatography was performed on 200 μm aluminum-foil-backed silica plates, and column chromatographic purifications were performed on either 100–200 or 200–300 mesh silica gel (see individual compound descriptions). ^{1}H NMR spectra were recorded at 500 MHz in $CDCl_3$ or DMSO-d_6 and are referenced to the residual protonated solvent resonance. ^{13}C NMR spectra were recorded at 125 MHz in $CDCl_3$ or DMSO-d_6, and are referenced to the solvent resonance. Chemical shifts (δ) are reported in parts per million and coupling constants (J) are in hertz (Hz). Where necessary, structural assessments were made with additional information from gCOSY, NOESY, HMQC, and HMBC experiments.

6-Chloro-9-[2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (1).[60]



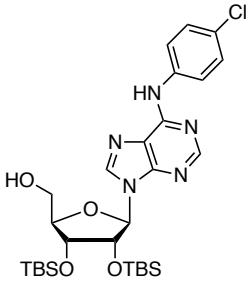
In an oven-dried 15 mL vial equipped with a stir bar, was placed 6-ClP-riboside (0.500 g, 1.74 mmol, 1.0 equiv) in DMF (4.7 mL), and *t*-BuMe$_2$SiCl (TBSCl, 1.31 g, 8.72 mmol, 5.0 equiv) was added. This was followed by the addition of imidazole (1.19 g, 17.4 mmol, 10.0 equiv). The vial was capped, and the mixture was stirred at room temperature for 36 h, at which time TLC analysis indicated complete silylation. Water (25 mL) was added, the mixture was diluted with EtOAc (10 mL), and transferred to a separatory funnel. Additional EtOAc (30 mL) was added into the separatory funnel, and the mixture was extracted. The separated aqueous layer was back-extracted with EtOAc (2 × 30 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a 100–200 mesh silica gel column packed in hexanes and sequentially eluted with hexanes and 10% EtOAc in hexanes gave 0.879 g (80% yield) of desired product **1** as a white solid. R_f (SiO_2/30% EtOAc in hexanes) = 0.78. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.74 (s, 1H), 8.55 (s, 1H), 6.13 (d, *J* = 4.9 Hz, 1H), 4.59 (t, *J* = 4.5 Hz, 1H), 4.31 (t, *J* = 3.8 Hz, 1H), 4.16 (d, *J* = 2.2 Hz, 1H), 4.02 (dd, *J* = 11.5, 3.3 Hz, 1H), 3.81 (dd, *J* = 11.5, 2.0 Hz, 1H), 0.96, 0.93, and 0.79 (3s, 27H), 0.16, 0.15, 0.10, 0.099, –0.03, and –0.24 (6s, 18H).

General procedure for the N-Arylation of 6-Chloro-9-[2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (1).

In an oven-dried, screwcap culture tube equipped with a stir bar was placed 2',3',5'-tri-*O*-(*t*-BuMe$_2$Si)-protected 6-ClP-riboside (**1**, 62.9 mg, 0.10 mmol, 1.0 equiv) in 0.1 M AcOH in EtOH (1 mL). The aryl amine (0.12 mmol, 1.2 equiv) was added, the tube was capped, and the mixture was heated at either 85–90 ~~°C~~ or at 120–125 °C. Reaction progress was monitored by TLC. At the end of the reaction, the mixture was diluted with EtOAc (5 mL) and transferred to a separatory funnel. Additional EtOAc (15 mL) was added, and the mixture was extracted with saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was separated and back-extracted with EtOAc (2 × 15 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification in each case was performed by column chromatography using an appropriate eluting solvent. All S_NAr reactions with aryl amines

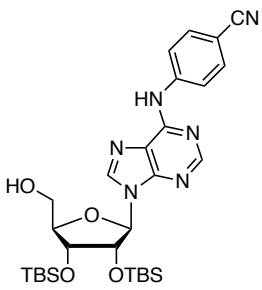
and purifications were performed using these protocols; specific details for each are provided under the individual compound headings.

2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-N^6-(4-chlorophenyl)adenosine (2).



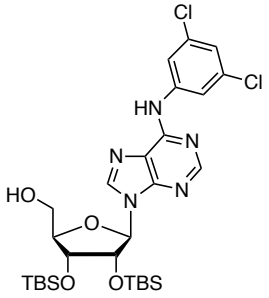
The reaction with *p*-chloroaniline (15.3 mg, 0.12 mmol) was conducted at 85–90 °C and was complete within 4 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in CH_2Cl_2 and sequentially eluted with CH_2Cl_2 and 10% EtOAc in CH_2Cl_2 gave 36.4 mg (60% yield) of desired product **2** as a white foam. R_f (SiO_2/30% EtOAc in hexanes) = 0.45. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (s, 1H), 7.88 (s, 1H), 7.80 (br s, 1H, partially overlapped on adjacent upfield d), 7.77 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 6.60 (dd, *J* = 12.0, 1.4 Hz, 1H), 5.81 (d, *J* = 7.9 Hz, 1H), 5.05 (dd, *J* = 7.9, 4.5 Hz, 1H), 4.34 (d, *J* = 4.5 Hz, 1H), 4.17 (broadened s, 1H), 3.95 (dt, *J* = 13.1, 1.7 Hz, 1H), 3.71 (td, *J* = 12.6, 1.4 Hz, 1H), 0.95 and 0.74 (2s, 18H), 0.13, 0.12, –0.13, and –0.61 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 152.6, 152.4, 148.5, 141.5, 137.0, 129.3, 129.1, 122.3, 121.8, 91.3, 89.9, 74.2, 63.2, 26.0, 25.9, 18.3, 18.0, –4.3, –4.36, –4.39, –5.7. HRMS (ESI/TOF) *m*/*z* calculated for $C_{28}H_{45}ClN_5O_4Si_2$ $[M + H]^+$: 606.2693, found 606.2716.

2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-N^6-(4-cyanophenyl)adenosine (3).



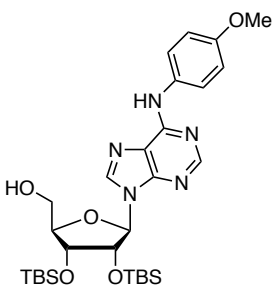
The reaction with *p*-cyanoaniline (14.2 mg, 0.12 mmol) was conducted at 85–90 °C and was complete within 7 h. Chromatography of the crude material on a 100–200 mesh silica gel column packed in CH_2Cl_2 and sequentially eluted with CH_2Cl_2, 5% CH_2Cl_2 in EtOAc, and 15% CH_2Cl_2 in EtOAc gave 25.5 mg (43% yield) of desired product **3** as a pale-brown, gummy solid. R_f (SiO_2/30% EtOAc in hexanes) = 0.30. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (s, 1H), 8.09 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.93 (s, 1H), 7.67 (d, *J* = 8.5 Hz, 2H), 6.44 (dd, *J* = 12.2, 1.8 Hz, 1H), 5.82 (d, *J* = 7.9 Hz, 1H), 5.04 (dd, *J* = 7.8, 4.5 Hz, 1H), 4.34 (d, *J* = 4.3 Hz, 1H), 4.18 (broadened s, 1H), 3.96 (dt, *J* = 12.9, 1.6 Hz, 1H), 3.72 (td, *J* = 12.6 Hz, 1.1 Hz, 1H), 0.95 and 0.74 (2s, 18H), 0.13, 0.12, –0.13, and –0.64 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 152.2, 152.0, 148.7, 142.7, 142.1, 133.5, 122.6, 119.8, 119.4, 106.2, 91.3, 89.9, 74.1, 74.09, 63.2, 26.0, 25.8, 18.3, 17.96, –4.3, –4.39, –4.4, –5.8. HRMS (ESI/TOF) *m*/*z* calculated for $C_{29}H_{44}N_6NaO_4Si_2$ $[M + Na]^+$: 619.2855, found 619.2872.

2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-N^6-(3,5-dichlorophenyl)adenosine (4).



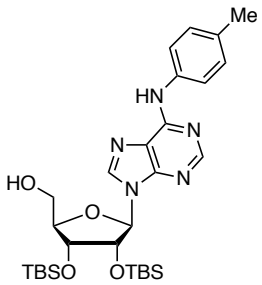
The reaction with 3,5-dichloroaniline (19.4 mg, 0.12 mmol) was conducted at 85–90 °C and was complete within 6.5 h. Chromatography of the crude material on a 100–200 mesh silica gel column packed in hexanes and sequentially eluted with hexanes and 30% EtOAc in hexanes gave 38.4 mg (60% yield, not based on recovered **17**) of desired product **4** as a white solid. 5'-Desilylated compound **17** (4.6 mg, 9% yield) was also isolated during the purification, as a white solid. R_f (SiO_2/30% EtOAc in hexanes) = 0.52. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (s, 1H), 7.90 (s, 1H), 7.85 (s, 2H), 7.81 (s, 1H), 7.11 (s, 1H), 6.46 (dd, *J* = 12.2, 1.8 Hz, 1H), 5.82 (d, *J* = 7.8 Hz, 1H), 5.05 (dd, *J* = 7.8, 4.5 Hz, 1H), 4.34 (d, *J* = 4.4 Hz, 1H), 4.18 (broadened s, 1H), 3.96 (dt, *J* = 13.0, 1.9 Hz, 1H), 3.72 (td, *J* = 12.6, 1.4 Hz, 1H), 0.96 and 0.74 (2s, 18H), 0.14, 0.13, –0.13, and –0.62 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 152.28, 152.27, 148.7, 141.9, 140.5, 135.4, 123.6, 122.4, 118.4, 91.3, 89.9, 74.26, 74.2, 63.2, 26.0, 25.9, 18.3, 18.0, –4.3, –4.36, –4.4, –5.7. HRMS (ESI/TOF) *m*/*z* calculated for $C_{28}H_{44}Cl_2N_5O_4Si_2$ $[M + H]^+$: 640.2303, found 640.2331.

2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-N^6-(4-methoxyphenyl)adenosine (5).



The reaction with *p*-anisidine (14.8 mg, 0.12 mmol) was conducted at 85–90 °C and was complete within 7 h. Chromatography of the crude material on a 100–200 mesh silica gel column packed in hexanes and sequentially eluted with hexanes and 30% EtOAc in hexanes gave 42.6 mg (71% yield) of desired product **5** as a colorless oil. R_f (SiO_2/30% EtOAc in hexanes) = 0.53. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.84 (s, 1H), 7.65 (d, *J* = 8.9 Hz, 2H), 7.62 (s, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.74 (dd, *J* = 10.5, 1.3 Hz, 1H), 5.79 (d, *J* = 7.9 Hz, 1H), 5.06 (dd, *J* = 7.8, 4.6 Hz, 1H), 4.34 (d, *J* = 4.4 Hz, 1H), 4.16 (broadened s, 1H), 3.95 (d, *J* = 12.9 Hz, 1H), 3.82 (s, 3H), 3.71 (t, *J* = 13.6 Hz, 1H), 0.95 and 0.75 (2s, 18H), 0.13, 0.12, –0.13, and –0.60 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 156.7, 153.2, 152.6, 148.2, 141.1, 131.2, 123.0, 122.0, 114.5, 91.3, 89.8, 74.3, 74.2, 63.3, 55.7, 26.0, 25.9, 18.3, 18.0, –4.3, –4.36, –4.39, –5.7. HRMS (ESI/TOF) *m*/*z* calculated for $C_{29}H_{47}N_5NaO_5Si_2$ $[M + Na]^+$: 624.3008, found 624.3013.

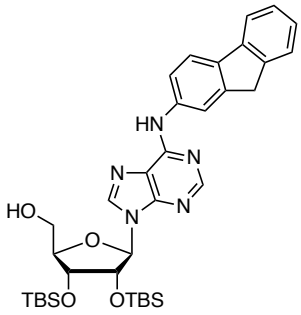
2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-N^6-(4-methylphenyl)adenosine (6).



The reaction with *p*-toluidine (12.9 mg, 0.12 mmol) was conducted at 85–90 °C and was complete within 4 h. Chromatography of the crude material on a 100–200 mesh silica gel column packed in CH_2Cl_2 and sequentially eluted with CH_2Cl_2, 5% EtOAc in CH_2Cl_2, and 15% EtOAc in CH_2Cl_2 gave 41.6 mg (71% yield) of desired product **6** as an off-white, gummy solid. R_f (SiO_2/30% EtOAc in hexanes) = 0.42. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.46 (s, 1H), 7.85 (s, 1H), 7.81 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 6.74 (dd, *J* = 12.1, 1.7 Hz, 1H), 5.80 (d, *J* = 7.9 Hz, 1H), 5.06 (dd, *J* = 7.9, 4.5 Hz, 1H), 4.34 (d, *J* = 4.5 Hz, 1H), 4.17 (broadened s, 1H), 3.95 (dt, *J* = 13.1, 1.9 Hz, 1H), 3.71 (td, *J* = 12.6, 1.4 Hz, 1H), 2.35 (s, 3H), 0.95 and 0.75 (2s, 18H), 0.13, 0.12, –0.13, and –0.60 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 153.1, 152.6, 148.3, 141.2, 135.7, 134.0, 129.8, 122.2, 121.1, 91.3, 89.8, 74.3, 74.2, 63.2, 26.0, 25.9, 21.1, 18.3, 18.0, –4.3, –4.37, –4.4, –5.7. HRMS (ESI/TOF) *m*/*z* calculated for $C_{29}H_{48}N_5O_4Si_2$ $[M + H]^+$: 586.3239, found 586.3251.

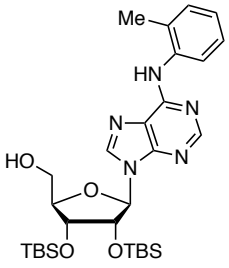
Reaction on a 1 mmol scale. In each of two oven-dried, screwcap culture tubes (ca. 30 mL capacity, with dimensions of 13.5 cm *L* × 1.2 cm i.d.) equipped with stir bars was placed 2',3',5'-tri-*O*-(*t*-BuMe$_2$Si)-protected 6-ClP-riboside (**1**, 314.7 mg, 0.50 mmol, 1.0 equiv) in 0.1 M AcOH in EtOH (5.5 mL). To each tube, *p*-toluidine (70.7 mg, 0.66 mmol, 1.3 equiv) was added, and the tubes were capped, and heated at 85–90 °C in a pre-equilibrated sand bath. Reaction progress was monitored by TLC and after 4.5 h, complete consumption of precursor **1** was observed. The two reaction mixtures were combined, diluted with EtOAc (10 mL), and transferred to a separatory funnel. Additional EtOAc (15 mL) was added, and the mixture was extracted with saturated aqueous $NaHCO_3$ (25 mL). The aqueous layer was separated and back-extracted with EtOAc (2 × 25 mL). The combined organic layer was washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the crude material by column chromatography on a 200–300 mesh silica gel column packed in CH_2Cl_2 and sequentially eluted with CH_2Cl_2, and 5% EtOAc in CH_2Cl_2 gave 412.9 mg (70% yield) of desired product **6** as a peach-colored foam. R_f (SiO_2/30% EtOAc in hexanes) = 0.45. The ^{1}H NMR spectrum of this product was comparable to that reported above.

2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-*N*^{6}-(fluoren-2-yl)adenosine (7).



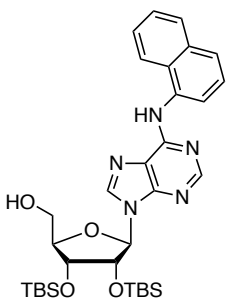
The reaction with 2-aminofluorene (21.7 mg, 0.12 mmol) was conducted at 85–90 °C and was complete within 6.5 h. Chromatography of the crude material on a 100–200 mesh silica gel column packed in CH_2Cl_2 and sequentially eluted with CH_2Cl_2 and 20% EtOAc in CH_2Cl_2 gave 43.1 mg (65% yield) of desired product **7** as a white solid. R_f (SiO_2/30% EtOAc in hexanes) = 0.69. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (s, 1H), 8.16 (s, 1H), 8.06 (s, 1H), 7.89 (s, 1H), 7.76 (dd, *J* = 12.3, 7.9 Hz, 2H), 7.65 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 1H), 6.82 (dd, *J* = 12.1, 1.6 Hz, 1H), 5.82 (d, *J* = 7.9 Hz, 1H), 5.06 (dd, *J* = 7.9, 4.5 Hz, 1H), 4.35 (d, *J* = 4.5 Hz, 1H), 4.19 (broadened s, 1H), 3.98 (dt, *J* = 13.2, 1.6 Hz, 1H), 3.94 (s, 2H), 3.72 (td, *J* = 12.6, 1.2 Hz, 1H), 0.96 and 0.75 (2s, 18H), 0.14, 0.12, –0.12, and –0.62 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 152.8, 152.5, 148.2, 144.6, 143.3, 141.5, 141.2, 138.0, 137.1, 126.9, 126.4, 125.1, 122.2, 120.4, 119.7, 119.5, 117.5, 91.2, 89.9, 74.2, 74.1, 63.2, 37.3, 26.0, 25.8, 18.3, 18.0, –4.39, –4.4, –5.8. HRMS (ESI/TOF) *m*/*z* calculated for $C_{35}H_{49}N_5NaO_4Si_2$ [M + Na]$^+$: 682.3215, found 682.3216.

2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-N^6-(2-methylphenyl)adenosine (8).



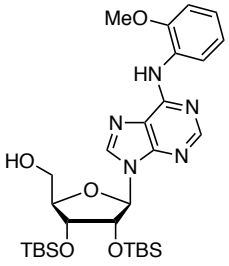
The reaction with *o*-toluidine (12.7 μL, 0.12 mmol) was conducted at 120–125 °C and was complete within 15 h. Chromatography of the crude material on a 100–200 mesh silica gel column packed in CH_2Cl_2 and sequentially eluted with 5% EtOAc in CH_2Cl_2 and 15% EtOAc in CH_2Cl_2, gave 35.7 mg (61% yield) of desired product **8** as a pale-brown solid. R_f (SiO_2/30% EtOAc in hexanes) = 0.49. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.83 (s, 1H), 7.60 (s, 1H), 7.31–7.26 (m, 2H), 7.15 (td, *J* = 7.4, 0.8 Hz, 1H), 6.72 (dd, *J* = 12.1, 1.7 Hz, 1H), 5.80 (d, *J* = 7.9 Hz, 1H), 5.07 (dd, *J* = 7.9, 4.5 Hz, 1H), 4.34 (d, *J* = 4.5 Hz, 1H), 4.17 (broadened s, 1H), 3.95 (dt, *J* = 13.1, 1.7 Hz, 1H), 3.71 (td, *J* = 12.6, 1.4 Hz, 1H), 2.35 (s, 3H), 0.96 and 0.76 (2s, 18H), 0.14, 0.12, –0.12, and –0.59 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 153.6, 152.7, 148.4, 141.3, 136.1, 131.1, 131.0, 127.0, 125.7, 124.1, 122.3, 91.3, 89.8, 74.3, 74.2, 63.2, 26.0, 25.9, 18.3, 18.2, 18.0, –4.3, –4.37, –4.4, –5.8. HRMS (ESI/TOF) *m*/*z* calculated for $C_{29}H_{47}N_5NaO_4Si_2$ [M + Na]$^+$: 608.3059, found 608.3060.

2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-N^6-(naphthalen-1-yl)adenosine (9).



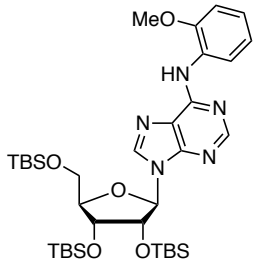
The reaction with 1-naphthylamine (17.2 mg, 0.12 mmol) was conducted at 120–125 °C. After 15 h, some precursor **1** remained unreacted. Chromatography of the crude material on a 100–200 mesh silica gel column packed in CH_2Cl_2 and sequentially eluted with CH_2Cl_2, 5% EtOAc in CH_2Cl_2, and 15% EtOAc in CH_2Cl_2 gave 42.9 mg (69% yield, not based on recovered **1**) of desired product **9** as a white solid. Precursor **1** (6.5 mg, 10%) was recovered during the purification. R_f (SiO_2/30% EtOAc in hexanes) = 0.53. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.15 (s, 1H), 8.11 (d, *J* = 7.4 Hz, 1H), 8.04–8.00 (m, 1H), 7.93–7.89 (m, 1H), 7.87 (s, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 7.54–7.50 (m, 2H), 6.69 (dd, *J* = 12.1, 1.7 Hz, 1H), 5.82 (d, *J* = 7.9 Hz, 1H), 5.09 (dd, *J* = 7.9, 4.5 Hz, 1H) 4.35 (d, *J* = 4.5 Hz, 1H), 4.18 (broadened s, 1H), 3.96 (dt, *J* = 13.1, 1.8 Hz, 1H), 3.71 (td, *J* = 12.6, 1.6 Hz, 1H), 0.97 and 0.77 (2s, 18H), 0.15, 0.13, –0.11, and –0.56 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 154.2, 152.7, 148.6, 141.5, 134.6, 132.9, 128.9, 128.4, 126.6, 126.4, 125.9, 122.4, 121.7, 121.6, 91.3, 89.9, 74.3, 74.2, 63.3, 26.0, 25.9, 18.3, 18.0, –4.3, –4.36, –4.38, –5.7. HRMS (ESI/TOF) *m*/*z* calculated for $C_{32}H_{48}N_5O_4Si_2$ $[M + H]^+$: 622.3239, found 622.3242.

2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-*N*^{6}-(2-methoxyphenyl)adenosine (10).



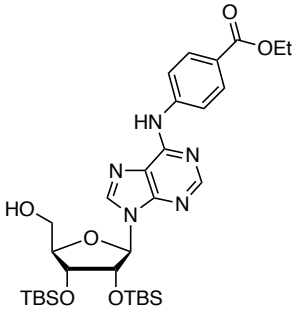
The reaction with *o*-anisidine (13.5 μL, 0.12 mmol) was conducted at 85–90 °C and was complete within 22 h. Chromatography of the crude material on a 100–200 mesh silica gel column packed in CH_2Cl_2 and sequentially eluted with CH_2Cl_2 and 10% EtOAc in CH_2Cl_2 gave 18.77 mg (19% yield) of desired product **10** as a colorless oil. R_f (SiO_2/30% EtOAc in hexanes) = 0.6. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.81–8.79 (m, 1H), 8.52 (s, 1H), 8.35 (s, 1H), 7.88 (s, 1H), 7.09–7.03 (m, 2H), 6.96–6.95 (m, 1H), 6.74 (dd, *J* = 12.1, 1.5 Hz, 1H), 5.81 (d, *J* = 7.9 Hz, 1H), 5.08 (dd, *J* = 7.9, 4.5 Hz, 1H), 4.35 (d, *J* = 4.5 Hz, 1H), 4.17 (broadened s, 1H), 3.98–3.96 (dt, *J* = 12.9, 1.9 Hz, 1H overlapped on adjacent upfield s, 3H), 3.72 (td, *J* = 12.6, 1.3 Hz, 1H), 0.96 and 0.75 (2s, 18H), 0.14, 0.12, –0.13, and –0.61 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 152.7, 152.4, 148.6, 148.2, 141.3, 128.3, 123.4, 122.8, 121.2, 120.0, 110.3, 91.3, 89.9, 74.3, 74.2, 63.3, 56.0, 26.0, 25.9, 18.3, 18.0, –4.33, –4.35, –4.4, –5.7. HRMS (ESI/TOF) *m*/*z* calculated for $C_{29}H_{47}N_5NaO_5Si_2$ $[M + Na]^+$: 624.3008, found 624.3029.

2',3',5'-Tri-*O*-(*tert*-butyldimethylsilyl)-N^6-(2-methoxyphenyl)adenosine (10').



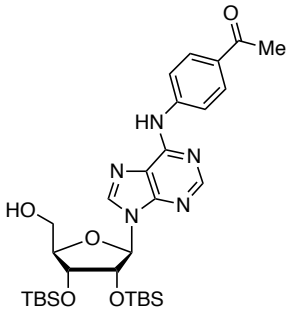
In addition to product **10** above, 29.1 mg of the faster-eluting, fully-silylated product **10'** (41% yield) was also obtained as a colorless oil. R_f (SiO_2/30% EtOAc in hexanes) = 0.80. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.76–8.73 (m, 1H), 8.53 (s, 1H), 8.23 (s, 1H), 8.15 (s, 1H), 7.04 (dd, *J* = 6.5, 2.9 Hz, 2H), 6.95–6.93 (m, 1H), 6.06 (d, *J* = 5.7 Hz, 1H), 4.77 (t, *J* = 4.7 Hz, 1H), 4.33 (t, *J* = 3.6 Hz, 1H), 4.14 (app q, *J* = 3.5 Hz, 1H), 4.04 (dd, *J* = 11.2, 4.5 Hz, 1H), 3.94 (s, 3H), 3.80 (dd, *J* = 11.3, 3.0 Hz, 1H), 0.96, 0.94, and 0.79 (3s, 27H), 0.14, 0.13, 0.116, 0.114, –0.05, and –0.27 (6s, 18H). The NMR data for **10'** are in agreement with those previously reported.[24] This compound was also utilized for desilylation (*vide infra*).

2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-N^6-(4-carboethoxyphenyl)adenosine (11).



The reaction with ethyl *p*-aminobenzoate (19.8 mg, 0.12 mmol) was conducted at 85–90 °C and was complete within 7 h. Chromatography of the crude material on a 100–200 mesh silica gel column packed in CH_2Cl_2 and sequentially eluted with CH_2Cl_2, 5% EtOAc in CH_2Cl_2, and 15% EtOAc in CH_2Cl_2 gave 36.1 mg (56% yield) of desired product **11** as a pale-brown, thick gum. R_f (SiO_2/30% EtOAc in hexanes) = 0.36. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (s, 1H), 8.09 (d, *J* = 8.7 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.91 (s, 1H), 7.88 (s, 1H), 6.52 (dd, *J* = 12.3, 1.9 Hz, 1H), 5.82 (d, *J* = 7.9 Hz, 1H), 5.06 (dd, *J* = 7.8, 4.5 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.35 (d, *J* = 4.5 Hz, 1H), 4.18 (broadened s, 1H), 3.97 (dt, *J* = 13.0, 1.6 Hz, 1H), 3.75–3.69 (m, 1H), 1.40 (t, *J* = 7.1 Hz, 3H), 0.96 and 0.75 (2s, 18H), 0.14, 0.13, –0.13, and –0.61 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.4, 152.4, 152.3, 148.7, 142.7, 141.8, 131.1, 125.5, 122.6, 119.2, 91.3, 89.9, 74.3, 74.2, 63.2, 61.0, 26.0, 25.9, 18.3, 18.0, 14.6, –4.34, –4.36, –4.4, –5.7. HRMS (ESI/TOF) *m*/*z* calculated for $C_{31}H_{49}N_5NaO_6Si_2$ $[M + Na]^+$: 666.3114, found 666.3104.

2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-N^6-(4-acetylphenyl)adenosine (12).



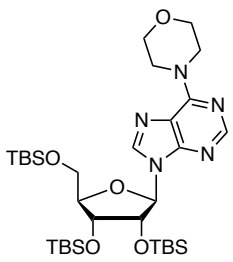
The reaction with 4'-aminoacetophenone (16.2 mg, 0.12 mmol) was conducted at 85–90 °C and was complete within 6 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes, 5% acetone in hexanes, and 30% acetone in hexanes gave 24.8 mg (40% yield) of desired product **12** as a white solid. R_f (SiO_2/30% EtOAc in hexanes) = 0.35. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (s, 1H), 8.04 (s, 1H overlapped on the upfield d), 8.02 (d, *J* = 9.0 Hz, 2H), 7.98 (d, *J* = 8.8 Hz, 2H), 7.92 (s, 1H), 6.50 (dd, *J* = 11.8, 1.0 Hz, 1H), 5.83 (d, *J* = 7.9 Hz, 1H), 5.06 (dd, *J* = 7.8, 4.6 Hz, 1H), 4.35 (d, *J* = 4.2 Hz, 1H), 4.18 (broadened s, 1H), 3.96 (dt, *J* = 13.0, 1.8 Hz, 1H), 3.75–3.72 (td, *J* = 12.7, 1.4 Hz, 1H), 2.60 (s, 3H), 0.96 and 0.75 (2s, 18H), 0.14, 0.13, –0.13, and –0.61 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.0, 152.3, 148.7, 143.0, 141.9, 132.5, 130.1, 122.7, 119.3, 110.2, 91.4, 89.9, 74.3, 74.2, 63.2, 26.6, 26.0, 25.9, 18.3, 18.0, –4.3, –4.35, –4.4, –5.7. HRMS (ESI/TOF) *m*/*z* calculated for $C_{30}H_{47}N_5NaO_5Si_2$ $[M + Na]^+$: 636.3008, found 636.3020.

General procedure for the *N*-Alkylation of 6-Chloro-9-[2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (1).

In an oven-dried, screwcap culture tube equipped with a stir bar, was placed 2',3',5'-tri-*O*-(*t*-BuMe_2Si)-protected 6-ClP-riboside (**1**, 62.9 mg, 0.10 mmol, 1.0 equiv) in 0.1 M AcOH in EtOH (1 mL). The alkyl amine (0.20 mmol, 2.0 equiv) was added, the tube was capped, and the mixture was heated at 85–90 °C. Reaction progress was monitored by TLC. At the end of the reaction, the mixture was diluted with EtOAc (5 mL), transferred to a separatory funnel, and extracted with saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was separated and back-extracted with EtOAc (2 × 5 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification in each case was performed by column chromatography using an appropriate solvent. All S_NAr reactions with alkyl amines and purifications were performed using these protocols, details for each are provided under the individual compound headings.

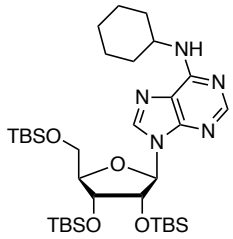
2',3',5'-Tri-*O*-(*tert*-butyldimethylsilyl)-6-(morpholin-4-yl)nebularine (13).

The reaction with morpholine (17.4 μL, 0.20 mmol) was complete within 1.5 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes and sequentially



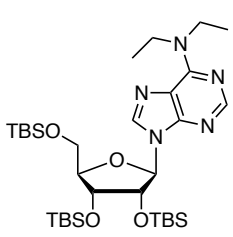
eluted with hexanes and 20% EtOAc in hexanes gave 63.3 mg (93% yield) of desired product **13** as a colorless oil. R_f (SiO_2/20% EtOAc in hexanes) = 0.52. ^{1}H NMR (500 MHz, $CDCl_3$): δ8.32 (s, 1H), 8.02 (s, 1H), 6.02 (d, *J* = 5.3 Hz, 1H), 4.71 (app t, *J* = 4.8 Hz, 1H), 4.32 (m overlapped on a br resonance, 5H), 4.10 (app q, *J* = 3.6 Hz, 1H), 4.00 (dd, *J* = 11.3, 4.3 Hz, 1H), 3.82 (app t, *J* = 4.8 Hz, 4H), 3.76 (dd, *J* = 11.3, 2.9 Hz, 1H), 0.93, 0.92, 0.79 (3s, 27H), 0.116, 0.110, 0.097, 0.092, –0.06, and –0.23 (6s, 18H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ154.0, 152.3, 151.1, 137.9, 120.7, 88.3, 85.6, 75.6, 72.3, 67.2, 62.8, 45.9, 26.3, 26.1, 25.9, 18.7, 18.3, 18.1, –4.2, –4.47, –4.5, –4.8, –5.1, –5.2. The NMR data are in agreement with those previously reported.[12]

2',3',5'-Tri-*O*-(*tert*-butyldimethylsilyl)-N^6-(cyclohexyl)nebularine (14).



The reaction with cyclohexylamine (22.9 μL, 0.20 mmol) did not reach completion even after 51 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes and 20% EtOAc in hexanes gave 63.3 mg (91% yield, not based on recovered **1**) of desired product **14** as a colorless oil. Precursor **1** (2.0 mg, 3%) was recovered during the purification. R_f (SiO_2/20% EtOAc in hexanes) = 0.59. ^{1}H NMR (500 MHz, $CDCl_3$): δ8.34 (s, 1H), 8.05 (s, 1H), 5.99 (d, *J* = 5.1 Hz, 1H), 5.59 (d, *J* = 7.1 Hz, 1H), 4.70 (app t, *J* = 4.5 Hz, 1H), 4.31 (app t, *J* = 3.6 Hz, 1H), 4.20–4.16 (br s,1H), 4.11 (app q, *J* = 3.4 Hz, 1H), 4.02 (dd, *J* = 11.3, 4.1 Hz, 1H), 3.77 (dd, *J* = 11.3, 2.5 Hz, 1H), 2.10 (dd, *J* = 12.4, 2.6 Hz, 2H), 1.77 (dt, *J* = 13.5, 3.8 Hz, 2H), 1.66 (dt, *J* = 13.1, 3.7 Hz, 1H), 1.52–1.41 (m, 2H), 1.32–1.21 (m, 3H), 0.94, 0.92, and 0.79 (3s, 27H), 0.12, 0.11, 0.095, 0.090, –0.05, and –0.22 (6s, 18H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ154.3, 153.3, 138.9, 120.3, 110.2, 88.4, 85.6, 75.9, 72.3, 62.8, 49.3, 33.6, 26.3, 26.1, 25.9, 25.87, 18.7, 18.3, 18.1, –4.2, –4.47, –4.48, –4.8, –5.1. HRMS (ESI/TOF) *m*/*z* calculated for $C_{34}H_{66}N_5O_4Si_3$ $[M + H]^+$: 692.4417, found 692.4423.

2',3',5'-Tri-*O*-(*tert*-butyldimethylsilyl)-N^6,N^6-(diethyl)nebularine (15).



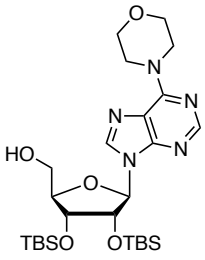
The reaction with *N*,*N*-diethylamine (20.7 μL, 0.20 mmol) was complete within 21 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes and 20% EtOAc in hexanes gave 61.5 mg (92% yield) of desired product **15** as a

colorless oil. R_f (SiO_2/20% EtOAc in hexanes) = 0.75. ^{1}H NMR (500 MHz, $CDCl_3$): δ8.29 (s,1H), 7.94 (s, 1H), 5.99 (d, *J* = 5.4 Hz, 1H), 4.80 (app t, *J* = 4.9 Hz, 1H), 4.33 (app t, *J* = 3.7 Hz, 1H), 4.10 (app q, *J* = 3.9 Hz, 1H), 4.03–3.97 (dd, *J* = 11.2, 4.8 Hz, partially overlapped on a br resonance, 5H), 3.76 (dd, *J* = 11.2, 3.3 Hz, 1H), 1.27 (t, *J* = 7.0 Hz, 6H), 0.93 and 0.78 (2s, 27H), 0.105 and 0.099 (2s, 12H), –0.06 and –0.23 (2s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ154.0, 152.6, 150.7, 137.6, 120.4, 88.3, 85.6, 75.2, 72.4, 62.9, 43.2, 26.3, 26.1, 25.9, 18.7, 18.3, 18.1, 13.7, –4.2, –4.5, –4.9, –5.1, –5.2. The NMR data of the compound are in agreement with those previously reported.[61]

Attempted Desilylation of 2',3',5'-Tri-*O*-(*tert*-butyldimethylsilyl)-6-(morpholin-4-yl)nebularine (13).

In an oven-dried, screwcap culture tube equipped with a stir bar was placed 2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)-6-(morpholin-4-yl)nebularine (**13**, 68.0 mg, 0.10 mmol, 1.0 equiv) in 0.1 M AcOH in EtOH (1 mL). The tube was capped and the mixture was heated at 65 °C for 4 h. TLC analysis indicated only starting material was present. Therefore, the mixture was heated at 90 °C for a total of 24 h. Again, TLC analysis indicated the presence of only starting material. The mixture was diluted with EtOAc (5 mL), transferred to a separatory funnel, and extracted with saturated aq. $NaHCO_3$ (5 mL). The aqueous layer was separated and back-extracted with EtOAc (2 × 5 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by column chromatography on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes and 20% EtOAc in hexanes led to recovery of 62.3 mg (92% yield) of precursor **13** as a white foam. R_f (SiO_2/20% EtOAc in hexanes) = 0.52. The NMR data of recovered compound **13** match those reported above.

Conditions A used for 5'-desilylation of 2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)-6-(morpholin-4-yl)nebularine (13).



In an oven-dried, screwcap culture tube equipped with a stir bar was placed 2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)-6-(morpholin-4-yl)nebularine (**13**, 68.0 mg, 0.10 mmol, 1.0 equiv) in 0.1 M AcOH in EtOH (1 mL). *p*-Chloroaniline•HCl (19.7 mg, 0.12 mmol, 1.2 equiv) was added, the tube was capped, and the mixture was heated at 65–70 °C for 30 h. TLC analysis showed the presence of

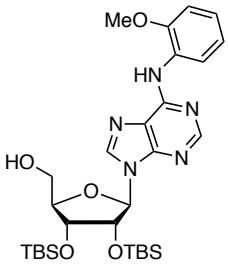
a small amount of compound **13**. The mixture was diluted with EtOAc (5 mL), transferred to a separatory funnel, and extracted with saturated aq. $NaHCO_3$ (5 mL). The aqueous layer was separated and back-extracted with EtOAc (2 × 5 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by column chromatography on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes, 10% EtOAc in hexanes, and 20% EtOAc in hexanes gave 30 mg (53% yield) of desilylated **16** as a colorless oil. R_f (SiO_2/20% EtOAc in hexanes) = 0.26. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.74 (s, 1H), 7.05–6.81 (br s, 1H), 5.75 (d, *J* = 7.9 Hz, 1H), 5.07 (dd, *J* = 7.9, 4.6 Hz, 1H), 4.32 (d, *J* = 4.6 Hz, 1H overlapped on the adjacent upfield br resonance), 4.37–4.25 (br, 4H), 4.14 (broadened s, 1H), 3.92 (dd, *J* = 13.0, 1.4 Hz, 1H), 3.81 (app t, *J* = 4.8 Hz, 4H), 3.68 (d, *J* = 13.0 Hz, 1H), 0.94 and 0.74 (2s, 18H), 0.12, 0.10, –0.15, and –0.60 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 154.3, 151.7, 149.7, 139.4, 121.8, 91.3, 89.8, 74.3, 73.7, 67.2, 63.3, 45.9, 26.0, 25.9, 18.3, 18.0, –4.3, –4.38, –4.4, –5.7. HRMS (ESI/TOF) *m*/*z* calculated for $C_{26}H_{48}N_5O_5Si_2$ $[M + H]^+$: 566.3188, found 566.3213.

Conditions B Used for 5'-Desilylation of ~~the~~ 6-Chloro-9-[2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (1), 2',3',5'-Tri-*O*-(*tert*-butyldimethylsilyl)-6-(morpholin-4-yl)nebularine (13), and 2',3',5'-Tri-*O*-(*tert*-butyldimethylsilyl)-N^6-(2-methoxyphenyl)adenosine (10').

In an oven-dried 8 mL screwcap vial equipped with a stir bar was placed trisilylated nucleoside precursor **1**, or the morpholinyl derivative **13**, or the *o*-methoxyphenyl derivative **10'** (1.0 equiv) in THF (8 mL/mmol of the nucleoside precursor). The solution was cooled to 0 °C, and 50% aq. TFA (4 mL/mmol of nucleoside precursor) was added dropwise. The vial was capped and the reaction mixture was stirred at 0 °C until complete consumption of the precursor (**1**, **13**, or **10'**) was observed. The reaction mixture was neutralized at 0 °C by the addition of saturated aq. $NaHCO_3$ (50 mL/mmol of the nucleoside precursor). EtOAc (50 mL/mmol of the nucleoside precursor) was added to the mixture and transferred to a separatory funnel. The aqueous layer was separated and back-extracted with EtOAc (50 mL × 2/mmol of nucleoside precursor). The combined organic layer was washed with brine (50 mL/mmol of the nucleoside precursor), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification in each

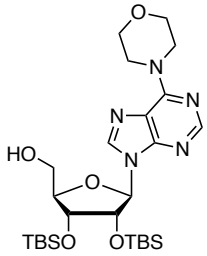
case was performed by column chromatography using an appropriate solvent. All 5'-desilylation reactions were performed using these protocols; details for each are provided under the individual compound headings.

2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-N^6-(2-methoxyphenyl)adenosine (10).



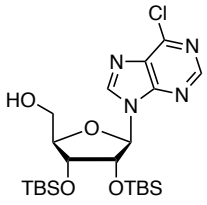
The reaction was performed with 17.0 mg (0.023 mmol) of N^6-(2-methoxyphenyl)adenosine derivative **10'** and was complete within 3 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes and 30% EtOAc in hexanes gave 10 mg (72% yield) of desired product **10** as a white solid. R_f (SiO_2/30% EtOAc in hexanes) = 0.38. The NMR data of compound **10** matched those reported above.

2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-6-(morpholin-4-yl)nebularine (16).



The reaction was performed with 68.0 mg (0.10 mmol) of morpholinyl nebularine derivative **13** and was complete within 2 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes and 30% EtOAc in hexanes gave 41.9 mg (74% yield) of desired product **16** as a white solid. R_f (SiO_2/20% EtOAc in hexanes) = 0.26. The NMR data of compound **16** matched those reported above.

6-Chloro-9-[2,3-di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-9*H*-purine (17).



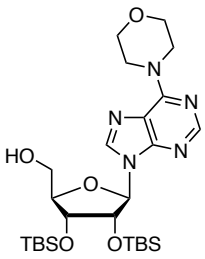
The reaction was performed with 62.9 mg (0.10 mmol) of 2',3',5'-tri-*O*-(*t*-BuMe$_2$Si)-protected 6-ClP-riboside **1** and was complete within 4 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in CH_2Cl_2 and sequentially eluted with CH_2Cl_2 and 5% MeOH in CH_2Cl_2 gave 40.9 mg (79% yield) of desired product **17** as a white solid. R_f (SiO_2/10% EtOAc in hexanes) = 0.25. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.22 (s, 1H), 5.88 (d, J = 7.5 Hz, 1H), 4.97 (dd, J = 7.7, 4.5 Hz, 1H), 4.34 (d, J = 4.4 Hz, 1H), 4.19 (broadened s, 1H), 3.96 (d, J = 13.2 Hz, 1H), 3.74 (d, J = 13.1 Hz, 1H), 0.95 and 0.74 (2s, 18H), 0.13, 0.12, –0.13, and –0.65 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 152.7, 151.6, 150.7, 145.8, 133.7, 91.5, 89.6, 74.3, 73.9, 63.0, 26.0, 25.8, 18.2, 17.9, –4.3, –4.38, –4.4, –5.7. The reaction was also performed on a 503.6 mg (0.80 mmol) scale

of compound **1**, conducted in two parts, followed by combining and purifying the product. The reaction gave 329.3 mg (80% yield) of desired product **17**. The NMR data of the compound was in agreement with those previously reported.[46]

General Procedure for the Reaction of 6-Chloro-9-[2,3-di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-9*H*-purine with Alkyl Amines.

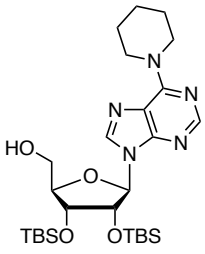
In an oven-dried 8 mL screwcap vial equipped with a stir bar, was placed 2',3'-di-*O*-(*t*-BuMe_2Si)-protected 6-ClP-riboside **17** (51.5 mg, 0.10 mmol, 1.0 equiv) in DME (1 mL), and the alkyl amine (0.25 mmol, 2.5 equiv) was added. The vial was capped and the reaction mixture was stirred at room temperature until complete consumption of precursor **17** was observed. The mixture was then evaporated under reduced pressure. Purification in each case was performed by column chromatography using an appropriate solvent. All displacement reactions of disilyl 6-chloropurine riboside **17** with alkyl amines were performed using these protocols. Details for each are provided under the individual compound headings.

9-[2,3-Di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-6-(morpholin-4-yl)-9*H*-purine (16).



The reaction with morpholine (21.8 μL, 0.25 mmol) was complete within 1 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in CH_2Cl_2 and sequentially eluted with CH_2Cl_2 and 70% CH_2Cl_2 in EtOAc gave 50.4 mg (89% yield) of desired product **16** as a white solid. R_f (SiO_2/80% CH_2Cl_2 in EtOAc) = 0.54. A reaction on a 206.1 mg (0.40 mmol scale) gave 201.3 mg (89% yield) of the desired product. The NMR data of compound **16** matched those reported above.

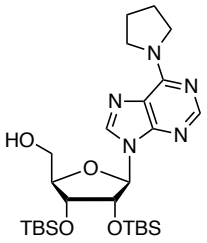
9-[2,3-Di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-6-(piperidin-1-yl)-9*H*-purine (18).



The reaction with piperidine (24.7 μL, 0.25 mmol) was complete within 1 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes and 30% EtOAc in hexanes gave 54.8 mg (97% yield) of desired product **18** as a white foam. R_f (SiO_2/20% EtOAc in hexanes) = 0.48. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.72 (s, 1H), 7.13–7.03 (br s, 1H), 5.73 (d, *J* = 7.9 Hz, 1H), 5.08 (dd, *J* = 7.8, 4.6 Hz, 1H), 4.31 (d, *J* = 4.5 Hz, 1H), 4.26–4.17 (br s, 4H), 4.13 (broadened s, 1H), 3.91 (d, *J* = 12.9 Hz, 1H), 3.67 (br t, *J* =

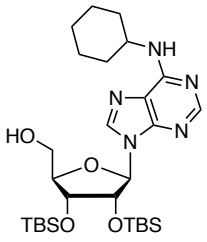
10.7 Hz, 1H), 1.73–1.67 (m, 6H), 0.93 and 0.74 (2s, 18H), 0.11, 0.10, –0.16, and –0.60 (4s, 12H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 154.2, 151.8, 149.4, 138.8, 121.7, 91.2, 89.7, 74.3, 73.6, 63.3, 46.8, 26.3, 26.0, 25.9, 24.9, 18.3, 18.0, –4.3, –4.39, –4.4, –5.7. HRMS (ESI/TOF) *m*/*z* calculated for $C_{27}H_{49}N_5NaO_4Si_2$ $[M + Na]^+$: 586.3215, found 586.3222. A reaction performed on a 128.8 mg (0.25 mmol scale) gave 129.4 mg (92% yield) of desired product **18**. The NMR data of compound **18** matched those reported above.

9-[2,3-Di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-6-(pyrrolidin-1-yl)-9*H*-purine (19).



The reaction with pyrrolidine (20.9 μL, 0.25 mmol) was complete within 1 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in CH_2Cl_2 and sequentially eluted with CH_2Cl_2 and 30% EtOAc in CH_2Cl_2 gave 51.0 mg (93% yield) of desired product **19** as a white foam. R_f (SiO_2/80% CH_2Cl_2 in hexanes) = 0.4. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.74 (s, 1H), 7.10 (d, 1H), 5.74 (d, *J* = 7.9 Hz, 1H), 5.07 (dd, *J* = 7.9, 4.6 Hz, 1H), 4.31 (d, *J* = 4.6 Hz, 1H), 4.14 and 4.12 (br overlapped on a broadened s, 3H), 3.92 (dd, *J* = 13.0, 1.5 Hz, 1H), 3.78–3.71 (br s, 2H), 3.69 (t, *J* = 12.0 Hz, 1H), 2.06 and 1.99 (2 × br, 4H), 0.93 and 0.74 (2s, 18H), 0.11, 0.10, –0.15, and –0.61 (4s, 12H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 153.4, 152.1, 148.8, 139.6, 122.1, 91.2, 89.8, 74.3, 73.7, 63.3, 49.2, 47.8, 26.4, 26.0, 25.9, 24.4, 18.3, 18.0, –4.3, –4.4, –4.43, –5.7. HRMS (ESI/TOF) *m*/*z* calculated for $C_{26}H_{48}N_5O_4Si_2$ $[M + H]^+$: 550.3239, found 550.3265.

2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-N^6-cyclohexyladenosine (20).



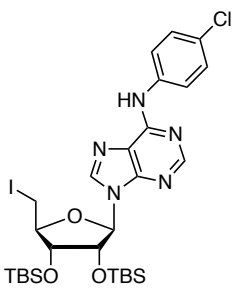
The reaction with cyclohexylamine (28.6 μL, 0.25 mmol) showed the presence of precursor **17** even after 46 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes and 30% EtOAc in hexanes gave 40.4 mg (70% yield, not based on recovered **17**) of desired product **20** as a colorless oil. Precursor **17** (3.2 mg, 6%) was recovered during the purification. R_f (SiO_2/30% EtOAc in hexanes) = 0.68. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.75 (s, 1H), 6.95–6.89 (br s, 1H), 5.75 (d overlapped with a br resonance, *J* = 7.8 Hz, 2H), 5.04 (dd, *J* = 7.4, 4.7 Hz, 1H), 4.32 (d, *J* = 4.4 Hz, 1H), 4.20–4.14 (br s overlapped with a br resonance), 3.92 (d, *J* = 13.0 Hz, 1H), 3.69 (t, *J* = 12.6 Hz, 1H), 2.11–2.08 (m, 2H), 1.81–1.76 (m, 2H), 1.68–1.60 (m, 1H), 1.51–1.44 (m, 2H), 1.38–1.21 (m, 3H), 0.94 and 0.74 (2s, 18H),

0.12, 0.11, –0.14, and –0.60 (4s, 12H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ154.7, 152.8, 147.7, 140.4, 121.6, 91.2, 89.8, 74.3, 74.1, 63.2, 49.5, 33.4, 26.0, 25.9, 25.7, 25.0, 18.3, 18.0, –4.3, –4.38, –4.4, –5.7. HRMS (ESI/TOF) *m*/*z* calculated for $C_{28}H_{51}N_5NaO_4Si_2$ $[M + Na]^+$: 600.3372, found 600.3392.

General Procedure for the Synthesis of 5'-Iodo Derivatives from 2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-*N*^{6}-(4-chlorophenyl)adenosine (2), 2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-*N*^{6}-(4-methylphenyl)adenosine (6), 9-[2,3-Di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-6-(morpholin-4-yl)-9*H*-purine (16), and 9-[2,3-Di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-6-(piperidin-1-yl)-9*H*-purine (18).

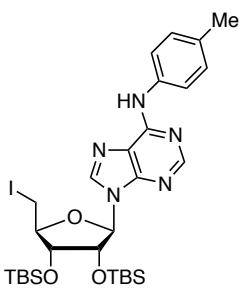
In an oven-dried 15 mL screwcap vial equipped with a stir bar was placed adenosine derivative **2**, or **6**, or nebularine derivative **16**, or **18** (1.00 equiv) in PhMe (1 mL/0.10 mmol of the precursor). PPh_3 (4.0 equiv), imidazole (4.0 equiv), and I_2 (3.0 equiv) were added. The vial was capped, and the mixture was heated at 110 ^{o}C until complete consumption of precursor (**2**, **6**, **16**, or **18**) was observed by TLC. The reaction mixture was cooled to room temperature, and saturated aq. $NaHCO_3$ (1 mL/0.10 mmol of the nucleoside precursor) was added. After the reaction mixture was stirred for 5 minutes, I_2 was added in small portions with stirring, until the color of iodine was retained in the PhMe layer. The reaction mixture was stirred for 10 minutes, and then saturated aq. $Na_2S_2O_3$ (1 mL/0.10 mmol of the nucleoside precursor) was added to the reaction mixture to remove excess I_2. The mixture was stirred for 5 additional minutes, at which time disappearance of the color or I_2 was observed. Then, the reaction mixture was diluted with EtOAc (3 mL/0.10 mmol of the nucleoside precursor), transferred to a separatory funnel and partitioned between EtOAc (5 mL/0.10 mmol of the nucleoside precursor) and water (10 mL/0.10 mmol of the nucleoside precursor). The aqueous layer was separated and back-extracted with EtOAc (2 $\times$ 5 mL/0.10 mmol of the nucleoside precursor). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification in each case was performed by column chromatography using an appropriate solvent. All iodination reactions were performed using these protocols; details for each are provided under the individual compound headings.

2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-5'-deoxy-5'-iodo-*N*^{6}-(4-chlorophenyl)adenosine (21).



The reaction was performed with 591.7 mg (0.98 mmol) of N^6-(4-chlorophenyl) nucleoside derivative **2** in two equal aliquots, using PPh_3 (1.0 g, 3.90 mmol), imidazole (265.7 mg, 3.90 mmol), and I_2 (743.1 mg, 2.93 mmol) and was complete within 1.5 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes and 20% EtOAc in hexanes gave 557.2 mg (80% yield) of desired product **21** as a white foam. R_f (SiO_2/20% EtOAc in hexanes) = 0.56. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (s, 1H), 7.99 (s, 1H), 7.85 (s, 1H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 2H), 5.88 (d, *J* = 5.7 Hz, 1H), 5.26 (dd, *J* = 5.7, 4.3 Hz, 1H), 4.39 (dd, *J* = 4.1, 2.8 Hz, 1H), 4.19 (ddd, *J* = 7.8, 5.4, 2.5 Hz, 1H), 3.73 (dd, *J* = 10.6, 7.8 Hz, 1H), 3.45 (dd, *J* = 10.7, 5.4 Hz, 1H), 0.96 and 0.78 (2s, 18H), 0.20, 0.16, –0.06, and –0.30 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 152.8, 152.3, 149.4, 141.5, 137.4, 129.2, 128.7, 121.7, 121.6, 90.3, 85.0, 75.3, 73.5, 26.1, 25.9, 18.3, 18.1, 6.0, –3.9, –4.1, –4.4, –4.9. HRMS (ESI/TOF) *m*/*z* calculated for $C_{28}H_{43}ClIN_5NaO_3Si_2$ [M + Na]$^+$: 738.1530, found 738.1551. The reaction was also performed on a 303.1 mg (0.5 mmol) scale of compound **2** and gave 270.3 mg (75% yield) of desired product **21**.

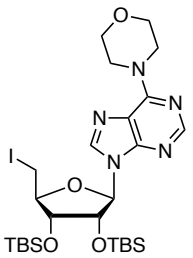
2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-5'-deoxy-5'-iodo-N^6-(4-methylphenyl)adenosine (22).



The reaction was performed with 255.0 mg (0.43 mmol) of N^6-(4-methylphenyl) nucleoside derivative **6** using PPh_3 (456.4 mg, 1.74 mmol), imidazole (118.4 mg, 1.74 mmol), and I_2 (331.2 mg, 1.30 mmol) and was complete within 1 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes and 30% EtOAc in hexanes gave 218.6 mg (72% yield) of desired product **22** as a white foam. R_f (SiO_2/20% EtOAc in hexanes) = 0.47. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.47 (s, 1H), 7.97 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.51 (s, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 5.87 (d, *J* = 5.8 Hz, 1H), 5.28 (dd, *J* = 5.8, 4.2 Hz, 1H), 4.41 (dd, *J* = 4.2, 2.6 Hz, 1H), 4.20 (ddd, *J* = 7.9, 5.4, 2.6 Hz, 1H), 3.75 (dd, *J* = 10.6, 7.9 Hz, 1H), 3.45 (dd, *J* = 10.6, 5.4 Hz, 1H), 2.35 (s, 3H), 0.96 and 0.79 (2s, 18H), 0.20, 0.16, –0.06, and –0.30 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 153.0, 152.8, 149.3, 141.1, 136.1, 133.6, 129.8, 121.6, 120.9, 90.3, 84.9, 75.4, 73.6, 26.1, 25.9, 21.1, 18.3, 18.1, 6.0, –3.9, –4.1, –4.4, –4.9. HRMS (ESI/TOF) *m*/*z* calculated for $C_{29}H_{46}IN_5NaO_3Si_2$ [M + Na]$^+$:

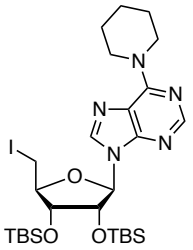
718.2076, found 718.2094. The reaction was also performed on a 183.8 mg (0.314 mmol) scale of compound **6** and gave 165.8 mg (76% yield) of desired product **22**.

9-[2,3-Di-*O*-(*tert*-butyldimethylsilyl)-5'-deoxy-5'-iodo-β-D-ribofuranosyl]-6-(morpholin-4-yl)-9*H*-purine (31).



The reaction was performed with 169.7 mg (0.30 mmol) of the morpholinyl nebularine derivative **16** using PPh_3 (314.7 mg, 1.2 mmol), imidazole (81.7 mg, 1.2 mmol), and I_2 (228.4 mg, 0.90 mmol) and was complete within 1 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes and eluted with hexanes followed by 20% EtOAc in hexanes gave 148.6 mg (73% yield) of **31** as pale-yellow foam. R_f (SiO_2/20% EtOAc in hexanes) = 0.51. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.32 (s, 1H), 7.92 (s, 1H), 5.86 (d, *J* = 5.4 Hz, 1H), 5.21 (t, *J* = 4.5 Hz, 1H) 4.36 (t, *J* = 3.4 Hz, 1H), 4.34–4.26 (br, 4H), 4.15 (ddd, *J* = 7.3, 5.1, 2.6 Hz, 1H), 3.84 (app t, *J* = 4.7 Hz, 4H), 3.73 (dd, *J* = 10.4, 7.2 Hz, 1H), 3.43 (dd, *J* = 10.8, 5.3 Hz, 1H), 0.95 and 0.80 (2s, 18H), 0.19, 0.15, –0.06 and –0.26 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ154.0, 152.3, 150.7, 139.2, 121.3, 90.2, 84.5, 75.4, 73.5, 67.2, 45.9, 26.1, 25.9, 18.3, 18.1, 6.3, –3.9, –4.1, –4.4, –4.8. HRMS (ESI/TOF) *m/z* calculated for $C_{26}H_{46}IN_5NaO_4Si_2$ $[M + Na]^+$: 698.2025, found 698.2034.

9-[2,3-Di-*O*-(*tert*-butyldimethylsilyl)-5'-deoxy-5'-iodo-β-D-ribofuranosyl]-6-(piperidin-1-yl)-9*H*-purine (32).



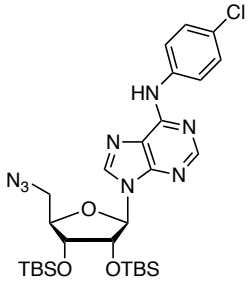
The reaction was performed with 141.0 mg (0.25 mmol) of the piperidinyl nebularine derivative **18** using PPh_3 (262.3 mg, 1.00 mmol), imidazole (68.1 mg, 1.00 mmol), and I_2 (190.3 mg, 0.75 mmol) and was complete within 1 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes and 20% EtOAc in hexanes gave 116.4 mg (69% yield) of desired product **32** as an off-white foam. R_f (SiO_2/10% EtOAc in hexanes) = 0.55. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.90 (s, 1H), 5.85 (d, *J* = 5.4 Hz, 1H), 5.20 (app t, *J* = 4.5 Hz, 1H), 4.36 (app t, *J* = 3.7 Hz, 1H), 4.29–4.18 (br, 4H), 4.15 (ddd, *J* = 7.6, 5.1, 2.8 Hz, 1H), 3.73 (dd, *J* = 10.7, 7.4 Hz, 1H), 3.43 (dd, *J* = 10.7, 5.4 Hz, 1H), 1.77–1.66 (m, 6H), 0.95 and 0.80 (2s, 18H), 0.19, 0.15, –0.06, and –0.25 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ154.0, 152.3, 150.5, 138.5, 121.1, 90.2, 84.4, 75.4, 73.5, 46.7, 26.3, 26.1, 25.9, 25.0, 18.3, 18.1,

6.3, –4.0, –4.1, –4.5, –4.8. HRMS (ESI/TOF) *m*/*z* calculated for $C_{27}H_{48}IN_5NaO_3Si_2$ $[M + Na]^+$: 696.2233, found 696.2254.

General Procedure for the Synthesis of 5'-Azido-2',3'-di-*O*-(*tert*-butyldimethylsilyl)-5'-deoxy-*N*^{6}-(4-chlorophenyl)adenosine (28), 5'-Azido-2',3'-di-*O*-(*tert*-butyldimethylsilyl)-5'-deoxy-*N*^{6}-(4-methylphenyl)adenosine (29), and 9-[5-Azido-2,3-di-*O*-(*tert*-butyldimethylsilyl)-5'-deoxy-β-D-ribofuranosyl]-6-(morpholin-4-yl)-9*H*-purine (34) from the Corresponding 5'-Iodo Nucleoside Precursors.

In an oven-dried 8 mL screwcap vial equipped with a stir bar was placed 5'-iodo nucleoside **21**, **22**, or **31** (1.0 equiv) in DMF (2.5 mL/0.25 mmol of the nucleoside precursor), NaN_3 (4.0 equiv) was added. The vial was capped, and the reaction mixture was heated at 110 °C for 1 h, at which time complete consumption of precursor (**21**, **22**, or **31)** was observed by TLC. EtOAc (3 mL/0.25 mmol of the nucleoside precursor) was added, and the mixture was transferred to a separatory funnel. Water (5 mL/0.25 mmol of the nucleoside precursor) and additional EtOAc (2 mL/0.25 mmol of the nucleoside precursor) were added, and mixture was extracted. The aqueous layer was separated and back-extracted with EtOAc (2 × 5 mL/0.25 mmol of the nucleoside precursor). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification in each case was performed by column chromatography using an appropriate solvent. All azidation reactions were performed using these protocols; details for each are provided under the individual compound headings.

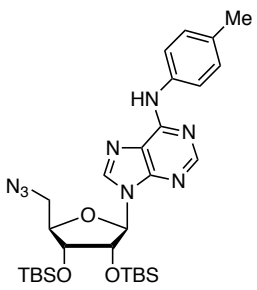
5'-Azido-2',3'-di-*O*-(*tert*-butyldimethylsilyl)-5'-deoxy-*N*^{6}-(4-chlorophenyl)adenosine (28).



The reaction performed with 179.0 mg (0.25 mmol) of the 5'-iodo *N*^{6}-(4-chlorophenyl) nucleoside derivative **21** and NaN_3 (65.0 mg, 1.0 mmol) was complete within 1 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes and 20% EtOAc in hexanes gave 123.1 mg (78% yield) of desired product **28** as a yellow oil. R_f (SiO_2/20% EtOAc in hexanes) = 0.48. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (s, 1H), 8.05 (s, 1H), 7.85 (s, 1H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 2H), 5.92 (d, *J* = 4.5 Hz, 1H), 4.96 (app t, *J* = 4.4 Hz, 1H), 4.32 (app t, *J* = 4.2 Hz, 1H), 4.21 (app q, *J* = 4.5 Hz, 1H), 3.73 (app d, *J* = 4.8 Hz, 2H), 0.94 and 0.83 (2s, 18H), 0.13, 0.12, –0.01, and –0.18 (4s, 12H). ^{13}C{^{1}H}

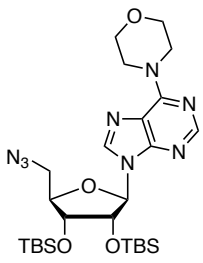
NMR (125 MHz, $CDCl_3$): δ152.9, 152.2, 149.4, 140.6, 137.5, 129.2, 128.7, 121.6, 121.4, 90.0, 83.3, 74.5, 72.7, 51.8, 26.0, 25.9, 18.3, 18.1, –4.2, –4.4, –4.6, –4.7. HRMS (ESI/TOF) *m*/*z* calculated for $C_{28}H_{43}ClN_8NaO_3Si_2$ $[M + Na]^+$: 653.2577, found 653.2573.

5'-Azido-2',3'-di-*O*-(*tert*-butyldimethylsilyl)-5'-deoxy-N^6-(4-methylphenyl)adenosine (29).



The reaction performed with 139.1 mg (0.20 mmol) of the 5'-iodo N^6-(4-methylphenyl) nucleoside derivative **22** and NaN_3 (52.0 mg, 0.80 mmol), was complete within 1 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes and 20% EtOAc in hexanes gave 110.6 mg (90% yield) of desired product **29** as a white foam. R_f (SiO_2/20% EtOAc in hexanes) = 0.41. ^{1}H NMR (500 MHz, $CDCl_3$): δ8.49 (s, 1H), 8.02 (s, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.53 (s, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 5.91 (d, *J* = 4.5 Hz, 1H), 4.98 (app t, *J* = 4.3 Hz, 1H), 4.33 (app t, *J* = 4.1 Hz, 1H), 4.21 (app q, *J* = 4.1 Hz, 1H), 3.73 (app d, *J* = 4.8 Hz, 2H), 2.35 (s, 3H), 0.94 and 0.83 (2s, 18H), 0.13, 0.12, –0.01, and –0.18 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 153.0, 152.7, 149.2, 140.3, 136.1, 133.6, 129.7, 121.3, 121.0, 90.0, 83.2, 74.5, 72.7, 51.9, 26.0, 25.9, 21.1, 18.2, 18.1, –4.2, –4.5, –4.6, –4.7. HRMS (ESI/TOF) *m*/*z* calculated for $C_{29}H_{46}N_8NaO_3Si_2$ $[M + Na]^+$: 633.3124, found 633.3129.

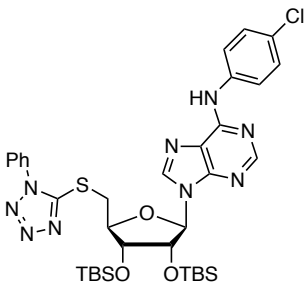
9-[5-Azido-2,3-di-*O*-(*tert*-butyldimethylsilyl)-5'-deoxy-β-D-ribofuranosyl]-6-(morpholin-4-yl)-9*H*-purine (34).



The reaction performed with 114.9 mg (0.17 mmol) of the 5'-iodo morpholinyl nebularine derivative **31** and NaN_3 (44.2 mg, 0.68 mmol) was complete within 1 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes and eluted with hexanes followed by 30% acetone in hexanes gave 87.6 mg (87% yield) of **34** as white foam. R_f (SiO_2/30% acetone in hexanes) = 0.52. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.98 (s, 1H), 5.91 (d, *J* = 4.0 Hz, 1H), 4.85 (t, *J* = 4.1 Hz, 1 H), 4.36–4.24 (m overlapping with a br, 5H), 4.20 (q, *J* = 4.6 Hz, 1H), 3.84 (app t, *J* = 4.8 Hz, 4H), 3.75 (dd, *J* = 13.2, 4.2 Hz, 1H), 3.70 (dd, *J* = 13.1, 4.9 Hz, 1H), 0.93 and 0.84 (2s, 18H), 0.11, 0.10, –0.00 and –0.12 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ154.0, 152.4, 150.6,

138.1, 120.9, 89.9, 82.7, 74.6, 72.4, 67.1, 51.7, 45.7, 26.0, 25.9, 18.2, 18.1, –4.2, –4.6(2C), –4.7. HRMS (ESI/TOF) m/z calculated for $C_{26}H_{46}N_8NaO_4Si_2$ $[M + Na]^+$: 613.3073, found 613.3085.

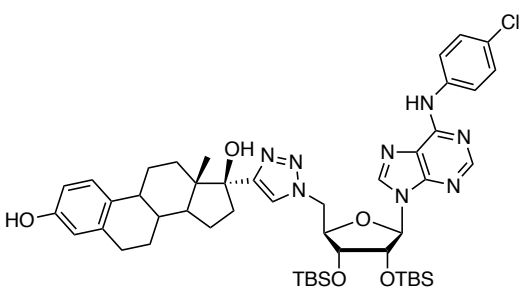
2',3'-Di-*O*-[(*tert*-butyldimethylsilyl)-5'-deoxy-5'-(1-phenyl-1*H*-tetrazol-5-yl)thio]-N^6-(4-chlorophenyl)adenosine (26).



In an oven-dried 15 mL screwcap vial equipped with a stir bar was placed 5'-iodo N^6-(4-chlorophenyl) nucleoside derivative **21** (379.6 mg, 0.53 mmol, 1.00 equiv) in acetone (3.0 mL). 1-Phenyl-1*H*-tetrazole-5-thiol (113.3 mg, 0.64 mmol, 1.2 equiv) and K_2CO_3 (366.2 mg, 2.65 mmol, 5.0 equiv) were added. The vial was capped, and the mixture was heated at 85 °C for 4 h, at which time TLC analysis indicated complete consumption of the precursor. The mixture was evaporated under reduced pressure, water (5 mL) and EtOAc (5 mL) were added, and the mixture was transferred to a separatory funnel. After extraction, the aqueous layer was separated and back-extracted twice with EtOAc (2 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by column chromatography on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes, 10% EtOAc in hexanes, 20% EtOAc in hexanes, and 30% EtOAc in hexanes gave 352.8 mg (87% yield) of desired product **26** as a peach-colored foam. R_f (SiO_2/30% EtOAc in hexanes) = 0.60. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.46 (s, 1H), 7.89 (s, 1H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.57 (s, 1H), 7.53–7.48 (m, 5H), 7.35 (d, *J* = 8.7 Hz, 2H), 5.86 (d, *J* = 6.5 Hz, 1H), 5.39 (dd, *J* = 6.3, 4.3 Hz, 1H), 4.49 (t, *J* = 6.7 Hz, 1H), 4.38 (dd, *J* = 4.0, 1.6 Hz, 1H), 4.04–4.03 (m, 2H), 0.95 and 0.77 (2s, 18H), 0.15, –0.08, and –0.40 (3s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 154.1, 152.6, 152.2, 149.3, 141.6, 137.3, 133.7, 130.4, 130.0, 129.3, 128.8, 123.9, 121.8, 121.7, 90.4, 84.4, 75.3, 73.3, 35.8, 26.0, 25.8, 18.3, 18.0, –4.3, –4.38, –4.4, –5.1. HRMS (ESI/TOF) *m*/*z* calculated for $C_{35}H_{48}ClN_9NaO_3SSi_2$ $[M + Na]^+$: 788.2720, found 788.2734.

1,2,3-Triazole-Bridged Estradiol Conjugated Derivative of 2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-N^6-(4-chlorophenyl)adenosine (30).

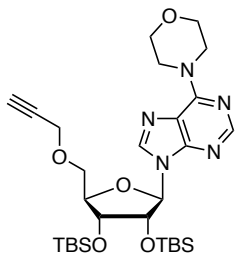
In an oven-dried 8 mL screwcap vial equipped with a stir bar, was placed 5'-azido N^6-(4-chlorophenyl) nucleoside derivative **28** (63.1 mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2:H_2O (0.55



mL:0.45 mL). 17-α-Ethynylestradiol (59.3 mg, 0.20 mmol, 2.0 equiv), $CuSO_4 \bullet 5H_2O$ (2.5 mg, 0.01 mmol, 0.1 equiv), and Na-ascorbate (4.0 mg, 0.02 mmol, 0.2 equiv) were added. The vial was capped, and the reaction mixture was stirred at room temperature for 2 h, at which time TLC analysis indicated complete consumption of the azide. EtOAc (3 mL) was added to the mixture and transferred to a separatory funnel. Water (5 mL) was added to the separatory funnel and the mixture was extracted. The separated aqueous layer was back-extracted with EtOAc (2 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the crude material on a silica gel column packed in hexanes and sequentially eluted with hexanes, 60% EtOAc in hexanes, and EtOAc, gave 67.4 mg (73% yield) of desired product **30** as a white solid. R_f (SiO_2/60% EtOAc in hexanes) = 0.41. ^{1}H NMR (500 MHz, $CDCl_3$): δ8.49 (s, 1H), 8.22 (s, 1H), 7.93 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.53 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.14 (br s, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.62 (d, *J* = 8.4, Hz, 1H), 6.57 (s, 1H), 5.93 (d, *J* = 6.4 Hz, 1H), 4.88 (dd, *J* = 14.2, 6.7 Hz, 1H), 4.82 (dd, *J* = 14.2, 4.4, 1H, partially overlapped with the adjacent upfield resonance), 4.81–4.78 (m, 1H), 4.45 (dd, *J* = 3.8, 2.3 Hz, 1H), 4.41 (ddd, *J* = 6.5, 4.2, 2.3 Hz, 1H), 3.37–3.29 (br, 1H), 2.79–2.66 (m, 2H), 2.38–2.32 (m, 1H), 2.07–2.02 (m, 2H), 1.91–1.86 (m, 1H), 1.83–1.78 (br m, 2H), 1.53–1.22 (m, 7H), 0.95 (2 × s, 12H), 0.75 (s, 9H), 0.14, 0.13, –0.07, and –0.37 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ153.93, 153.9, 153.1, 152.2, 149.3, 141.0, 138.4, 137.3, 132.5, 129.1, 128.8, 126.5, 123.5, 121.8, 120.8, 115.7, 113.1, 89.5, 84.4, 82.7, 73.6, 73.5, 51.7, 48.5, 47.4, 43.4, 39.6, 38.0, 33.1, 29.8, 27.4, 26.4, 26.0, 25.8, 23.6, 18.2, 18.0, 14.4, –4.26, –4.37, –4.4, –5.0. HRMS (ESI/TOF) *m*/*z* calculated for $C_{48}H_{68}ClN_8O_5Si_2$ [M + H]$^+$: 927.4534, found 927.4544.

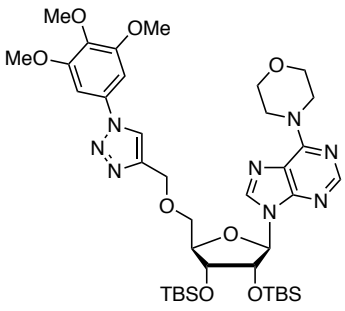
2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-5'-*O*-propynyl-*N*^{6}-(morpholin-4-yl)nebularine (35).

In an oven-dried 8 mL screwcap vial equipped with a stir bar was placed the morpholinyl nebularine derivative **16** (169.7 mg, 0.30 mmol, 1.0 equiv) in THF (1.8 mL), and the mixture was



cooled to 0 °C. NaH (60% in mineral oil, 60.0 mg, 1.5 mmol, 5.0 equiv) was added, the vial was capped, and the mixture was stirred at 0 °C for 10 minutes. This was followed by the addition of 80 wt % propargyl bromide in PhMe (66.8 μL, 0.75 mmol, 2.50 equiv). The mixture was brought to room temperature over 1 h, at which time TLC analysis indicated approximately 5% of unreacted precursor **16**. Water (3 mL) was added, and the mixture was transferred to a separatory funnel and extracted with EtOAc (5 mL). The aqueous layer was back-extracted with EtOAc (2 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by column chromatography on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes, 20% EtOAc in hexanes, and 30% EtOAc in hexanes gave 156.8 mg (86% yield) of desired product **35** as a pale-yellow gum. R_f (SiO_2/50% EtOAc in hexanes) = 0.35. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (s, 1H), 8.17 (s, 1H), 6.03 (d, *J* = 3.8 Hz, 1H), 4.57 (t, *J* = 3.9 Hz, 1H), 4.34–4.27 (m superimposed on a br, 5H), 4.26 (br s, 2H), 4.24–4.22 (m, 1H), 3.90 (dd, *J* = 10.6, 3.0 Hz, 1H), 3.83 (app t, *J* = 4.8 Hz, 4H), 3.76 (dd, *J* = 10.7, 3.3 Hz, 1H), 2.47 (t, *J* = 2.2 Hz, 1H), 0.91 and 0.85 (2s, 18H), 0.09, 0.07, 0.00, and –0.03 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 154.0, 152.5, 150.9, 137.8, 120.6, 89.1, 83.2, 79.3, 76.2, 75.4, 71.8, 68.7, 67.3, 58.8, 45.8, 26.1, 26.0, 18.3, 18.2, –4.1, –4.5, –4.6, –4.7. HRMS (ESI/TOF) *m*/*z* calculated for $C_{29}H_{49}N_5O_5NaSi_2$ [M + Na]$^+$: 626.3164, found 626.3192.

2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-5'-((3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-*N*^{6}-(morpholin-4-yl)nebularine (36).



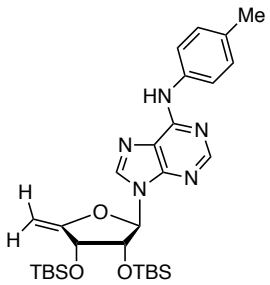
In an oven-dried 8 mL screwcap vial equipped with a stir bar was placed morpholinyl nebularine 5'-propargyl ether **35** (120.8 mg, 0.20 mmol, 1.0 equiv) in *t*-BuOH (1.2 mL) and H_2O (1.2 mL). 5-Azido-1,2,3-trimethoxybenzene (50.2 mg, 0.24 mmol, 1.2 equiv), $CuSO_4$•$5H_2O$ (12.5 mg, 0.05 mmol, 25 mol %), and Na-ascorbate (9.9 mg, 0.05 mmol, 0.25 equiv) were added. The vial was capped, and the mixture was stirred at room temperature for 1 h, at which time TLC analysis indicated complete consumption of alkyne **35**. Water (3 mL) was added, and the mixture was transferred to a separatory funnel and extracted with EtOAc (5 mL). The aqueous layer was back-extracted with

EtOAc (2 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by column chromatography on a 200–300 mesh silica gel column packed in 20% EtOAc in hexanes and sequentially eluted with 20% EtOAc in hexanes, and 80% EtOAc in hexanes gave 124.9 mg (77% yield) of desired product **36** as a white foam. R_f (SiO_2/50% EtOAc in hexanes) = 0.21. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (s, 1H), 8.17 (s, 1H), 7.95 (s, 1H), 6.92 (s, 2H), 6.00 (d, *J* = 3.8 Hz, 1H), 4.83 (ABq, *J* = 12.6 Hz, 2H), 4.63 (t, *J* = 4.0 Hz, 1H), 4.35 (t, *J* = 4.7 Hz, 1H), 4.28–4.24 (m, 5H), 3.96 (dd, *J* = 10.7, 3.0 Hz, 1H), 3.91 (s, 6H), 3.89 (s, 3H), 3.83 (dd, *J* = 10.7, 3.8 Hz, 1H, partially overlapped with the adjacent upfield app t), 3.80 (app t, *J* = 4.8 Hz, 4H), 0.90 and 0.84 (2s, 18H), 0.07, 0.06, –0.01, and –0.07 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 154.1, 154.0, 152.4, 150.9, 145.5, 138.7, 137.9, 133.0, 121.2, 120.7, 98.8, 89.2, 83.4, 75.8, 71.9, 69.6, 67.2, 65.1, 61.2, 56.7, 45.8, 26.0, 25.9, 18.3, 18.1, –4.1, –4.5, –4.7. HRMS (ESI/TOF) *m*/*z* calculated for $C_{38}H_{61}N_8O_8Si_2$ $[M + H]^+$: 813.4145, found 813.4141.

General Procedure for the Synthesis of 2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-4',5'-didehydro-5'-deoxy-*N*^{6}-(4-methylphenyl)adenosine (27) and 2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-4',5'-didehydro-5'-deoxy-6-(piperidin-1-yl)nebularine (33) from the Corresponding Iodo Nucleoside Precursors.

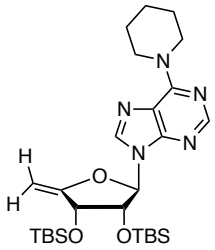
In an oven-dried 8 mL screwcap vial equipped with a stir bar was placed the 5'-iodo nucleoside **22** or **32** (1.0 equiv) in THF (1 mL), and DBU (4.0 equiv) was added. The vial was capped, and the mixture was heated at 60 °C, until the complete consumption of the precursor (**22** or **32**) was observed by TLC. Saturated aq. $NaHCO_3$ (5 mL) was added, and the mixture transferred to a separatory funnel and extracted with EtOAc (10 mL). The aqueous layer was back-extracted with EtOAc (2 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification in each case was performed by column chromatography using an appropriate solvent. All elimination reactions were performed using these protocols; details for each are provided under the individual compound headings.

2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-4',5'-didehydro-5'-deoxy-*N*^{6}-(4-methylphenyl)adenosine (27).



The reaction of 5'-iodo N^6-(4-methylphenyl) nucleoside derivative **22** (69.5 mg, 0.10 mmol) and DBU (59.8. μL, 0.40 mmol) was complete within 4 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes, 5% acetone in hexanes, and 20% acetone in hexanes gave 52.6 mg (93% yield) of desired product **27** as a white foam. R_f (SiO_2/5 % acetone in hexanes) = 0.11. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.52 (s,1H), 7.90 (s, 1H), 7.69 (s, 1H), 7.65 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 6.14 (d, J = 6.3 Hz, 1H), 5.11 (dd, J = 6.1, 4.3 Hz, 1H), 4.60 (d, J = 4.1 Hz, 1H), 4.54 (d, J = 1.8 Hz, 1H), 4.30 (d, J = 1.8 Hz, 1H), 2.35 (s, 3H), 0.95 and 0.76 (2s, 18H), 0.16, –0.06, and –0.31 (3s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 160.8, 153.4, 152.7, 149.6, 140.2, 136.0, 133.7, 129.8, 121.3, 121.0, 89.5, 87.1, 74.6, 72.5, 26.0, 25.8, 21.1, 18.4, 18.1, –4.1, –4.3, –4.4, –5.1. HRMS (ESI/TOF) m/z calculated for $C_{29}H_{45}N_5NaO_3Si_2$ [M + Na]$^+$: 590.2953, found 590.2964.

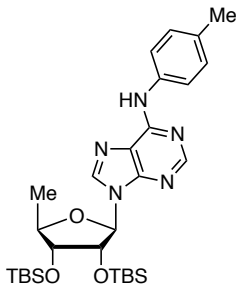
2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-4',5'-didehydro-5'-deoxy-6-(piperidin-1-yl)nebularine (33).



The reaction of 5'-iodo piperidinyl nebularine derivative **32** (67.4 mg, 0.10 mmol) and DBU (59.8 μL, 0.40 mmol) was complete within 2 h. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes and 30% EtOAc in hexanes gave 46.4 mg (85% yield) of desired product **33** as a pale-yellow oil. R_f (SiO_2/10% EtOAc in hexanes) = 0.38. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (s, 1H), 7.77 (s, 1H), 6.10 (d, J = 6.1 Hz, 1H), 5.06 (dd, J = 5.9, 4.4 Hz, 1H), 4.59 (d, J = 4.2 Hz, 1H), 4.50 (d, J = 1.9 Hz, 1H), 4.26 (d, J = 1.9 Hz, 1H, partially overlapped with the adjacent upfield br resonance), 4.25–4.18 (br, 4H), 1.73–1.68 (m, 6H), 0.94 and 0.79 (2s, 18H), 0.14, –0.07, and –0.28 (3s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 161.0, 154.0, 152.8, 151.0, 137.5, 120.9, 89.4, 86.7, 74.4, 72.5, 46.7, 26.3, 26.0, 25.8, 25.0, 18.4, 18.1, –4.1, –4.3, –4.4, –5.1. HRMS (ESI/TOF) m/z calculated for $C_{27}H_{47}N_5NaO_3Si_2$ [M + Na]$^+$: 568.3110, found 568.3099.

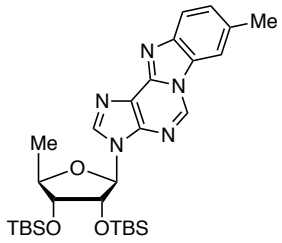
2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-5'-deoxy-N^6-(4-methylphenyl)adenosine (23).

In an oven-dried 50 mL round-bottom flask equipped with a stir bar was placed 5'-iodo N^6-(4-methylphenyl) nucleoside derivative **22** (69.5 mg, 0.10 mmol, 1.0 equiv) in MeOH (4 mL). iPr_2NEt (191.6 μL, 1.10 mmol, 11.0 equiv) and 20 wt % $Pd(OH)_2$/C (42.1 mg) were added. The flask was



evacuated and filled with H_2 gas. The mixture was stirred under an atmosphere of H_2 gas for 1 h, at room temperature, at which time TLC analysis showed complete consumption of precursor **22**. The mixture was filtered through Celite, the residue was washed with MeOH (100 mL), and the filtrate was evaporated. Purification of the crude material by column chromatography on a 200–300 mesh silica gel column packed in hexanes and sequentially eluted with hexanes and 30% EtOAc in hexanes gave 50.8 mg (89% yield) of desired product **23** as a white foam. R_f (SiO_2/20% EtOAc in hexanes) = 0.29. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.90 (s, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.51 (s, 1H), 7.19 (d, *J* = 8.2 Hz, 2H), 5.87 (d, *J* = 4.4 Hz, 1H), 4.94 (app t, *J* = 4.3 Hz, 1H), 4.23 (qd, *J* = 6.5, 4.5 Hz, 1H), 4.06 (app t, *J* = 4.4 Hz, 1H), 2.35 (s, 3H), 1.46 (d, *J* = 6.5 Hz, 3H), 0.94 and 0.83 (2s, 18H), 0.11, 0.10, –0.01, and –0.17 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 153.0, 152.7, 149.3, 140.1, 136.1, 133.6, 129.8, 121.5, 121.0, 90.2, 80.9, 77.0, 74.9, 26.1, 26.0, 21.1, 19.2, 18.3, 18.1, –4.1, –4.4, –4.5, –4.6. HRMS (ESI/TOF) *m*/*z* calculated for $C_{29}H_{47}N_5NaO_3Si_2$ $[M + Na]^+$: 592.3110, found 592.3122.

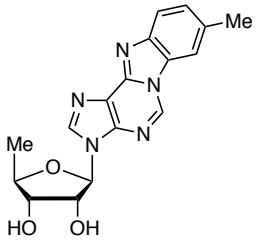
2',3'-Di-*O*-(*tert*-butyldimethylsilyl)-5'-deoxy-8-methyl-3*H*-benzo[4,5]imidazo[2,1-*i*]purine Ribonucleoside (24).



In an oven-dried 8 mL screwcap vial equipped with a stir bar was placed the N^6-(4-methylphenyl) nucleoside derivative **23** (56.9 mg, 0.10 mmol, 1.0 equiv) in HFIP (1 mL), and PIDA (41.8 mg, 0.13 mmol, 1.3 equiv) was added. The vial was capped and the mixture was stirred at room temperature for 1 h, at which time TLC analysis indicated complete consumption of precursor **23**. The mixture was evaporated under reduced pressure. Purification of the crude material by column chromatography on a 200–300 mesh silica gel column packed in hexanes, and sequentially eluted with hexanes and 50% EtOAc in hexanes gave 50.8 mg (89% yield) of desired product **24** as a pale-yellow solid. R_f (SiO_2/50% EtOAc in hexanes) = 0.27. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.03 (s, 1H), 8.07 (s, 1H), 7.84 (d, 1H, *J* = 8.3 Hz), 7.72 (s, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 6.00 (d, *J* = 3.8 Hz, 1H), 4.73 (app t, *J* = 4.0 Hz, 1H), 4.27 (qd, *J* = 6.5, 5.2 Hz, 1H), 4.00 (dd, *J* = 5.2, 4.3 Hz, 1H), 2.54 (s, 3H), 1.47 (d, *J* = 6.5 Hz, 3H), 0.93 and 0.85 (2s, 18H), 0.10, 0.08, 0.01, and –0.10 (4s, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 144.0, 142.9, 140.3, 139.6, 135.1, 132.6,

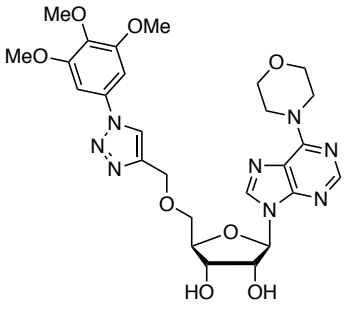
128.1, 127.7, 124.2, 120.1, 110.2, 90.3, 80.5, 76.9, 75.9, 26.0, 25.9, 21.9, 19.1, 18.3, 18.1, –4.1, –4.5, –4.51, –4.6. HRMS (ESI/TOF) *m*/*z* calculated for $C_{29}H_{45}N_5NaO_3Si_2$ $[M + Na]^+$: 590.2953, found 590.2957.

5'-Deoxy-8-methyl-3*H*-benzo[4,5]imidazo[2,1-*i*]purine ribonucleoside (25).



In an oven-dried 8 mL screwcap polypropylene vial equipped with a stir bar was placed the benzo[4,5]imidazo[2,1-*i*]purine ribonucleoside **24** (46.5 mg, 0.082 mmol, 1.0 equiv) in THF (0.81 mL), and $Et_3N•3HF$ (43.0 μL, 0.27 mmol, 3.3 equiv) was added. The vial was capped, and the mixture was stirred at room temperature for 42 h, at which time TLC analysis indicated complete desilylation. The mixture was evaporated by a stream of air using a polyethylene pipet. The residue was dissolved in CH_2Cl_2 (25 mL), transferred to a 50 mL round-bottom flask, and evaporated under reduced pressure. Purification of the crude material by column chromatography on a 200–300 mesh silica gel column packed in EtOAc and sequentially eluted with EtOAc, 10% MeOH in EtOAc, 20% MeOH in EtOAc, and 30% MeOH in EtOAc gave 25.0 mg (90% yield) of desired product **25** as a white solid. R_f (SiO_2/40% MeOH in EtOAc) = 0.59. ^{1}H NMR (500 MHz, DMSO): δ9.74 (s, 1H), 8.56 (s, 1H), 8.23 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 6.03 (d, *J* = 4.9 Hz, 1H), 4.67 (app t, *J* = 5.0 Hz, 1H), 4.05 (app quint, *J* = 5.7 Hz, 1H), 4.00 (app t, *J* = 5.0 Hz, 1H), 2.56 (s, 3H), 1.36 (d, *J* = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO): δ143.9, 142.6, 141.2, 140.6, 138.1, 131.8, 128.4, 127.9, 122.5, 119.1, 112.4, 88.8, 80.6, 75.2, 74.2, 21.8, 19.5. HRMS (ESI/TOF) *m*/*z* calculated for $C_{17}H_{18}N_5O_3$ $[M + H]^+$: 340.1404, found 340.1415.

5'-((3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-*N*^{6}-(morpholin-4-yl)nebularine (37).



In an oven-dried 8 mL screwcap polypropylene vial equipped with a stir bar was placed morpholinyl nebularine 5'-triazole derivative **36** (97.6 mg, 0.12 mmol, 1.0 equiv) in THF (1.2 mL), and $Et_3N•3HF$ (64.5 μL, 0.40 mmol, 3.3 equiv) was added. The vial was capped, and the mixture was stirred at room temperature for 45 h, at which time TLC analysis indicated complete desilylation. The mixture was evaporated by a stream of air using a polyethylene pipet. The residue was dissolved in CH_2Cl_2 (25

mL), transferred to a 50 mL round-bottom flask, and evaporated under reduced pressure. The resulting product upon washing with aliquots of 1:1 Et_2O/MeOH (40 mL total) gave 60.2 mg (86% yield) of desired product **37** as a white solid. R_f (SiO_2/20% MeOH in EtOAc) = 0.11. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H), 8.03 (s, 1H), 7.83 (s, 1H), 6.90 (s, 2H), 5.98 (d, *J* = 4.9 Hz, 1H), 4.73 (s, 2H), 4.49 (app t, *J* = 5.0 Hz, 1H), 4.46–4.44 (m, 1H), 4.44–4.41 (m, 1H), 4.32–4.23 (br, 4H), 3.92 (s, 6H), 3.89 (s, 3H), 3.85 (dd, *J* = 10.6, 3.4 Hz, 1H), 3.81–3.77 (m, 5H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 154.0, 153.8, 151.9, 149.9, 145.2, 138.5, 136.9, 132.8, 121.3, 120.3, 98.7, 90.1, 84.9, 76.1, 71.7, 70.2, 67.1, 64.8, 61.2, 56.6, 45.8. HRMS (ESI/TOF) *m*/*z* calculated for $C_{26}H_{33}N_8O_8$ $[M + H]^+$: 585.2416, found 585.2440.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.XXXXXXX.

^{1}H and ^{13}C NMR spectra for the compounds described as well as two-dimensional NMR spectra for selected compounds.

FAIR data, including the NMR FID files, for compounds **1**–**37** (ZIP).

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Author Contributions

DS and SS performed the experimental work and product characterization and generated data for the Results and Discussion as well as the Experimental Section. PP assisted with gathering NMR data and with aspects of data interpretation, when needed. LY obtained the high-resolution mass spectral data. MKL conceived the project, provided guidance, and wrote the manuscript.

Notes

The authors declare no competing financial interest.

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