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Azide−Tetrazole Equilibrium of C-6 Azidopurine Nucleosides and Their Ligation Reactions with Alkynes

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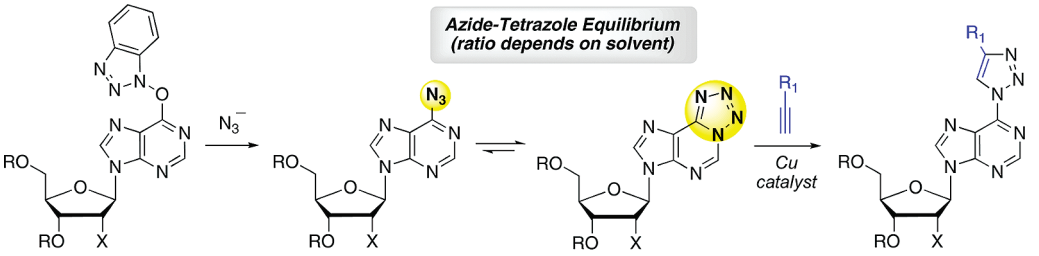

Facile syntheses of C-6 azidopurine ribonucleosides and 2′-deoxyribonucleosides have been developed. For silyl- and acetyl-protected as well as unprotected nucleosides, access to the azido derivatives could be readily attained via displacement of BtO^- from the O^6-(benzotriazol-1-yl)inosine nucleosides by azide anion. Use of diphenylphosphoryl azide/DBU as a simple route to the acetyl-protected azido nucleosides was also evaluated, but this proved to be inferior. Since these azido nucleosides can exist in an azide·tetrazole equilibrium, the effect of solvent polarity on this equilibrium was investigated. Subsequently, a detailed analysis of Cu-mediated azide−alkyne ("click") ligation was undertaken. Biphasic CH_2Cl_2/H_2O medium proved to be best for the ligation reactions, suppressing the undesired azide reduction that was competing. Interestingly, although the tetrazolyl isomer predominates (ca. 80%) in CD_2Cl_2 and in CD_2Cl_2/D_2O, the Cu-catalyzed click reactions proceed smoothly with the silyl-protected ribo- and 2′-deoxyribonucleosides, leading to the C-6 triazolyl products in good to excellent yields. Thus, depletion of the azido form from the reaction mixture shifts the azide·tetrazole equilibrium, eventually resulting in complete consumption of azide and tetrazole. In several cases, major and minor azide−alkyne ligation products were observed, and characterization data are provided for both. In order to confirm the regiochemistry leading to the major isomer, one product was crystallized and evaluated by X-ray crystallography. The Cu-catalyzed azide−alkyne ligation is clearly efficient and significantly superior to thermal reactions, which were slow. Biological evaluation showed low cytotoxicities for the agents, suggesting their usefulness as biological probes.

Introduction

The Huisgen azide−alkyne cycloaddition reaction, leading to the formation of triazoles, is one of the most atom-economical transformations.[1−7] In 2002, the use of Cu^I-mediated azide−alkyne ligation was reported to proceed in a facile and regioselective manner, producing the 1,4-disubstituted triazoles in

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preference to the 1,5-isomers.[8] Soon after, a convenient method involving the use of Cu^{II} was discovered that was more reliable and superior than that utilizing Cu^{I}.[9] This method has become highly popular and has impacted areas such as polymer, materials, carbohydrate, and biological chemistry.

Nucleosides are central to a variety of biological processes, and the ability to modify nucleosides via facile approaches is of high importance for developing novel applications in biochemistry, biology, and medicine. The nucleoside scaffold has proven to be highly versatile, modification of which has resulted in a wide range of pharmacologically important entities. For example, modification of the adenosine core has the potential to yield new compounds such as those possessing activity at the adenosine receptors.[10,11] Azide−alkyne click reactions have found a variety of applications in nucleoside chemistry recently,[12] and the importance of click reactions in the field of nucleosides has recently been reviewed.[13] However, in the current literature azidopurine nucleoside derivatives have received very little attention as reactive partners in these reactions. To our knowledge, there are only two reports of azide−alkyne ligation reactions wherein C-2 azidopurine nucleoside analogues have been utilized.[14,15] Since there could be differences in reactivity at the various positions of purine nucleosides and because the azide−alkyne ligation reactions of 6-azidopurine nucleosides could be a powerful tool for biomolecular modification, we became interested in this class of reactions. The present paper describes a facile approach to 6-azidopurine nucleosides, their behavior in solution, and their ability to partner in Cu-catalyzed ligation reactions with alkynes.

Results and Discussion

Synthesis of the 6-Azidopurine Nucleoside Derivatives. At the beginning of our studies, the first question was whether a reliable method to synthesize 6-azidopurine ribo- and 2′-deoxyribonucleosides could be found. Three methods have been reported in the literature for the synthesis of 6-azido-9-β-D-ribofuranosylpurine. The oldest method involves conversion of 6-chloro-9-β-D-ribofuranosylpurine to an unstable 6-hydrazino derivative followed by treatment with nitrous acid.[16] The acidic conditions are obviously not compatible with the labile 2′-deoxyribonucleosides. In a second method, 6-methylsulfonyl-9-β-D-ribofuranosylpurine was converted to the azidopurine nucleoside.[17] It has been noted in these reports that displacement of chloride from 6-chloro-9-β-D-ribofuranosylpurine by azide ion results in decomposition.[16,17] Consistent with these observations, more recent syntheses of 6-azido-9-β-D-ribofuranosylpurine[18] and 6-azido-9-β-D-arabinofuranosylpurine[19] by replacement of chloride with azide gave low 21% and 38.4% yields of the respective azidopurine nucleoside analogues. Given these relatively unsatisfactory methods, we opted to develop a new synthesis of 6-azido-9-(2-deoxy-β-D-ribofuranosyl)-purine as well as 6-azido-9-β-D-ribofuranosylpurine.

We have recently reported facile, high-yielding syntheses of O^6-(benzotriazol-1-yl)inosine and 2′-deoxyinosine derivatives.[20−22] We reasoned that these compounds could be convenient precursors to the 6-azidopurine nucleoside derivatives (Scheme 1).

As shown in Scheme 1, silylated 2′-deoxyinosine **1a** and inosine **1b** as well as the unprotected nucleosides **1e** and **1f** were converted to the O^6-(benzotriazol-1-yl) derivatives via known procedures.[20] Using similar methodology, the previously undescribed acetate-protected compounds **2c** and **2d** were prepared as well. Table 1 summarizes the conditions used for the conversion of **2a**−**f** to azido nucleosides **3a**−**f**.

Although reactions of **2a** and **2b** could be conducted in DMF as solvent, competing formation of small amounts of the N^6, N^6-dimethylamino nucleoside derivative prompted the use of DMSO. These reactions proceeded smoothly and in high yields. Reactions of the unprotected derivatives **2e** and **2f** were somewhat problematic considering solubility as well as ease of product isolation. In both cases, polymer-supported azide[23] proved to be useful for the conversion. With the deoxy derivative **2e**, reasonable reaction was attained in water. We have demonstrated that O^6-(benzotriazoly-1-yl) nucleoside analogues are relatively stable toward hydroxylic solvents such as water and alcohol under neutral conditions.[20,24] Thus, the

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SCHEME 1. Synthesis of C-6 Azidopurine Nucleoside Analogues from the O^6-(Benzotriazol-1-yl)inosine Derivatives

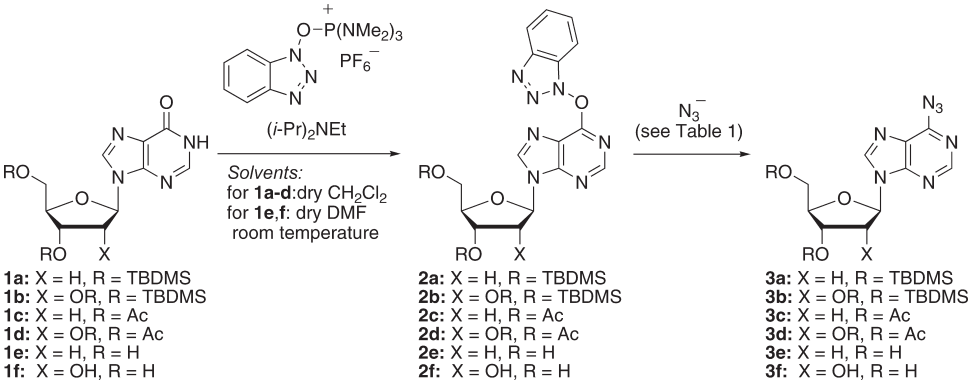

TABLE 1. Conditions for the Conversion of O^6-(Benzotriazol-1-yl)-inosine Derivatives 2a−f to the Azido Nucleosides 3a−f

entry	substrate	conditions	product: yield[a] (%)
1	**2a**	NaN_3, DMSO, 40 °C, 2 h	**3a**: 99
2	**2b**	NaN_3, DMSO, 40 °C, 3.5 h	**3b**: 96
3	**2c**	NaN_3, DMSO, rt, 1 h	**3c**: 95
4	**2d**	NaN_3, DMSO, rt, 1 h	**3d**: 75
5	**2e**	polymer-supported N_3^-, H_2O, 50 °C, 3.5 h	**3e**: 59
6	**2f**	polymer-supported N_3^-, DMF, 50 °C, 5 h	**3f**: 70

[a]Yields of isolated and purified products.

modest yield in this case may not be due to hydrolysis. With the ribose derivative **2f**, DMF proved to be optimal for workup and isolation reasons. In principle, cleavage of protecting groups in **3a−d** should also readily yield the unprotected compounds **3e**,**f**.

Next, we considered a more direct access to protected 6-azidopurine nucleosides by conversion of the amide carbonyl to a leaving group in situ. For this, we decided to use diphenylphosphoryl azide [$(PhO)_2P(O)N_3$, DPPA] in conjunction with a base. Mechanistically, deprotonation of the amide and reaction with DPPA would produce a diphenyl phosphate intermediate that could undergo subsequent S_NAr reaction with azide anion (Scheme 2).

On the basis of this rationale, **1c** and **1d** were exposed to DPPA and DBU in THF at 0 °C followed by warming to 60 °C. Azido nucleosides **3c** and **3d** were produced in yields of 67% and 41%, respectively, after purification. Interestingly, a similar reaction of silylated derivative **1a** led to only a 36% isolated yield of **3a**, perhaps indicating some influence of the saccharide protecting group on the efficiency of the S_NAr reaction. Thus, displacement reactions on O^6-(benzotriazol-1-yl) derivatives **2a−f** by azide offer generally good access to C−6 azidopurine nucleosides.

Azide−Tetrazole Equilibium of the 6-Azidopurine Nucleoside Derivatives. It is known that both 6-azidopurine as well as the corresponding ribonucleoside can exist in the alternate tetrazolyl forms.[16,25,26] In fact, in DMSO-d_6, 6-azidopurine as well as its N7- and N9-benzyl derivatives exist exclusively as the tetrazolyl isomers, and the azido forms are observable only upon protonation with trifluoroacetic acid.[25,26] Similarly, in the solid state, 6-azidopurine ribonucleoside exists as the tetrazolyl isomer lacking an IR absorption at 2000−2200 cm^{-1} corresponding to the azido tautomer.[16,18] Since the subsequent stage of our work entailed the development of azide−alkyne ligation chemistry, we wanted to evaluate the influence solvent polarity elicits on the equilibrium involving the azido nucleosides and the corresponding tetrazolo[5,1-*i*]purinyl isomers. For this analysis, ^{1}H NMR spectroscopy appeared to be optimal since the H-2 and H-8 resonances of the azido and tetrazolyl isomers are well resolved and diagnostic. In the tetrazolyl forms of 6-azidopurine, its N9- and N7-benzyl derivatives, H-2 appears at ∼9.7−10 ppm, whereas H-8 appears at ∼8.6−9.4 ppm.[26] On the other hand, in the azido isomers of the same purine derivatives, the line separation between the H-2 and H-8 resonances is much smaller, with H-2 appearing at ∼9.1−9.2 ppm and the H-8 at ∼8.8−9.1 ppm (see Table S1 in the Supporting Information).[26] Thus, H-2 of the tetrazolyl isomer appears farther downfield compared to its H-8 resonance as well as the H-2 and H-8 resonances of the azido tautomer.[26] On the basis of these as well as NOESY data from **3b** (in acetone-d_6) and **3d** (in $CDCl_3$) showing correlation between H-1′ and H-8, we determined the chemical shifts of purinyl H-2, H-8 and the saccharide H-1′ in the azido (**A**) and tetrazolyl (**T**) forms of compounds **3a−f** . These results are shown in Table 2.

For determining the proportion of the azido and tetrazolyl forms in **3a−f**, the H-2 and H-8 resonances were related to the H-1′ resonances of the two isomers. The integrals of the H-1′ resonances were then used to determine the ratios of the two isomeric forms. Several solvents were selected with varying dielectric constants (ε), and the results are shown in Table 3.

With this analysis, it became clear that generally the proportion of the tetrazolyl isomer increases with increasing solvent dielectric constant. This is consistent with prior results on 6-azidopurine, where lower solvent dielectric constant has been implicated in tetrazole destabilization.[25] In fact, in chloroform, about 40−50% of the tetrazolyl form is present (the triacetates **3c** and **3d** show a slightly higher proportion of the azido form in chloroform). In THF as well as in dichloromethane, which are close in dielectric constant, the tetrazolyl form is major. Finally, in acetone and DMSO the tetrazolyl form predominates. For unprotected **3e**, where analysis was possible in THF, a greater proportion of the azido isomer is observed in THF than in DMSO. The ratio of these isomers in **3e** is also consistent with data for the other azidopurine nucleoside derivatives shown in Table 3.

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SCHEME 2. Synthesis of 3c and 3d via Reaction of 1c and 1d with $(PhO)_2P(O)N_3$/DBU

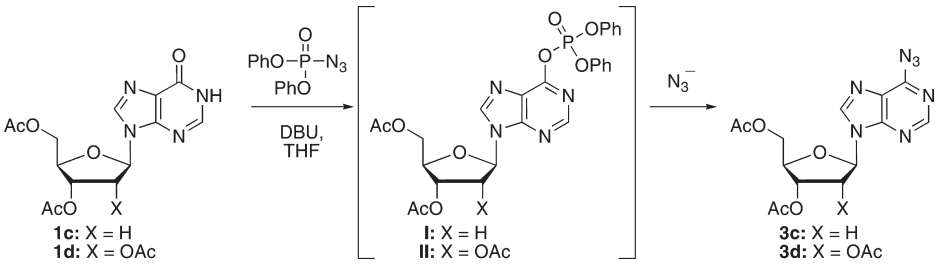
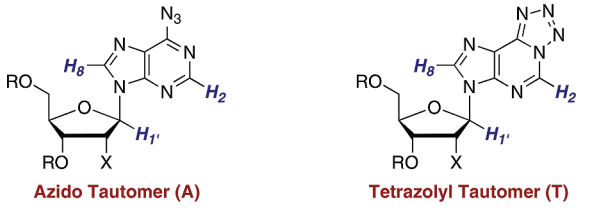


TABLE 2. Chemical Shifts (δ ppm) of Purinyl H-2, H-8 and the Sugar H-1′ in the Azido and Tetrazolyl Isomers of 3a–f



		azido form (**A**)			tetrazolyl form (**T**)		
compd	solvent	H-2	H-8	H-1′	H-2	H-8	H-1′
3a	$CDCl_3$	8.63	8.33	6.47	9.51	8.57	6.61
	THF-d_8	8.58	8.36	6.45	9.78	8.54	6.60
	CD_2Cl_2	8.63	8.33	6.47	9.51	8.57	6.61
	acetone-d_6	8.65	8.51	6.54	9.91	8.69	6.70
	DMSO-d_6				10.14	8.82	6.57
3b	$CDCl_3$	8.65	8.41	6.10	9.49	8.66	6.25
	THF-d_8	8.60	8.46	6.07	9.82	8.66	6.24
	CD_2Cl_2	8.64	8.40	6.09	9.52	8.67	6.25
	acetone-d_6	8.68	8.59	6.17	9.97	8.78	6.33
	DMSO-d_6				10.19	8.88	6.17
3c	$CDCl_3$	8.67	8.18	6.47	9.53	8.40	6.59
	THF-d_8	8.60	8.35	6.48	9.81	8.52	6.62
	CD_2Cl_2	8.65	8.19	6.48	9.54	8.42	6.60
	acetone-d_6	8.68	8.53	6.57	9.95	8.71	6.73
	DMSO-d_6				10.16	8.87	6.61
3d	$CDCl_3$	8.68	8.15	6.21	9.54	8.38	6.33
	THF-d_8	8.62	8.35	6.27	9.83	8.52	6.41
	CD_2Cl_2	8.67	8.16	6.22	9.56	8.41	6.36
	acetone-d_6	8.70	8.53	6.36	9.97	8.71	6.52
	DMSO-d_6				10.19	8.88	6.46
3e[a]	THF-d_8	8.57	8.46	6.48	9.78	8.68	6.64
	DMSO-d_6				10.13	8.88	6.57
3f[a]	DMSO-d_6				10.15	8.93	6.15

[a]Solubility constraints precluded assessment in other solvents.

It stands to reason, therefore, that only the tetrazolyl form of azidopurine nucleoside **3f** could be detected in the solid state and as a solution in DMSO.[16,18,28] These observations then led to the obvious question: *Do the azide–tetrazole mixtures undergo efficient ligation ("click") reactions with alkynes?* The answer to this is not obvious in the context of a recent report showing 2-azido-3-phenylpyridine to exist as the 8-phenyltetrazolo[1,5-*a*]pyridine and being recalcitrant toward the Staudinger reaction with PPh_3.[29] Also, it has been

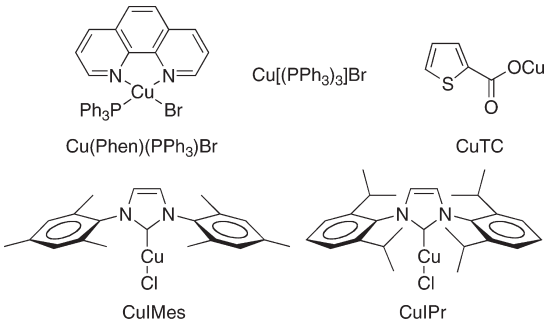


FIGURE 1. Other copper catalysts tested for the azide–alkyne ligation.

speculated that some of the lower yielding azide–alkyne ligations involving a C-2 azidopurine nucleoside could be due to the presence of the tetrazolyl tautomer.[13]

Thus, we began screening conditions for the Cu-catalyzed azide–alkyne ligation[8,9] reaction between **3a** and phenylacetylene. At the outset, the $CuSO_4$/Na ascorbate system in *t*-BuOH/H_2O was chosen.[9] However, under these conditions, an incomplete reaction was observed after 3.5 h at room temperature, with only 26% product formation. Importantly, 11% reduction of the azide to the amine was observed (entry 1 in Table 4), and the resulting disilyl 2′-deoxyadenosine was isolated and identified. This clearly points to the facile reducibility of the azide functionality in **3a**, which contrasts with the reactivity of simpler azides where such reduction is generally not observed under the click reaction conditions.

On the basis of the results obtained above, we screened azide–alkyne ligation conditions extensively (Table 4), and in subsequent reactions TLC analysis was conducted to include detection (UV visualization) of the azide reduction. Replacing *t*-BuOH with THF or toluene did not provide any significant improvement (entries 2 and 3). Several other Cu catalysts shown in Figure 1 were also evaluated, and Table 4 lists some representative results.

From these experiments two important features emerged. Use of a biphasic CH_2Cl_2/H_2O system[30] was important for successful reaction. Second, and more significantly, despite a major proportion of the tetrazolyl tautomer in this solvent system, reactions with phenylacetylene proceeded smoothly. To illustrate this point, ^{1}H NMR data for **3a** and **3b** were obtained in CD_2Cl_2/10% D_2O. In this solvent, the amounts of the azido and tetrazolyl forms of **3a** were 18.4% and 81.6%, respectively, whereas for **3b** they were 21% and 79%, respectively. These ratios are very similar to the data obtained in

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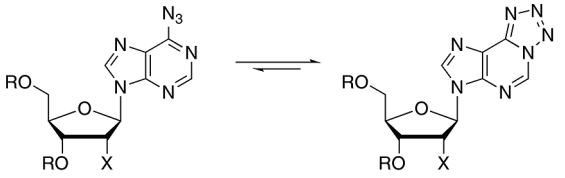
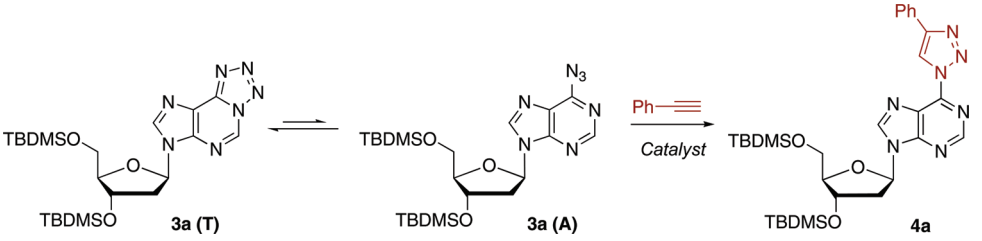
TABLE 3. Percentage Populations of the Azido (A) and Tetrazolyl (T) Isomers of 3a−f in Various Solvents[a]



	$CDCl_3$, ε = 4.8		THF-d_8, ε = 7.6		CD_2Cl_2, ε = 8.9		acetone-d_6, ε = 20.6		DMSO-d_6, ε = 46.5	
compd	% A	% T	% A	% T	% A	% T	% A	% T	% A	% T
3a	46.0	54.0	14.8	85.2	20.8	79.2	7.5	92.5	0.1	99.9
3b	47.6	52.4	16.5	83.5	19.7	80.3	8.2	91.8	0.1	99.9
3c	56.9	43.1	14.1	85.9	27.5	72.5	6.2	93.8	0.9	99.1
3d	61.9	38.1	16.9	83.1	31.4	68.6	7.6	92.4	1.9	98.1
3e	nd[b]	nd[b]	15.1	84.9	nd[b]	nd[b]	nd[b]	nd[b]	0.1	99.9
3f	nd[b]	nd[b]	nd[b]	nd[b]	nd[b]	nd[b]	nd[b]	nd[b]	0.9	99.1

[a]The dielectric constants (ε) of the corresponding protio solvents are reported (ref 27). [b]Solubility constraints precluded assessment.

TABLE 4. Evaluation of Conditions for the Reaction of 3a with Phenylacetylene



entry	catalyst	solvent	temp (°C), time (h)	results[a,b]
1	$CuSO_4$/Na ascorbate	1:1 *t*-BuOH/H_2O	rt, 3.5	incomplete reaction: **3a**, 63%; **4a**, 26%; reduction, 11%
2	$CuSO_4$/Na ascorbate	1:1 THF/H_2O	rt, 6	incomplete reaction: **3a**, 46%; **4a**, 30%; reduction, 24%
3	$CuSO_4$/Na ascorbate	1:1 toluene/H_2O	rt, 6	incomplete reaction: **3a**, 67%; **4a**, 22%; reduction, 11%
4	$CuSO_4$/Na ascorbate	1:1 $CHCl_3$/H_2O	rt, 2	**4a**, 78% yield[c]
5	$CuSO_4$/Na ascorbate	1:1 CH_2Cl_2/H_2O	rt, 3.5	**4a**, 81% yield
6	Cu(Phen)(PPh_3)Br	1:1 CH_2Cl_2/H_2O	rt, 24	**4a**, 46% yield
7	Cu(PPh_3)$_3$Br	1:1 CH_2Cl_2/H_2O	rt, 15	**4a**, 73% yield; an uncharacterized byproduct was also formed
8	CuIMes	1:1 CH_2Cl_2/H_2O	rt, 20	incomplete reaction: **3a**, 60%; **4a**, 29%; reduction, 11%
9	CuIPr	1:1 CH_2Cl_2/H_2O	rt, 24	no reaction, only **3a** present
10	CuCl	1:1 CH_2Cl_2/H_2O	rt, 5	**4a**, 76% yield
11	CuTC	1:1 CH_2Cl_2/H_2O	rt, 6	**4a**, 63% yield
12	Cu/C and 2 molar equiv of Et_3N	1,4-dioxane	rt, 15, then 60, 1.5	**4a**, 51%; reduction, 38%
13	Cu/C	1,4-dioxane	rt, 23	no reaction, only **3a** present
14	Cu/C	1:1 CH_2Cl_2/H_2O	rt, 2.5	no reaction, only **3a** present

[a]In reactions that proceeded to completion, yield reported is that of isolated and purified **4a**. [b]In some cases, the reduction product 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine was isolated and characterized. In other cases, this product was detected by TLC (UV visualization) and the amount formed was estimated by ^{1}H NMR analyses of the crude reaction mixtures. [c]By TLC, reaction was less clean compared to entry 5.

CD_2Cl_2 alone (Table 3), indicating that the azide/tetrazole ratio is not substantially altered in the presence of water.

Once conditions leading to successful click reactions were realized, attention was focused on the issue of regiochemistry. In reactions of simpler systems, only 1,4-disubstituted triazoles are formed in the Cu-catalyzed azide−alkyne ligation reactions.[9] We wanted to assess whether this was also the case with these nucleoside substrates, which can demonstrate complex reactivities. Thus, a reaction of **3a** and 4-ethynyltoluene was conducted under the optimized conditions. In addition to a major product, a minor, more polar material was observed by TLC (spectral data could not be obtained on the minor product as it was formed to a very low extent). It proved difficult, however, to ascertain the exact regioisomeric structure of the major product. Therefore, we attempted structure evaluation by X-ray analysis. Gratifyingly, the major product from the reaction of **3a** and 4-ethynyltoluene could be crystallized as long needles from hexanes. The X-ray structure (Figure 2) clearly indicated this to be the anticipated 1,4-disubstituted triazole derivative (a pdb file as well as ORTEP are included in the Supporting Information). The crystal structure shows that the purine and the triazole rings are nearly coplanar, with a *syn*-conformation of the purine around the glycosidic bond, and a 3′-*endo* sugar ring pucker.

In order to compare the catalyzed reaction with the uncatalyzed process, two different reactions were conducted. In one case, a mixture of **3a** and 4-ethynyltoluene was heated at 85 °C in 1:3 MeOH−H_2O. This reaction, which was incomplete at 36 h, gave 48% of the 1,4-disubstituted

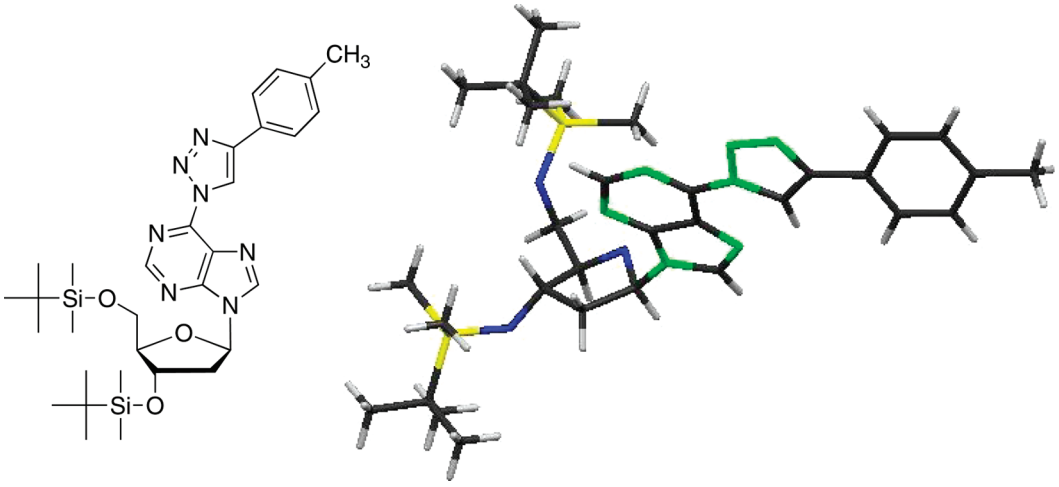


FIGURE 2. X-ray structure of the click reaction product of **3a** and 4-ethynyltoluene.

triazole, 5% of the 1,5-isomer, and 18% of recovered **3a**. A second reaction between **3a** and 4-ethynyltoluene was conducted in toluene at 65 °C. This reaction was incomplete at 120 h and showed ~10% **3a**, ~80% of the 1,4-disubstituted triazole, as well as ~10% of the 1,5-isomer (estimates based upon ^{1}H NMR analysis of the crude reaction mixture). These results clearly indicate that the rate of the ligation reaction benefits significantly from Cu catalysis.

The next stage involved an analysis of the generality of the azide−alkyne ligation reaction using the optimized conditions ($CuSO_4$/Na ascorbate in CH_2Cl_2/H_2O). A range of alkynes underwent successful ligation with **3a** and **3b** in good yields and within reasonably short reaction times (Table 5). In many cases, particularly with the ribosides, additional minor products could be isolated. From the NMR as well as the HRMS data, these minor compounds are quite possibly the 1,5-disubstituted azide−alkyne ligation products. Where possible, characterization data for the minor products are presented in the Experimental Section as well.

These results also indicate a point of departure in the reactivity of nucleoside azides in comparison to those of simpler azides. From a mechanistic consideration[31] (Scheme 3), it appears that a major and a minor process are in operation, leading to the two regioisomeric products. Since no product formation was observed by simply stirring 4-ethynyltoluene and **3b** in CH_2Cl_2/H_2O at room temperature for 48 h, it is likely that the minor 1,5-disubstituted products also arise via a catalyzed process (after 48 h at 100 °C, 32% of **3b**, 16% of the major and 2.5% of the minor cycloaddition products were isolated from this reaction). Although it is difficult to rationalize why the reaction partitions through the minor pathway, it is possible that presence of the subsitutent (R) and the nucleoside (*Nuc*) on vicinal carbons is not completely sterically disfavored.

We were curious to evaluate the azide−alkyne ligation reactions of 4-azidoquinazoline, which is indicated in the literature to exist as the corresponding tetrazolo[1,5-*c*]quinazoline.[32] Several attempts were directed at the reaction of this compound with phenylacetylene (Scheme 4), and these included the reaction conditions used herein, $CuSO_4$/Na ascorbate in *t*-BuOH/H_2O at room temperature and at 50 °C, as well as a reaction in the presence of excess alkyne in refluxing toluene. No product formation was observed under any of these conditions. These results are also indicative of the markedly different reactivity 6-azidopurine nucleoside derivatives possess in comparison to this simpler model.

Finally, it was of interest to determine the biological activities of these new triazolyl nucleoside analogues. Ribo- and 2′-deoxyribonucleosides are typically of low toxicity to human cells. Compounds **4a**−**g** and **5a**−**g** were desilylated to yield the free nucleosides (Scheme 5). The desilylated compounds were tested for antiproliferative activity (range of concentrations tested was 1−100 μM, 72 h continuous exposure) against a panel of human cancer cell lines: wild-type $p53^{+/+}$ and $p53^{-/-}$ HCT116 colon carcinoma cells and paclitaxel sensitive (1A9) and resistant (1A9/PTX10 and 1A9/PTX22) ovarian carcinoma cells. Only weak antiproliferative or cytotoxic actions were noted for compounds **6e**, **6f**, **6g**, **7d**, and **7f** (Table S2 in the Supporting Information). All these new agents are presently being tested for inhibitory activities against a panel of kinases, phosphatases, polymerases, and reverse transcriptases, and the results will be reported in due course.

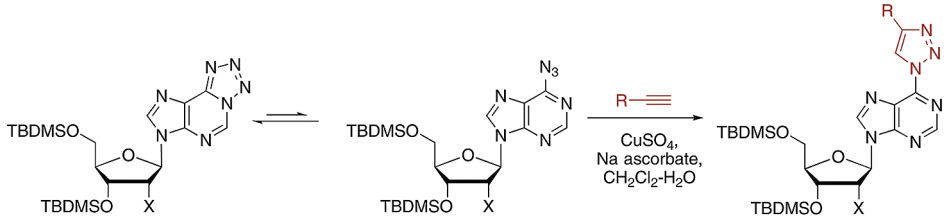
Conclusions

We have demonstrated that O^6-(benzotriazol-1-yl)inosine and 2′-deoxyinosine derivatives are excellent substrates for conversion to the C-6 azidopurine nucleoside derivatives in a simple operation using azide anion. The azido nucleosides exist in equilibrium with the tetrazolyl forms, and increasing solvent dielectric constant generally increases the proportion of the tetrazolyl tautomer. Despite the azide·tetrazole equilibrium, successful azide−alkyne click reactions can be accomplished using $CuSO_4$/Na ascorbate. However, the biphasic CH_2Cl_2/H_2O solvent system is required for successful reaction, where the competing reduction of the azide to the amine is suppressed. In contrast to click reactions of simpler organic azides, those of the C-6 azido nucleoside analogues are less regioselective, and minor amounts of the 1,5-disubstituted triazoles were isolated and characterized in some cases. By X-ray crystallographic analysis, the structure of

(31) Ahlquist, M.; Fokin, V. V. *Organometallics* **2007**, *26*, 4389–4391.

(32) Wan, Z.-K.; Wacharasindhu, S.; Levins, C. G.; Lin, M.; Tabei, K.; Mansour, T. S. *J. Org. Chem.* **2007**, *72*, 10194–10210.

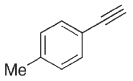
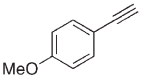
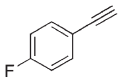
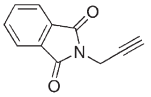
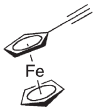
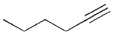
TABLE 5. Azide−Alkyne Click Reactions of Nucleosides 3a and 3b



3a (T): X = H
3b (T): X = OTBDMS

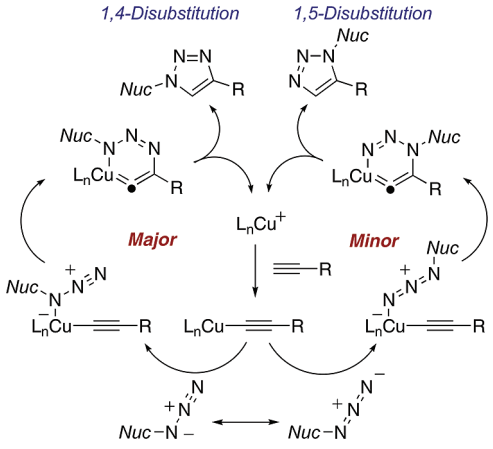
3a (A): X = H
3b (A): X = OTBDMS

4a-g: X = H
5a-g: X = OTBDMS

entry	substrate	alkyne	reaction time and temp	product: yield[a]
1	**3a**		4.0 h, room temp	**4a**: 77%
2	**3b**		4.0 h, room temp	**5a**: 90% **5a'**: 2%[b]
3	**3a**		4.0 h, room temp	**4b**: 87%
4	**3b**		4.0 h, room temp	**5b**: 90%
5	**3a**		4.0 h, room temp	**4c**: 90%
6	**3b**		3.5 h, room temp	**5c**: 94% **5c'**: 3%[b]
7	**3a**		4.5 h, room temp	**4d**: 92%
8	**3b**		4.0 h, room temp	**5d**: 82% **5d'**: 1%[b]
9	**3a**		7.0 h, 40 °C	**4e**: 95%
10	**3b**		4.0 h, 40 °C	**5e**: 76% **5e'**: 3%[b]
11	**3a**		4.0 h, room temp	**4f**: 83% **4f'**: 6%[b]
12	**3b**		4.0 h, room temp	**5f**: 71% **5f'**: 10%[b]
13	**3a**		4.5 h, room temp	**4g**: 75%
14	**3b**		4.5 h, room temp	**5g**: 81%

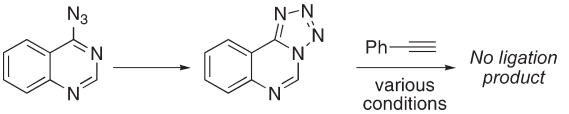
[a]Yields of isolated and purified products. [b]The isomeric 1,5-disubstituted triazole was also isolated as a minor byproduct.

SCHEME 3. Plausible Mechanistic Pathways Leading to the Regioisomeric Products

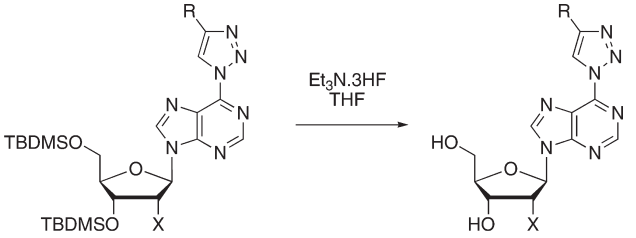


the major product from a reaction between **3a** and 4-ethynyltoluene was shown to be the 1,4-disubstituted triazole. To our knowledge, this is the first report describing a simple, unifying synthesis of C-6 azidopurine 2′-deoxyribo- and ribonucleosides, their behavior in solution, and their use in click reactions with alkynes. In contrast to the successful reactions of the

SCHEME 4. Attempted Ligation of Tetrazolo[1,5-*c*]quinazoline with Phenylacetylene



SCHEME 5. Desilylation of the Click Products



4a-g: X = H
5a-g: X = OTBDMS

6a-g: X = H
7a-g: X = OH

6-azidopurine nucleosides, azide−alkyne ligation reactions of tetrazolo[1,5-*c*]quinazoline were unsuccessful. This demonstrates markedly different behavior of the 6-azidopurine nucleosides in comparison to the simpler heterocycle.

Experimental Section

Please see the Supporting Information for general experimental methods.

3′,5′-Di-*O*-acetyl-O^6-(benzotriazol-1-yl)-2′-deoxyinosine (2c). In a clean, dry 100 mL round-bottomed flask equipped with a stirring bar were placed 2′-deoxyinosine 3′,5′-diacetate **1c** (300 mg, 0.893 mmol) and BOP (790 mg, 1.79 mmol) in anhydrous CH_2Cl_2 (8.0 mL). To this stirred mixture was added (*i*-Pr)$_2$NEt (0.31 mL, 1.79 mmol), and the stirring was continued at room temperature for 22 h. The mixture was evaporated to dryness, and the residue was redissolved in EtOAc. The mixture was washed with water (3×) and then with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using 30% EtOAc in hexanes to provide **2c** as a white foamy solid (382 mg, 94% yield). R_f (silica gel, 10% EtOAc in hexanes) = 0.70. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (s, 1H, Ar-H), 8.33 (s, 1H, Ar-H), 8.14 (d, 1H, Ar-H, J = 8.3 Hz), 7.58−7.41 (m, 3H, Ar-H), 6.52 (t, 1H, H-1′, J = 6.5 Hz), 5.46 (br s, 1H, H-3′), 4.44−4.36 (m, 3H, 1H-4′, 2H-5′), 3.00 (app quint, 1H, H-2′, $J_{app} \approx$ 7.1 Hz), 2.71 (ddd, 1H, H-2′, J = 2.6, 6.0, 14.1 Hz), 2.15 and 2.10 (2s, 6H, $OCOCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.4, 159.4, 153.7, 151.9, 143.7, 143.3, 129.0, 125.1, 120.8, 108.8, 85.5, 83.1, 74.4, 63.8, 37.9, 21.1, 21.0. HRMS (ESI): calcd for $C_{20}H_{19}N_7O_6Na$ [M + Na]$^+$ 476.1295, found 476.1292.

2′,3′,5′-Tri-*O*-acetyl-O^6-(benzotriazol-1-yl)inosine (2d). This compound was prepared by the procedure described for **2c** using **1d** (300 g, 0.761 mmol), BOP (673 mg, 1.52 mmol), anhydrous CH_2Cl_2 (8.0 mL), and (*i*-Pr)$_2$NEt (0.26 mL, 1.52 mmol). The crude product was purified by column chromatography on silica gel using 40% EtOAc in hexanes to provide **2d** as a white foamy solid (353 mg, 91% yield). R_f (silica gel, 20% EtOAc in hexanes) = 0.32. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (s, 1H, Ar-H), 8.30 (s, 1H, Ar-H), 8.14 (d, 1H, Ar-H, J = 8.3 Hz), 7.57−7.46 (m, 3H, Ar-H), 6.27 (d, 1H, H-1′, J = 5.1 Hz), 5.96 (t, 1H, H-2′, J = 5.4 Hz), 5.60 (t, 1H, H-3′, J = 5.1 Hz), 4.51−4.38 (m, 3H, H-4′, 2H-5′), 2.16, 2.14, and 2.10 (3s, 9H, $OCOCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 169.7, 169.5, 159.5, 153.8, 152.1, 143.6, 143.5, 129.0, 125.1, 120.7, 120.3, 108.8, 87.1, 80.7, 73.3, 70.6, 63.0, 53.6, 20.9, 20.7, 20.5. HRMS (ESI): calcd for $C_{22}H_{21}N_7O_8Na$ [M + Na]$^+$ 534.1349, found 534.1351.

6-Azido-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (3a). In a clean, dry 50 mL round-bottomed flask equipped with a stirring bar were placed O^6-(benzotriazol-1-yl)-2′,3′-di-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (**2a**) (1.036 g, 1.73 mmol) and NaN_3 (326 mg, 5.0 mmol) in anhydrous DMSO (8.6 mL). The reaction mixture was flushed with nitrogen gas and stirred under a nitrogen balloon at 40 °C for 2 h. The reaction mixture was transferred to a separatory funnel and partitioned between EtOAc and a 1:1 mixture of water−brine. The organic layer was washed with 1:1 water −brine mixture (4×), then with water (3×), and finally with brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Filtration of the crude material through a silica gel plug using 20% EtOAc in hexanes solution afforded **3a** as a clear gum (871 mg, 99%). R_f (silica gel, 1% MeOH in CH_2Cl_2) = 0.12. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.14 (s, 1H, Ar-H), 8.82 (s, 1H, Ar-H), 6.57 (t, 1H, H-1′, J = 6.5 Hz), 4.64 (m, 1H, H-3′), 3.91 (m, 1H, H-4′), 3.82 (dd, 1H, H-5′, J = 5.2, 11.0 Hz), 3.70 (dd, 1H, H-5′, J = 4.0, 11.0 Hz), 2.88 (app quint, 1H, H-2′, $J_{app} \approx$ 6.0 Hz), 2.46 (m, 1H, H-2′), 0.89 and 0.82 (2s, 18H, *t*-Bu), 0.11, 0.02, and −0.001 (3s, 12H, Si-CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 145.3, 142.5, 141.5, 135.9, 120.4, 87.3, 84.2, 71.5, 62.3, 39.9, 25.7, 25.6, 17.9, 17.6, −4.8, −5.0, −5.6. HRMS (ESI): calcd for $C_{22}H_{39}N_7O_3Si_2Na$ [M + Na]$^+$ 528.2545, found 528.2534.

6-Azido-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (3b). In a clean, dry round-bottomed flask equipped with a stirring bar were placed O^6-(benzotriazol-1-yl)-2′,3′,5′-tri-*O*-(*tert*-butyldimethylsilyl)inosine (**2b**) (2.55 g, 3.51 mmol) and NaN_3 (684 mg, 10.53 mmol) in anhydrous DMSO (17.5 mL). The reaction mixture was flushed with nitrogen gas and stirred under a nitrogen balloon at 40 °C for 3.5 h. The reaction mixture was transferred to a separatory funnel and partitioned between EtOAc and a 1:1 mixture of water−brine. The organic layer was washed with 1:1 water−brine mixture (4×), then with water (3×), and finally with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Filtration of the crude material through a silica gel plug using 20% EtOAc in hexanes afforded **3b** as a white foam (2.14 g, 96% yield). R_f (silica gel, 20% EtOAc in hexanes) = 0.46. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.19 (s, 1H, Ar-H), 8.88 (s, 1H, Ar-H), 6.17 (d, 1H, H-1′, J = 5.5 Hz), 4.79 (t, 1H, H-2′, J = 4.7 Hz), 4.37 (m, 1H, H-3′) 4.10−4.06 (m, 1H, H-4′), 4.02 (dd, 1H, H-5′, J = 5.6, 11.0 Hz), 3.80 (dd, 1H, H-5′, J = 3.0, 11.0 Hz), 0.93, 0.91, and 0.74 (3s, 27H, *t*-Bu), 0.14, 0.11, −0.05, and −0.28 (4s, 18H, Si-CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 145.3, 142.5, 141.8, 136.2, 120.3, 87.8, 85.3, 75.2, 71.6, 62.1, 25.8, 25.7, 25.4, 18.0, 17.7, 17.4, −4.6, −4.9, −5.4, −5.5, −5.6. HRMS (ESI): calcd for $C_{28}H_{53}N_7O_4Si_3Na$ [M + Na]$^+$ 658.3359, found 658.3340.

6-Azido-9-(2-deoxy-3,5-di-*O*-acetyl-β-D-ribofuranosyl)purine (3c). From the O^6-(Benzotriazol-1-yl)-2′-deoxyinosine Diacetate. In a clean, dry vial equipped with a stirring bar were placed O^6-(benzotriazol-1-yl)-2′-deoxyinosine diacetate **2c** (249 mg, 0.550 mmol) and NaN_3 (107 mg, 1.65 mmol) in DMSO (2.5 mL). The mixture was flushed with nitrogen gas and stirred at room temperature for 1 h at which time TLC indicated the reaction to be complete. The mixture was diluted with EtOAc and transferred to a separatory funnel. The mixture was extracted with 1:1 water−brine (3×), water (3×), and finally once with brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column using 40% EtOAc in hexanes afforded **3c** as a white foamy material (195 mg, 95% yield).

From 2′-Deoxyinosine Diacetate. In a clean, dry reaction vial equipped with a stirring bar were placed 2′-deoxyinosine-3′,5′-diacetate (**1c**) (500 mg, 1.487 mmol) and THF (3.0 mL). The mixture was cooled with stirring to 0 °C in an ice bath. DPPA (0.48 mL, 2.23 mmol) and DBU (0.34 mL, 2.23 mmol) were added. The nitrogen gas-flushed mixture was allowed to stir at ice bath temperature for 5 min and then at room temperature for 10 min. Finally, the mixture was stirred in a 60 °C sandbath for 1 h. Another aliquot of DPPA (0.48 mL, 2.23 mmol) and DBU (0.34 mL, 2.23 mmol) were added, and the reaction was continued for an additional 1 h. The mixture was evaporated to dryness, and the residue was dissolved in CH_2Cl_2 and washed with water followed by brine. Chromatographic purification on a silica gel column using 2% MeOH/50% EtOAc/48% hexanes afforded **3c** as a yellow foam (362 mg, 67%). R_f (silica gel, 80% EtOAc in hexanes) = 0.26. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.16 (s, 1H, Ar-H), 8.87 (s, 1H, Ar-H), 6.61 (t, 1H, H-1′, J = 6.8 Hz), 5.50−5.41 (m, 1H, H-3′), 4.37−4.29 (m, 2H, H-4′, H-5′), 4.24 (dd, 1H, H-5′, J = 5.5, 11.4 Hz), 3.15 (app quint, 1H, H-2′, $J_{app} \approx$ 7.1 Hz), 2.74−2.66 (m, 1H, H-2′), 2.11 and 2.01 (2s, 6H, $OCOCH_3$). ^{13}C NMR (125 MHz, DMSO-d_6): δ 170.1, 170.0, 145.4, 142.8, 141.6, 136.1, 120.6, 84.4, 82.1, 74.0, 63.4, 36.1, 20.8, 20.5. HRMS (ESI): calcd for $C_{14}H_{15}N_7O_5Na$ [M + Na]$^+$ 384.1027, found 384.1027.

6-Azido-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine (3d). From the O^6-(Benzotriazol-1-yl)inosine Triacetate. In a clean, dry vial equipped with a stirring bar were placed O^6-(benzotriazol-1-yl)-inosine triacetate **2d** (281 mg, 0.550 mmol) and NaN_3 (107 mg, 1.65 mmol) in DMSO (2.5 mL). The mixture was flushed with nitrogen gas and stirred at room temperature for 1 h at which time TLC indicated the reaction to be complete. The mixture was diluted

with EtOAc and transferred to a separatory funnel. The mixture was extracted with 1:1 water−brine (3×), water (3×), and finally once with brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column using 40% EtOAc in hexanes afforded **3d** as a white foamy material (173 mg, 75% yield).

From Inosine Triacetate. In a clean, dry reaction vial equipped with a stirring bar were placed inosine-2′,3′,5′-triacetate (**1d**) (600 mg, 1.521 mmol) and THF (3.6 mL). The mixture was cooled with stirring to 0 °C in an ice bath. DPPA (0.49 mL, 2.28 mmol) and DBU (0.35 mL, 2.28 mmol) were added. The nitrogen gas-flushed mixture was allowed to stir at the ice bath temperature for 5 min and then at room temperature for 10 min. Finally, the mixture was stirred in a 60 °C sandbath for 1 h. Another aliquot of DPPA (0.49 mL, 2.28 mmol) and DBU (0.35 mL, 2.28 mmol) were added, and the reaction was continued for an additional 1 h. The mixture was evaporated to dryness, and the residue was dissolved in CH_2Cl_2 and washed with water followed by brine. Chromatographic purification on a silica gel column using 60% EtOAc in hexanes afforded **3d** as a yellow foam (266 mg, 41% yield). R_f (silica gel, 80% EtOAc in hexanes) = 0.35. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.19 (s, 1H, Ar-H), 8.88 (s, 1H, Ar-H), 6.46 (d, 1H, H-1′, J = 5.0 Hz), 5.98 (t, 1H, H-2′, J = 5.4 Hz), 5.63 (t, 1H, H-3′, J = 5.3 Hz), 4.47 (br s, 1H, H-4′), 4.43 (dd, 1H, H-5′, J = 2.9, 12.0 Hz), 4.30 (dd, 1H, H-5′, J = 5.3, 12.0 Hz), 2.14, 2.05, and 2.04 (3s, 3H, $OCOCH_3$). ^{13}C NMR (125 MHz, DMSO-d_6): δ 170.0, 169.4, 169.2, 145.4, 143.3, 141.3, 136.3, 120.8, 86.4, 79.8, 72.6, 69.8, 62.7, 20.5, 20.3, 20.2. HRMS (ESI): calcd for $C_{16}H_{17}N_7O_7Na$ [M + Na]$^+$ 442.1082, found 442.1077.

6-Azido-9-(2-deoxy-β-D-ribofuranosyl)purine (3e). In a clean, dry reaction vial equipped with a stirring bar were placed O^6-(benzotriazol-1-yl)-2′-deoxyinosine **2e** (150 mg, 0.406 mmol) and polymer-supported azide[23] (530 mg, 0.406 mmol). Water (3.75 mL) was added, the reaction mixture was flushed with nitrogen gas and allowed to stir in a 50 °C sandbath for 3.5 h. The reaction mixture was filtered and evaporated to dryness under reduced pressure. The residue was washed with Et_2O to afford **3e** as a white powder (66 mg, 59% yield). R_f (silica gel, 10% MeOH in CH_2Cl_2) = 0.2. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.13 (s, 1H, Ar-H), 8.88 (s, 1H, Ar-H), 6.57 (t, 1H, H-1′, J = 6.5 Hz), 5.40 (d, 1H, OH, J = 4.3 Hz), 4.98 (t, 1H, OH J = 5.4 Hz), 4.46 (m, 1H, H-3′), 3.93 (app q, 1H, H-4′, $J_{app} \approx$ 4.1 Hz), 3.68−3.61 (m, 1H, H-5′), 3.59−3.53 (m, 1H, H-5′), 2.75 (app quint, 1H, H-2′, $J_{app} \approx$ 6.5 Hz), 2.44 (ddd, 1H, H-2′, J = 3.9, 6.3, 13.3 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 145.4, 142.5, 141.6, 135.9, 120.5, 88.2, 84.4, 70.3, 61.3, 39.8. HRMS (ESI): calcd for $C_{10}H_{11}N_7O_3Na$ [M + Na]$^+$ 300.0816, found 300.0818.

6-Azido-9-(β-D-ribofuranosyl)purine (3f). In a clean, dry reaction vial equipped with a stirring bar were placed O^6-(benzotriazol-1-yl)inosine **2f** (150 mg, 0.389 mmol) and polymer-supported azide[23] (530 mg, 0.406 mmol). DMF (3.9 mL) was added, and the reaction mixture was flushed with nitrogen gas and allowed to stir in a 50 °C sandbath for 5 h. The reaction mixture was filtered, and the DMF was coevaporated with toluene. The residue was washed with Et_2O to afford **3f** as a white powder (80 mg, 70% yield). R_f (silica gel, 10% MeOH in CH_2Cl_2) = 0.19. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.15 (s, 1H, Ar-H), 8.93 (s, 1H, Ar-H), 6.15 (d, 1H, H-1′, J = 5.1 Hz), 5.63 (d, 1H, OH, J = 5.6 Hz), 5.30 (d, 1H, OH, J = 5.2 Hz), 5.10 (t, 1H, OH, J = 5.3 Hz), 4.57 (q, 1H, H-2′, J = 5.2 Hz), 4.20 (q, 1H, H-3′, J = 4.6 Hz), 4.02 (m, 1H, H-4′), 3.76−3.68 (m, 1H, H-5′), 3.65−3.56 (m, 1H, H-5′). ^{13}C NMR (125 MHz, DMSO-d_6): δ 145.4, 142.6, 141.9, 136.1, 120.2, 88.3, 85.7, 74.5, 70.0, 60.9. HRMS (ESI): calcd for $C_{10}H_{11}N_7O_4Na$ [M + Na]$^+$ 316.0765, found 316.0765.

Typical Procedure for Azide−Alkyne Ligation: Synthesis of 6-(4-Phenyl-1,2,3-triazol-1-yl)-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (4a). In a clean, dry vial equipped with a stirring bar were placed the azido nucleoside **3a** (240 mg, 0.474 mmol), CH_2Cl_2 (1.6 mL), and phenylacetylene (104 μL, 0.949 mmol). An aqueous solution of sodium ascorbate (0.047 mmol, 0.95 mL of freshly prepared 0.05 M solution) was added followed by an aqueous solution of $CuSO_4$ (24 μmol, 0.60 mL of freshly prepared 0.04 M solution). The mixture was stirred at room temperature for 4 h, at which time TLC indicated the reaction to be complete. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification on a silica gel column using 20% EtOAc in hexanes afforded **4a** as an off-white foam (222 mg, 77% yield). R_f (silica gel, 20% EtOAc in hexanes) = 0.18. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.35 (s, 1H, Ar-H), 8.96 (s, 1H, Ar-H), 8.59 (s, 1H, Ar-H), 8.02 (d, 2H, Ar-H, J = 7.2 Hz), 7.49 (t, 2H, Ar-H, J = 7.6 Hz), 7.40 (t, 1H, Ar-H, J = 7.3 Hz), 6.61 (t, 1H, H-1′, J = 6.4 Hz), 4.65 (m, 1H, H-3′), 4.09 (q, 1H, H-4′, J = 3.2 Hz), 3.91 (dd, 1H, H-5′, J = 3.8, 11.3 Hz), 3.81 (dd, 1H, H-5′, J = 2.9, 11.3 Hz), 2.68 (app quint, 1H, H-2′, $J_{app} \approx$ 6.4 Hz), 2.54 (ddd, 1H, H-2′, J = 3.8, 6.1, 13.1 Hz), 0.93 and 0.92 (2s, 18H, *t*-Bu), 0.13 and 0.11 (2s, 12H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0, 152.3, 148.5, 144.9, 144.7, 130.1, 129.1, 128.9, 126.4, 123.4, 120.1, 88.5, 85.2, 72.1, 62.9, 41.8, 26.2, 25.9, 18.6, 18.2, −4.4, −4.6, −5.1, −5.2. HRMS (ESI): calcd for $C_{30}H_{45}N_7O_3Si_2Na$ [M + Na]$^+$ 630.3015, found 630.2999.

6-[4-(4-Methylphenyl)-1,2,3-triazol-1-yl]-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (4b). Synthesized from **3a** (195 mg, 0.385 mmol) and 4-ethynyltoluene (98 μL, 0.773 mmol). Chromatography of the crude reaction mixture on a silica gel column using 10% EtOAc in hexanes yielded **4b** as a white foamy solid (209 mg, 87% yield). R_f (silica gel, 20% EtOAc in hexanes) = 0.22. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.30 (s, 1H, Ar-H), 8.95 (s, 1H, Ar-H), 8.58 (s, 1H, Ar-H), 7.90 (d, 1H, Ar-H, J = 8.0 Hz), 7.29 (d, 2H, Ar-H, J = 8.0 Hz), 6.61 (t, 1H, H-1′, J = 6.3 Hz), 4.65 (m, 1H, H-3′), 4.08 (q, 1H, H-4′, J = 3.2 Hz), 3.91 (dd, 1H, H-5′, J = 3.9, 11.2 Hz), 3.81 (dd, 1H, H-5′, J = 2.9, 11.2 Hz), 2.68 (app quint, 1H, H-2′, $J_{app} \approx$ 6.4 Hz), 2.54 (ddd, 1H, H-2′, J = 3.8, 6.1, 13.1 Hz), 2.41 (s, 3H, CH_3), 0.93 and 0.92 (2s, 18H, *t*-Bu), 0.12 and 0.11 (2s, 12H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0, 152.4, 148.5, 145.0, 144.7, 138.8, 129.8, 127.2, 126.3, 123.4, 119.7, 88.5, 85.2, 72.1, 63.0, 41.8, 26.2, 26.0, 21.6, 18.6, 18.2, −4.4, −4.6, −5.1, −5.2. HRMS (ESI): calcd for $C_{31}H_{47}N_7O_3Si_2Na$ [M + Na]$^+$ 644.3171, found 644.3154.

6-[4-(4-Methoxyphenyl)-1,2,3-triazol-1-yl]-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (4c). Synthesized from **3a** (204 mg, 0.400 mmol) and 4-ethynylanisole (102.5 μL, 0.807 mmol). Chromatography of the crude reaction mixture a silica gel column using 10% EtOAc in hexanes yielded **4c** as a white foamy solid (231 mg, 90% yield). R_f (silica gel, 20% EtOAc in hexanes) = 0.43. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.25 (s, 1H, Ar-H), 8.95 (s, 1H, Ar-H), 8.58 (s, 1H, Ar-H), 7.94 (d, 2H, Ar-H, J = 8.8 Hz), 7.01 (d, 2H, Ar-H, J = 8.8 Hz), 6.61 (t, 1H, H-1′, J = 6.4 Hz), 4.65 (m, 1H, H-3′), 4.08 (q, 1H, H-4′, J = 3.2 Hz), 3.91 (dd, 1H, H-5′, J = 3.8, 11.3 Hz), 3.87 (s, 3H, OCH_3), 3.81 (dd, 1H, H-5′, J = 2.9, 11.3 Hz), 2.67 (app quint, 1H, H-2′, $J_{app} \approx$ 6.4 Hz), 2.54 (ddd, 1H, H-2′, J = 3.8, 6.1, 13.1 Hz), 0.93 and 0.92 (2s, 18H, *t*-Bu), 0.12 and 0.11 (2s, 12H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.2, 154.0, 152.3, 148.3, 145.0, 144.6, 127.8, 123.3, 122.7, 119.1, 114.5, 88.5, 85.1, 72.1, 62.9, 55.6, 41.8, 26.2, 25.9, 18.6, 18.2, −4.4, −4.6, −5.1, −5.2. HRMS (ESI): calcd for $C_{31}H_{47}N_7O_4Si_2Na$ [M + Na]$^+$ 660.3120, found 660.3105.

6-[4-(4-Fluorophenyl)-1,2,3-triazol-1-yl]-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (4d). Synthesized from **3a** (210 mg, 0.415 mmol) and 1-ethynyl-4-fluorobenzene (95 μL, 0.830 mmol). Chromatography of the crude reaction mixture on a silica gel column using 20% EtOAc in hexanes yielded **4d** as a yellow, crystalline solid (240 mg, 92%

yield). R_f (silica gel, 40% EtOAc in hexanes) = 0.36. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.30 (s, 1H, Ar-H), 8.96 (s, 1H, Ar-H), 8.60 (s, 1H, Ar-H), 7.99 (dd, 2H, Ar-H, $J_{H,H}$ = 8.6 Hz, $J_{F,H}$ = 5.4 Hz), 7.17 (t, 2H, Ar-H, $J_{H,H}$ = $J_{F,H}$ = 8.6 Hz), 6.61 (t, 1H, H-1′, J = 6.3 Hz), 4.65 (m, 1H, H-3′), 4.08 (q, 1H, H-4′, J = 3.2 Hz), 3.91 (dd, 1H, H-5′, J = 3.7, 11.2 Hz), 3.81 (dd, 1H, H-5′, J = 2.9, 11.2 Hz), 2.68 (app quint, 1H, H-2′, $J_{app} \approx$ 6.4 Hz), 2.54 (ddd, 1H, H-2′, J = 3.8, 6.0, 13.0 Hz), 0.93 and 0.92 (2s, 18H, *t*-Bu), 0.12 and 0.11 (2s, 12H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.0 (d, $^1J_{C,F}$ = 248.1 Hz), 153.8, 152.1, 147.4, 144.6, 144.5, 128.0 (d, $^3J_{C,F}$ = 8.2 Hz), 126.0 (d, $^4J_{C,F}$ = 3.2 Hz), 123.1, 119.6, 115.9 (d, $^2J_{C,F}$ = 21.8 Hz), 88.3, 84.9, 71.9, 62.7, 41.6, 25.9, 25.6, 18.4, 18.0, −4.6, −4.8, −5.3, −5.5. HRMS (ESI): calcd for $C_{30}H_{44}FN_7O_3Si_2Na$ [M + Na]$^+$ 648.2920, found 648.2911.

6-[4-(*N*-Phthalimidomethyl)-1,2,3-triazol-1-yl]-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (4e). Synthesized from **3a** (190 mg, 0.376 mmol) and *N*-propargylphthalimide (139 mg, 0.751 mmol). Chromatography of the crude reaction mixture on a silica gel column using 10% EtOAc in hexanes yielded **4e** as an off-white, foamy solid (246 mg, 95% yield). R_f (silica gel, 20% EtOAc in hexanes) = 0.15. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.10 (s, 1H, Ar-H), 8.90 (s, 1H, Ar-H), 8.55 (s, 1H, Ar-H), 7.88 (dd, 2H, Ar-H, J = 3.1, 5.4 Hz), 7.73 (dd, 2H, Ar-H, J = 3.0, 5.4 Hz), 6.57 (t, 1H, H-1′, J = 6.4 Hz), 5.16 (s, 2H, NCH_2), 4.64 (m, 1H, H-3′), 4.06 (q, 1H, H-4′, J = 3.3 Hz), 3.89 (dd, 1H, H-5′, J = 3.9, 11.2 Hz), 3.79 (dd, 1H, H-5′, J = 3.1, 11.2 Hz), 2.64 (app quint, 1H, H-2′, $J_{app} \approx$ 6.4 Hz), 2.52 (ddd, 1H, H-2′, J = 3.8, 6.0, 13.0 Hz), 0.92 and 0.90 (2s, 18H, *t*-Bu), 0.11, 0.092, and 0.088 (3s, 12H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 154.1, 152.2, 144.8, 143.6, 134.3, 132.3, 123.7, 123.6, 123.5, 88.5, 85.1, 72.1, 62.9, 41.8, 33.3, 26.2, 25.9, 18.6, 18.2, −4.5, −4.6, −5.2, −5.3. HRMS (ESI): calcd for $C_{33}H_{46}N_8O_5Si_2Na$ [M + Na]$^+$ 713.3022, found 713.2999.

6-(4-Ferrocenyl-1,2,3-triazol-1-yl)-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (4f). Synthesized from **3a** (209 mg, 0.413 mmol) and ethynylferrocene (173 mg, 0.820 mmol). Chromatography of the crude reaction mixture on a silica gel column using 15% acetone in hexanes yielded **4f** as a brown, foamy solid (247 mg, 83% yield). R_f (silica gel, 15% acetone in hexanes) = 0.22. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.99 (s, 1H, Ar-H), 8.94 (s, 1H, Ar-H), 8.58 (s, 1H, Ar-H), 6.60 (t, 1H, H-1′, J = 6.3 Hz), 4.88 (br t, 2H, ferrocenyl-H), 4.65 (m, 1H, H-3′), 4.36 (t, 2H, ferrocenyl-H, J = 1.8 Hz), 4.12 (s, 5H, ferrocenyl-H), 4.08 (q, 1H, H-4′, J = 3.2 Hz), 3.91 (dd, 1H, H-5′, J = 3.9, 11.2 Hz), 3.81 (dd, 1H, H-5′, J = 2.9, 11.2 Hz), 2.67 (app quint, 1H, H-2′, $J_{app} \approx$ 6.4 Hz), 2.54 (ddd, 1H, H-2′, J = 3.9, 6.0, 13.0 Hz), 0.93 and 0.92 (2s, 18H, *t*-Bu), 0.12 and 0.11 (2s, 12H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0, 152.3, 147.9, 144.9, 144.5, 123.3, 118.8, 88.5, 85.1, 74.6, 72.1, 69.9, 69.2, 67.3, 62.9, 41.8, 26.2, 25.9, 18.7, 18.2, −4.4, −4.6, −5.1, −5.2. HRMS (ESI): calcd for $C_{34}H_{49}FeN_7O_3Si_2Na$ [M + Na]$^+$ 738.2677, found 738.2677.

Minor Isomer: 6-(5-Ferrocenyl-1,2,3-triazol-1-yl)-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (4f′). Obtained 18.4 mg (6% yield) of a reddish-brown solid. R_f (silica gel, 15% acetone in hexanes) = 0.14. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.97 (s, 1H, Ar-H), 8.55 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 6.61 (t, 1H, H-1′, J = 6.5 Hz), 4.64 (m, 1H, H-3′), 4.58 (m, 2H, ferrocenyl-H), 4.27 (m, 2H, ferrocenyl-H), 4.07 (q, 1H, H-4′, J = 3.1 Hz), 3.99 (s, 5H, ferrocenyl-H), 3.88 (dd, 1H, H-5′, J = 3.9, 11.2 Hz), 3.80 (dd, 1H, H-5′, J = 2.9, 11.2 Hz), 2.64 (app quint, 1H, H-2′, $J_{app} \approx$ 6.4 Hz), 2.52 (ddd, 1H, H-2′, J = 3.7, 6.0, 13.0 Hz), 0.93 and 0.90 (2s, 18H, *t*-Bu), 0.12, 0.09, and 0.08 (3s, 12H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 151.9, 147.1, 145.5, 138.9, 133.3, 128.6, 88.5, 85.1, 72.1, 70.6, 70.0, 69.6, 69.5, 63.0, 41.9, 26.2, 26.0, 18.7, 18.2, −4.4, −4.6, −5.1, −5.2. HRMS (ESI): calcd for $C_{34}H_{49}FeN_7O_3Si_2Na$ [M + Na]$^+$ 738.2677, found 738.2655.

6-[4-(1-Butyl)-1,2,3-triazol-1-yl]-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (4g). Synthesized from **3a** (190 mg, 0.375 mmol) and 1-hexyne (82.5 μL, 0.751 mmol). Chromatography of the crude reaction mixture on a silica gel column using 20% EtOAc in hexanes yielded **4g** as a white solid (166 mg, 75% yield). R_f (silica gel, 20% EtOAc in hexanes) = 0.16. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.91 (s, 1H, Ar-H), 8.81 (s, 1H, Ar-H), 8.53 (s, 1H, Ar-H), 6.58 (t, 1H, H-1′, J = 6.3 Hz), 4.64 (m, 1H, H-3′), 4.07 (m, 1H, H-4′), 3.89 (dd, 1H, H-5′, J = 3.9, 11.2 Hz), 3.79 (dd, 1H, H-5′, J = 2.9, 11.2 Hz), 2.87 (t, 2H, butyl-CH_2, J = 7.8 Hz), 2.66 (app quint, 1H, H-2′, $J_{app} \approx$ 6.4 Hz), 2.50 (ddd, 1H, H-2′, J = 3.8, 5.9, 13.0 Hz), 1.76 (quint, 2H, butyl-CH_2, J = 7.6 Hz), 1.44 (sextet, 2H, butyl-CH_2, J = 7.4 Hz), 0.95 (t, 3H, butyl-CH_3, J = 7.3 Hz), 0.92 and 0.90 (2s, 18H, *t*-Bu), 0.11 and 0.09 (2s, 12H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.9, 152.3, 149.4, 145.1, 144.5, 123.3, 121.4, 88.5, 85.1, 72.1, 62.9, 41.7, 31.5, 26.2, 25.9, 25.5, 22.5, 18.6, 18.2, 14.0, −4.5, −4.6, −5.2, −5.3. HRMS (ESI): calcd for $C_{28}H_{49}N_7O_3Si_2Na$ [M + Na]$^+$ 610.3328, found 610.3328.

6-(4-Phenyl-1,2,3-triazol-1-yl)-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (5a). Synthesized from **3b** (200 mg, 0.314 mmol) and phenylacetylene (69.0 μL, 0.628 mmol). Chromatography of the crude reaction mixture on a silica gel column using 20% EtOAc in hexanes yielded **5a** as a brown crystalline solid (210 mg, 90% yield). R_f (silica gel, 20% acetone in hexanes) = 0.49. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.34 (s, 1H, Ar-H), 8.95 (s, 1H, Ar-H), 8.64 (s, 1H, Ar-H), 8.0 (d, 2H, Ar-H, J = 7.5 Hz), 7.45 (t, 2H, Ar-H, J = 7.6 Hz), 7.36 (t, 1H, Ar-H, J = 7.4 Hz), 6.2 (d, 1H, H-1′, J = 5.1 Hz), 4.65 (t, 1H, H-2′, J = 4.6 Hz), 4.33 (t, 1H, H-3′, J = 3.9 Hz), 4.18 (q, 1H, H-4′, J = 3.0 Hz), 4.04 (dd, 1H, H-5′, J = 3.5, 11.3 Hz), 3.82 (dd, 1H, H-5′, J = 2.3, 11.3 Hz), 0.97, 0.94, and 0.79 (3s, 27H, *t*-Bu), 0.17, 0.16, 0.11, 0.10, −0.02, and −0.23 (6s, 18H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.3, 152.3, 148.4, 144.9, 130.0, 129.0, 128.7, 126.7, 123.2, 120.1, 88.6, 86.0, 76.5, 72.1, 62.6, 26.2, 25.9, 25.7, 18.7, 18.2, 18.0, −4.2, −4.4, −4.5, −4.8, −5.2. HRMS (ESI): calcd $C_{36}H_{59}N_7O_4Si_3Na$ [M + Na]$^+$ 760.3829, found 760.3826.

Minor Isomer: 6-(5-Phenyl-1,2,3-triazol-1-yl)-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (5a′). Obtained 4.4 mg (2% yield) of a brown solid. R_f (silica gel, 20% acetone in hexanes) = 0.19. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.82 (s, 1H, Ar-H), 8.55 (s, 1H, Ar-H), 7.93 (s, 1H, Ar-H), 7.36−7.28 (m, 5H, Ar-H), 6.19 (d, 1H, H-1′, J = 5.1 Hz), 4.60 (t, 1H, H-2′, J = 4.7 Hz), 4.31 (t, 1H, H-3′, J = 3.8 Hz), 4.17 (m, 1H, H-4′), 4.02 (dd, 1H, H-5′, J = 3.7, 11.5 Hz), 3.81 (dd, 1H, H-5′, J = 2.4, 11.5 Hz), 0.95, 0.94, and 0.79 (3s, 27H, *t*-Bu), 0.13, 0.11, 0.10, −0.02, and −0.25 (5s, 18H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.5, 152.1, 146.9, 145.7, 139.5, 133.9, 129.4, 128.8, 127.7, 127.1, 88.7, 86.1, 76.5, 72.1, 62.7, 26.3, 26.0, 25.9, 18.8, 18.3, 18.0, −4.2, −4.4, −4.5, −4.8, −5.1. HRMS (ESI): calcd $C_{36}H_{59}N_7O_4Si_3Na$ [M + Na]$^+$ 760.3829, found 760.3829.

6-[4-(4-Methylphenyl)-1,2,3-triazol-1-yl]-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (5b). Synthesized from **3b** (200 mg, 0.314 mmol) and 4-ethynyltoluene (79.5 μL, 0.629 mmol). Chromatography of the crude reaction mixture on a silica gel column using 10% acetone in hexanes yielded **5b** as a light-yellow solid (214 mg, 90% yield). R_f (silica gel, 10% acetone in hexanes) = 0.29. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.31 (s, 1H, Ar-H), 8.96 (s, 1H, Ar-H), 8.67 (s, 1H, Ar-H), 7.90 (d, 2H, Ar-H, J = 8.0 Hz), 7.29 (d, 2H, Ar-H, J = 8.0 Hz), 6.22 (d, 1H, H-1′, J = 5.2 Hz), 4.66 (t, 1H, H-2′, J = 4.6 Hz), 4.33 (t, 1H, H-3′, J = 3.9 Hz), 4.19 (q, 1H, H-4′, J = 3.1 Hz), 4.05 (dd, 1H, H-5′, J = 3.5, 11.4 Hz), 3.83 (dd, 1H, H-5′, J = 2.5, 11.4 Hz), 2.41 (s, 3H, CH_3), 0.98, 0.95, and 0.80 (3s, 27H, *t*-Bu), 0.18, 0.17, 0.12, 0.11, −0.01, and −0.22 (6s, 18H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.4, 152.4, 148.6, 145.1, 145.0, 138.8, 129.8, 127.3, 126.4, 123.3, 119.7, 88.7, 86.1, 76.5, 72.2, 62.7, 26.3,

26.1, 25.8, 21.5, 18.8, 18.3, 18.0, −4.2, −4.4, −4.5, −4.8, −5.1. HRMS (ESI): calcd for $C_{37}H_{61}N_7O_4Si_3Na$ [M + Na]$^+$ 774.3985, found 774.3986.

6-[4-(4-Methoxyphenyl)-1,2,3-triazol-1-yl]-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (5c). Synthesized from **3b** (200 mg, 0.314 mmol) and 4-ethynylanisole (81.3 μL, 0.628 mmol). Chromatography of the crude reaction mixture on a silica gel column using 20% EtOAc in hexanes yielded **5c** as a white, foamy solid (228 mg, 94% yield). R_f (silica gel, 20% EtOAc in hexanes) = 0.29. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.27 (s, 1H, Ar-H), 8.95 (s, 1H, Ar-H), 8.63 (s, 1H, Ar-H), 7.94 (d, 2H, Ar-H, J = 8.8 Hz), 7.01 (d, 2H, Ar-H, J = 8.8 Hz), 6.22 (d, 1H, H-1′, J = 5.8 Hz), 4.66 (t, 1H, H-2′, J = 4.7 Hz), 4.33 (t, 1H, H-3′, J = 3.9 Hz), 4.19 (q, 1H, H-4′, J = 3.0 Hz), 4.05 (dd, 1H, H-5′, J = 3.6, 11.5 Hz), 3.87 (s, 3H, OCH_3), 3.83 (dd, 1H, H-5′, J = 2.4, 11.5 Hz), 0.98, 0.95, and 0.80 (3s, 27H, *t*-Bu), 0.18, 0.17, 0.12, 0.11, −0.01, and −0.23 (6s, 18H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.2, 154.4, 152.4, 148.4, 145.0, 144.9, 127.8, 123.3, 122.8, 119.2, 114.5, 88.7, 86.0, 76.5, 72.1, 62.7, 55.6, 26.3, 26.0, 25.8, 18.8, 18.3, 18.0, −4.2, −4.4, −4.5, −4.8, −5.1. HRMS (ESI): calcd for $C_{37}H_{61}N_7O_5Si_3Na$ [M + Na]$^+$ 790.3934, found 790.3933.

Minor isomer: 6-[5-(4-Methoxyphenyl)-1,2,3-triazol-1-yl]-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (5c′). Obtained 9.1 mg (3% yield) of a clear, gummy material. R_f (silica gel, 20% EtOAc in hexanes) = 0.10. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.84 (s, 1H, Ar-H), 8.55 (s, 1H, Ar-H), 7.88 (s, 1H, Ar-H), 7.22 (d, 2H, Ar-H, J = 8.8 Hz), 6.83 (d, 2H, Ar-H, J = 8.8 Hz), 6.19 (d, 1H, H-1′, J = 5.1 Hz), 4.60 (t, 1H, H-2′, J = 4.7 Hz), 4.32 (t, 1H, H-3′, J = 3.9 Hz), 4.17 (m, 1H, H-4′), 4.02 (dd, 1H, H-5′, J = 3.7, 11.5 Hz), 3.81 (merged with OCH_3 resonance, 1H, H-5′), 3.80 (s, 3H, OCH_3), 0.95, 0.94, and 0.79 (3s, 27H, *t*-Bu), 0.13, 0.11, 0.10, −0.02, and −0.25 (5s, 18H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.5, 154.5, 152.1, 146.9, 145.7, 139.4, 133.4, 130.2, 127.9, 119.3, 114.3, 88.7, 86.0, 76.5, 72.1, 62.7, 55.5, 26.3, 26.0, 25.8, 18.8, 18.3, 18.0, −4.2, −4.4, −4.5, −4.8, −5.1. HRMS (ESI): calcd for $C_{37}H_{61}N_7O_5Si_3Na$ [M + Na]$^+$ 790.3934, found 790.3944.

6-[4-(4-Fluorophenyl)-1,2,3-triazol-1-yl]-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (5d). Synthesized from **3b** (200 mg, 0.314 mmol) and 1-ethynyl-4-fluorobenzene (72.0 μL, 0.629 mmol). Chromatography of the crude reaction mixture on a silica gel column using 10% EtOAc in hexanes yielded **5d** as a light-yellow, foamy solid (194 mg, 82% yield). R_f (silica gel, 20% EtOAc in hexanes) = 0.41. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.32 (s, 1H, Ar-H), 8.96 (s, 1H, Ar-H), 8.64 (s, 1H, Ar-H), 7.99 (dd, 2H, Ar-H, $J_{H,H}$ = 8.6 Hz, $J_{F,H}$ = 5.3 Hz), 7.17 (t, 2H, Ar-H, $J_{H,H}$ = $J_{F,H}$ = 8.6 Hz), 6.23 (d, 1H, H-1′, J = 5.1 Hz), 4.66 (t, 1H, H-2′, J = 4.6 Hz), 4.33 (t, 1H, H-3′, J = 3.9 Hz), 4.19 (m, 1H, H-4′), 4.05 (dd, 1H, H-5′, J = 3.3, 11.3 Hz), 3.84 (dd, 1H, H-5′, J = 2.2, 11.3 Hz), 0.98, 0.95, and 0.80 (3s, 27H, *t*-Bu), 0.18, 0.17, 0.11, −0.013, and −0.23 (5s, 18H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.2 (d, $^1J_{C,F}$ = 248.1 Hz), 154.5, 152.4, 147.6, 145.1, 144.9, 128.2 (d, $^3J_{C,F}$ = 8.2 Hz), 126.3 (d, $^4J_{C,F}$ = 5.1 Hz), 123.3, 119.9, 116.1 (d, $^2J_{C,F}$ = 21.8 Hz), 88.7, 86.1, 76.5, 72.1, 62.7, 26.3, 26.1, 25.8, 18.8, 18.3, 18.1, −4.2, −4.4, −4.5, −4.8, −5.1. HRMS (ESI): calcd for $C_{36}H_{58}FN_7O_4Si_3Na$ [M + Na]$^+$ 778.3734, found 778.3721.

Minor Isomer: 6-[5-(4-Fluorophenyl)-1,2,3-triazol-1-yl]-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (5d′). Obtained 2.9 mg (1% yield) of a clear, gummy material. R_f (silica gel, 20% EtOAc in hexanes) = 0.08. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.83 (s, 1H, Ar-H), 8.56 (s, 1H, Ar-H), 7.91 (s, 1H, Ar-H), 7.29 (dd, 2H, Ar-H, $J_{H,H}$ = 8.7 Hz, $J_{F,H}$ = 5.2 Hz), 7.01 (t, 2H, Ar-H, $J_{H,H}$ = $J_{F,H}$ = 8.7 Hz), 6.19 (d, 1H, H-1′, J = 5.1 Hz), 4.58 (t, 1H, H-2′, J = 4.6 Hz), 4.31 (t, 1H, H-3′, J = 3.9 Hz), 4.19 (m, 1H, H-4′), 4.02 (dd, 1H, H-5′, J = 3.4, 11.5 Hz), 3.81 (dd, 1H, H-5′, J = 2.2, 11.5 Hz), 0.95, 0.94, and 0.79 (3s, 27H, *t*-Bu), 0.13, 0.11, 0.10, −0.02, and −0.25 (5s, 18H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.4 (d, $^1J_{C,F}$ = 250.3 Hz), 154.6, 152.1, 146.5, 145.7, 138.6, 133.9, 130.8 (d, $^3J_{C,F}$ = 8.6 Hz), 127.6, 123.3, 116.0 ($^2J_{C,F}$ = 22.0 Hz), 88.7, 86.1, 76.6, 72.1, 62.7, 26.3, 26.0, 25.8, 18.8, 18.3, 18.0, −4.2, −4.4, −4.5, −4.8, −5.1. HRMS (ESI): calcd for $C_{36}H_{58}FN_7O_4Si_3Na$ [M + Na]$^+$ 778.3734, found 778.3739.

6-[4-(*N*-Phthalimidomethyl)-1,2,3-triazol-1-yl]-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (5e). Synthesized from **3b** (200 mg, 0.314 mmol) and *N*-propargylphthalimide (0.132 g, 0.628 mmol). Chromatography of the crude reaction mixture on a silica gel column using 15% EtOAc in hexanes yielded **5e** as an off-white, foamy solid (196 mg, 76% yield). R_f (silica gel, 25% EtOAc in hexanes) = 0.22. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.11 (s, 1H, Ar-H), 8.90 (s, 1H, Ar-H), 8.61 (s, 1H, Ar-H), 7.88 (dd, 2H, Ar-H, J = 2.9, 5.4 Hz), 7.72 (dd, 2H, Ar-H, J = 2.9, 5.4 Hz), 6.19 (d, 1H, H-1′, J = 4.9 Hz), 5.16 (s, 2H, NCH_2), 4.63 (t, 1H, H-2′, J = 4.3 Hz), 4.31 (m, 1H, H-3′), 4.17 (m, 1H, H-4′), 4.03 (dd, 1H, H-5′, J = 3.4, 11.7 Hz), 3.81 (dd, 1H, H-5′, J = 2.4, 11.7 Hz), 0.96, 0.94, and 0.78 (3s, 27H, *t*-Bu), 0.16, 0.15, 0.10, −0.03, and −0.25 (5s, 18H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.6, 154.2, 152.1, 145.0, 144.6, 143.4, 134.1, 132.1, 123.5, 123.4, 123.2, 88.5, 85.8, 76.2, 71.9, 62.4, 33.1, 26.1, 25.8, 25.6, 18.5, 18.1, 17.8, −4.4, −4.6, −4.7, −5.0, −5.3. HRMS (ESI): calcd for $C_{39}H_{60}N_8O_6Si_3Na$ [M + Na]$^+$ 843.3836, found 843.3833.

Minor Isomer: 6-[5-(*N*-Phthalimidomethyl)-1,2,3-triazol-1-yl]-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]-purine (5e′). Obtained 8.5 mg (3% yield) of an off-white, gummy material. R_f (silica gel, 25% EtOAc in hexanes) = 0.10. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.95 (s, 1H, Ar-H), 8.66 (s, 1H, Ar-H), 7.86 (dd, 2H, Ar-H, J = 3.1, 5.4 Hz), 7.75 (dd, 2H, Ar-H, J = 3.4, 5.4 Hz), 7.69 (s, 1H, Ar-H), 6.26 (d, 1H, H-1′, J = 5.1 Hz), 5.55 (s, 2H, NCH_2), 4.64 (t, 1H, H-2′, J = 4.6 Hz), 4.34 (t, 1H, H-3′, J = 3.9 Hz), 4.21−4.17 (m, 1H, H-4′), 4.04 (dd, 1H, H-5′, J = 3.4, 11.5 Hz), 3.83 (dd, 1H, H-5′, J = 2.2, 11.5 Hz), 0.96, 0.95, and 0.82 (3s, 27H, *t*-Bu), 0.16, 0.15, 0.12, 0.001, and −0.19 (5s, 18H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 154.7, 151.7, 146.6, 145.5, 135.2, 134.6, 134.5, 132.0, 125.7, 123.9, 88.6, 86.0, 76.6, 72.1, 62.7, 33.3, 26.4, 26.1, 25.9, 18.8, 18.3, 18.1, −4.1, −4.4, −4.5, −4.7, −5.1. HRMS (ESI): calcd for $C_{39}H_{60}N_8O_6Si_3Na$ [M + Na]$^+$ 843.3836, found 843.3830.

6-(4-Ferrocenyl-1,2,3-triazol-1-yl)-9-[2,3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (5f). Synthesized from **3b** (200 mg, 0.314 mmol) and ethynylferrocene (0.132 g, 0.628 mmol). Chromatography of the crude reaction mixture on a silica gel column using 5% acetone in hexanes yielded **5f** as a reddish-brown, foamy solid (189 mg, 71% yield). R_f (silica gel, 10% acetone in hexanes) = 0.18. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.99 (s, 1H, Ar-H), 8.94 (s, 1H, Ar-H), 8.64 (s, 1H, Ar-H), 6.21 (d, 1H, H-1′, J = 5.1 Hz), 4.88 (br s, 2H, ferrocenyl-H), 4.65 (t, 1H, H-2′, J = 4.5 Hz), 4.36 (br s, 2H, ferrocenyl-H), 4.33 (t, 1H, H-3′, J = 4.0 Hz), 4.19 (m, 1H, H-4′), 4.12 (s, 5H, ferrocenyl-H), 4.05 (dd, 1H, H-5′, J = 3.3, 11.5 Hz), 3.83 (dd, 1H, H-5′, J = 2.0, 11.5 Hz), 0.98, 0.94, and 0.81 (3s, 27H, *t*-Bu), 0.18, 0.16, 0.11, 0.107, −0.01, and −0.20 (6s, 18H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.4, 152.4, 147.9, 145.0, 144.9, 123.3, 118.8, 88.7, 85.9, 76.4, 74.7, 72.1, 69.9, 69.2, 67.3, 62.7, 26.3, 26.0, 25.9, 18.8, 18.3, 18.0, −4.2, −4.4, −4.5, −4.7, −5.1. HRMS (ESI): calcd for $C_{40}H_{63}FeN_7O_4Si_3Na$ [M + Na]$^+$ 868.3491, found 868.3487.

Minor Isomer: 6-(5-Ferrocenyl-1,2,3-triazol-1-yl)-9-[2,3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (5f′). Obtained 28.3 mg (10% yield) of a brown solid. R_f (silica gel, 40% EtOAc in hexanes) = 0.41. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.98 (s, 1H, Ar-H), 8.60 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 6.22 (d, 1H, H-1′, J = 5.1 Hz), 4.60 (t, 1H, H-2′, J = 4.6 Hz), 4.41 (m, 2H, ferrocenyl-H), 4.32 (t, 1H, H-3′, J = 4.0 Hz), 4.25 (m, 2H, ferrocenyl-H), 4.18 (q, 1H, H-4′, J = 3.1 Hz), 4.02 (dd, 1H, H-5′,

J = 3.4, 11.5 Hz), 3.99 (s, 5H, ferrocenyl-H), 3.81 (dd, 1H, H-5′, J = 2.4, 11.5 Hz), 0.943, 0.939, and 0.81 (3s, 27 H, *t*-Bu), 0.14, 0.13, 0.10, −0.005, and −0.20 (5s, 18H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.4, 152.0, 147.1, 145.7, 138.9, 133.3, 128.5, 88.7, 85.9, 76.6, 72.0, 70.0, 69.5, 69.4, 62.6, 53.6, 26.3, 26.0, 25.9, 18.8, 18.3, 18.0, −4.2, −4.4, −4.5, −4.7, −5.1. HRMS (ESI): calcd for $C_{40}H_{63}FeN_7O_4Si_3Na$ $[M + Na]^+$ 868.3491, found 868.3489.

6-[4-(1-Butyl)-1,2,3-triazol-1-yl]-9-[2,3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (5g). Synthesized from **3b** (200 mg, 0.314 mmol) and 1-hexyne (72.2 μL, 0.628 mmol). Chromatography of the crude reaction mixture on a silica gel column using 5% acetone in hexanes yielded **5g** as a yellow, foamy solid (184 mg, 81% yield). R_f (silica gel, 10% acetone in hexanes) = 0.22. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.92 (s, 1H, Ar-H), 8.85 (s, 1H, Ar-H), 8.59 (s, 1H, Ar-H), 6.20 (d, 1H, H-1′, J = 5.1 Hz), 4.65 (t, 1H, H-2′, J = 4.6 Hz), 4.32 (t, 1H, H-3′, J = 3.9 Hz), 4.18 (q, 1H, H-4′, J = 3.0 Hz), 4.03 (dd, 1H, H-5′, J = 3.7, 11.3 Hz), 3.82 (dd, 1H, H-5′, J = 2.5, 11.3 Hz), 2.88 (t, 2H, butyl-CH_2, J = 7.7 Hz), 1.77 (quint, 2H, butyl-CH_2, J = 7.6 Hz), 1.45 (sextet, 2H, butyl-CH_2, J = 7.4 Hz), 0.97, 0.94, and 0.79 (overlapping 3s and t, 30H, *t*-Bu and butyl-CH_3), 0.17, 0.16, 0.11, 0.10, −0.02, and −0.24 (6s, 18H, Si−CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.4, 152.4, 149.4, 145.2, 144.8, 123.3, 121.4, 88.7, 86.1, 76.4, 72.2, 62.7, 31.6, 26.3, 26.1, 25.8, 25.5, 22.5, 18.8, 18.3, 18.1, 14.0, −4.2, −4.4, −4.5, −4.8, −5.1. HRMS (ESI): calcd for $C_{34}H_{63}N_7O_4Si_3Na$ $[M + Na]^+$ 740.4142, found 740.4139.

General Method for Desilylation of the Click Products. Synthesis of 6-(4-Phenyl-1,2,3-triazol-1-yl]-9-(2-deoxy-β-D-ribofuranosyl)purine (6a). In a clean, dry plastic vial equipped with a stirring bar was placed the nucleoside derivative **4a** (91.2 mg, 0.150 mmol) in anhydrous THF (2.0 mL). $Et_3N\cdot 3HF$ (85 μL, 0.525 mmol) was added to the stirring mixture at room temperature. After 34 h at room temperature, TLC indicated complete consumption of the starting material at which time the mixture was evaporated to dryness under a stream of nitrogen gas. Chromatographic purification on a silica gel column using 3-5% MeOH in hexanes afforded **6a** as white powder (54.6 mg, 96% yield). R_f (silica gel, 10% MeOH in CH_2Cl_2) = 0.30. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.62 (s, 1H, Ar-H), 9.04 (s, 1H, Ar-H), 9.03 (s, 1H, Ar-H), 8.07 (d, 2H, Ar-H, J = 7.3 Hz), 7.53 (t, 2H, Ar-H, J = 7.6 Hz), 7.43 (t, 1H, Ar-H, J = 7.4 Hz), 6.57 (t, 1H, H-1′, J = 6.5 Hz), 5.40 (d, 1H, OH, J = 4.2 Hz), 5.01 (t, 1H, OH, J = 5.5 Hz), 4.49 (m, 1H, H-3′), 3.94 (app q, 1H, H-4′, $J_{app} \approx$ 3.6 Hz), 3.66 (m, 1H, H-5′), 3.07 (m, 1H, H-5′), 2.83 (m, 1H, H-2′), 2.43 (m, 1H, H-2′, superimposed with solvent). ^{13}C NMR (125 MHz, acetone-d_6 + 4 drops of DMSO-d_6): δ 155.2, 152.7, 148.5, 147.2, 145.6, 131.2, 130.0, 129.6, 126.9, 124.5, 121.6, 89.8, 86.0, 72.1, 62.9, 41.7. HRMS (ESI): calcd for $C_{18}H_{18}N_7O_3$ $[M + H]^+$ 380.1466, found 380.1465.

6-[4-(4-Methylphenyl)-1,2,3-triazol-1-yl]-9-(2-deoxy-β-D-ribofuranosyl)purine (6b). Desilylation of **4b** (93.3 mg, 0.150 mmol) with $Et_3N\cdot 3HF$ (0.15 mL, 0.901 mmol) and chromatographic purification as for **6a** afforded **6b** as white powder (43.9 mg, 74% yield). R_f (silica gel, 10% MeOH in CH_2Cl_2) = 0.32. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.55 (s, 1H, Ar-H), 9.03 (s, 1H, Ar-H), 9.02 (s, 1H, Ar-H), 7.95 (d, 2H, Ar-H, J = 7.8 Hz), 7.33 (d, 2H, Ar-H, J = 7.8 Hz), 6.57 (t, 1H, H-1′, J = 6.6 Hz), 5.40 (d, 1H, OH, J = 4.1 Hz), 5.01 (t, 1H, OH, J = 5.2 Hz), 4.49 (br m, 1H, H-3′), 3.93 (app q, 1H, H-4′, J_{app} = 3.8 Hz), 3.66 (m, 1H, H-5′), 3.57 (m, 1H, H-5′), 2.83 (app quint, 1H, H-2′, $J_{app} \approx$ 6.5 Hz), 2.43 (ddd, 1H, H-2′, J = 4.5, 6.5, 13.1 Hz). ^{13}C NMR (125 MHz, acetone-d_6 + 15 drops of DMSO-d_6): δ 154.8, 152.3, 148.0, 146.9, 145.1, 138.9, 130.2, 127.9, 126.4, 124.0, 120.8, 89.3, 85.3, 71.5, 62.3, 40.7, 21.3. HRMS (ESI): calcd for $C_{19}H_{20}N_7O_3$ $[M + H]^+$ 394.1622, found 394.1619.

6-[4-(4-Methoxyphenyl)-1,2,3-triazol-1-yl]-9-(2-deoxy-β-D-ribofuranosyl)purine (6c). Desilylation of **4c** (95.7 mg, 0.150 mmol) with $Et_3N\cdot 3HF$ (85 μL, 0.525 mmol) and chromatographic purification as for **6a** afforded **6c** as white powder (50.8 mg, 83% yield). R_f (silica gel, 10% MeOH in CH_2Cl_2) = 0.32. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.50 (s, 1H, Ar-H), 9.02 (s, 1H, Ar-H), 9.01 (s, 1H, Ar-H), 7.99 (d, 2H, Ar-H, J = 8.8 Hz), 7.08 (d, 2H, Ar-H, J = 8.8 Hz), 6.57 (t, 1H, H-1′, J = 6.6 Hz), 4.48 (m, 1H, H-3′), 3.93 (app q, 1H, H-4′, $J_{app} \approx$ 4.0 Hz), 3.66 (dd, 1H, H-5′, J = 4.6, 11.7 Hz), 3.57 (dd, 1H, H-5′, J = 4.5, 11.7 Hz), 2.82 (app quint, 1H, H-2′, $J_{app} \approx$ 6.5 Hz), 2.43 (ddd, 1H, H-2′, J = 3.9, 6.3, 13.5 Hz). ^{13}C NMR (125 MHz, acetone-d_6 + 15 drops of DMSO-d_6): δ 160.9, 155.0, 152.6, 148.2, 147.0, 145.4, 128.1, 124.3, 123.5, 120.4, 115.3, 89.6, 85.7, 71.8, 62.6, 55.9, 41.3. HRMS (ESI): calcd for $C_{19}H_{20}N_7O_4$ $[M + H]^+$ 410.1571, found 410.1570.

6-[4-(4-Fluorophenyl)-1,2,3-triazol-1-yl]-9-(2-deoxy-β-D-ribofuranosyl)purine (6d). Desilylation of **4d** (93.9 mg, 0.150 mmol) with $Et_3N\cdot 3HF$ (85 μL, 0.525 mmol) and chromatographic purification as for **6a** afforded **6d** as white solid (50.8 mg, 83% yield). R_f (silica gel, 10% MeOH in CH_2Cl_2) = 0.37. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.62 (s, 1H, Ar-H), 9.04 (s, 1H, Ar-H), 9.03 (s, 1H, Ar-H), 8.13 (dd, 2H, Ar-H, $J_{H,H}$ = 8.6 Hz, $J_{F,H}$ = 5.5 Hz), 7.37 (t, 2H, Ar-H, $J_{H,H}$ = $J_{F,H}$ = 8.6 Hz), 6.57 (t, 1H, H-1′, J = 6.3 Hz), 5.39 (br s, 1H, OH), 5.01 (br s, 1H, OH), 4.49 (m, 1H, H-3′), 3.94 (app q, 1H, H-4′, $J_{app} \approx$ 4.1 Hz), 3.66 (dd, 1H, H-5′, J = 4.5, 11.4 Hz), 3.57 (dd, 1H, H-5′, J = 4.2, 11.4 Hz), 2.83 (app quint, 1H, H-2′, $J_{app} \approx$ 6.5 Hz), 2.43 (ddd, 1H, H-2′, J = 3.7, 6.3, 13.3 Hz). ^{13}C NMR (125 MHz, acetone-d_6 + 10 drops of DMSO-d_6): δ 163.4 (d, $^1J_{C,F}$ = 245.7 Hz), 155.2, 152.6, 147.3, 147.2, 145.5, 129.0 (d, $^3J_{C,F}$ = 8.3 Hz), 127.6 (d, $^4J_{C,F}$ = 3.2 Hz), 124.5, 121.4, 116.8 ($^2J_{C,F}$ = 21.9 Hz), 89.7, 85.9, 72.0, 62.7, 41.5. HRMS (ESI): calcd for $C_{18}H_{17}FN_7O_3$ $[M + H]^+$ 398.1371, found 398.1386.

6-[4-(*N*-Phthalimidomethyl)-1,2,3-triazol-1-yl]-9-(2-deoxy-β-D-ribofuranosyl)purine (6e). Desilylation of **4e** (112.9 mg, 0.163 mmol) with $Et_3N\cdot 3HF$ (85 μL, 0.525 mmol) and chromatographic purification as for **6a** afforded **6e** as white solid (64.5 mg, 85% yield). R_f (silica gel, 10% MeOH in CH_2Cl_2) = 0.27. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.22 (s, 1H, Ar-H), 9.00 (s, 1H, Ar-H), 8.98 (s, 1H, Ar-H), 7.92 (m, 2H, Ar-H), 7.87 (m, 2H, Ar-H), 6.54 (t, 1H, H-1′, J = 6.6 Hz), 5.03 (s, 2H, NCH_2), 4.46 (m, 1H, H-3′), 3.92 (app q, 1H, H-4′, $J_{app} \approx$ 4.0 Hz), 3.64 (dd, 1H, H-5′, J = 4.5, 11.8 Hz), 3.55 (dd, 1H, H-5′, J = 4.5, 11.8 Hz), 2.79 (app quint, 1H, H-2′, $J_{app} \approx$ 6.5 Hz), 2.41 (ddd, 1H, H-2′, J = 3.9, 6.3, 13.3 Hz). ^{13}C NMR (125 MHz, acetone-d_6 + 15 drops of DMSO-d_6): δ 168.2, 154.8, 152.4, 147.0, 144.9, 144.2, 135.2, 132.7, 124.4, 123.9, 89.3, 85.4, 71.5, 62.4, 41.0, 33.5. HRMS (ESI): calcd for $C_{21}H_{19}N_8O_5$ $[M + H]^+$ 463.1473, found 463.1476.

6-(4-Ferrocenyl-1,2,3-triazol-1-yl)-9-(2-deoxy-β-D-ribofuranosyl)purine (6f). Desilylation of **4f** (107.3 mg, 0.150 mmol) with $Et_3N\cdot 3HF$ (85 μL, 0.525 mmol) and chromatographic purification as for **6a** afforded **6f** as an orange solid (51.8 mg, 71% yield). R_f (silica gel, 10% MeOH in CH_2Cl_2) = 0.26. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.23 (s, 1H, Ar-H), 9.02 (s, 1H, Ar-H), 9.01 (s, 1H, Ar-H), 6.57 (t, 1H, H-1′, J = 6.6 Hz), 4.95 (br t, 2H, ferrocenyl-H, J = 1.5 Hz), 4.48 (m, 1H, H-3′), 4.40 (br t, 2H, ferrocenyl-H, J = 1.5 Hz), 4.10 (s, 5H, ferrocenyl-H), 3.94 (app q, 1H, H-4′, $J_{app} \approx$ 4.3 Hz), 3.66 (dd, 1H, H-5′, J = 4.6, 11.7 Hz), 3.57 (dd, 1H, H-5′, J = 4.4, 11.7 Hz), 2.81 (app quint, 1H, H-2′, $J_{app} \approx$ 6.5 Hz), 2.43 (ddd, 1H, H-2′, J = 4.0, 6.3 13.3 Hz). ^{13}C NMR (125 MHz, acetone-d_6 + 10 drops of DMSO-d_6): δ 155.3, 152.8, 148.2, 147.1, 145.8, 124.5, 120.4, 90.0, 86.2, 76.1, 72.3, 70.6, 70.0, 68.0, 63.0, 41.9. HRMS (ESI): calcd for $C_{22}H_{21}FeN_7O_3Na$ $[M + Na]^+$ 510.0948, found 510.0948.

6-[4-(1-Butyl)-1,2,3-triazol-1-yl]-9-(2-deoxy-β-D-ribofuranosyl)purine (6g). Desilylation of **4g** (88.2 mg, 0.150 mmol) with $Et_3N\cdot 3HF$ (85 μL, 0.525 mmol) and chromatographic purification as for **6a** afforded **6g** as a clear, gummy material (38.0 mg, 70% yield). R_f (silica gel, 10% MeOH in CH_2Cl_2) = 0.35. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.98 (s, 1H, Ar-H), 8.97 (s, 1H, Ar-H), 8.96 (s, 1H, Ar-H), 6.55 (t, 1H, H-1′, J = 6.6 Hz), 5.39

(d, 1H, OH, J = 4.4 Hz), 4.99 (t, 1H, OH, J = 5.5 Hz), 4.47 (m, 1H, H-3′), 3.93 (app q, 1H, H-4′, $J_{app} \approx 4.0$ Hz), 3.65 (m, 1H, H-5′), 3.56 (m, 1H, H-5′), 2.84−2.76 (m, 3H, H-2′ and butyl-CH_2), 2.42 (ddd, 1H, H-2′, J = 3.9, 6.3, 13.3 Hz), 1.64 (quint, 2H, butyl-CH_2, J = 7.5 Hz), 1.38 (sextet, 2H, butyl-CH_2, J = 7.4 Hz), 0.93 (t, 3H, butyl-CH_3, J = 7.3 Hz). ^{13}C NMR (125 MHz, acetone-d_6 + 15 drops of DMSO-d_6): δ 154.7, 152.4, 149.0, 146.7, 145.3, 123.8, 122.5, 89.3, 85.4, 71.5, 62.4, 41.0, 31.8, 25.4, 22.6, 14.1. HRMS (ESI): calcd for $C_{16}H_{22}N_7O_3$ $[M + H]^+$ 360.1779, found 360.1791.

6-(4-Phenyl-1,2,3-triazol-1-yl)-9-(β-D-ribofuranosyl)purine (7a). Desilylation of **5a** (110.7 mg, 0.150 mmol) with $Et_3N \cdot 3HF$ (0.12 mL, 0.75 mmol) and chromatographic purification on a silica gel column using 3-7% MeOH in hexanes afforded **7a** as a white, fluffy solid (57.3 mg, 96% yield). R_f (silica gel, 10% MeOH in CH_2Cl_2) = 0.28. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.62 (s, 1H, Ar-H), 9.09 (s, 1H, Ar-H), 9.05 (s, 1H, Ar-H), 8.05 (d, 2H, Ar-H, J = 7.3 Hz), 7.53 (t, 2H, Ar-H, J = 7.5 Hz), 7.43 (t, 1H, Ar-H, J = 7.6 Hz) 6.15 (d, 1H, H-1′, J = 4.9 Hz), 5.62 (d, 1H, OH, J = 5.6 Hz), 5.28 (d, 1H, OH, J = 5.1 Hz), 5.14 (t, 1H, OH, J = 5.1 Hz), 4.65 (m, 1H, H-2′), 4.24 (m, 1H, H-3′), 4.03 (m, 1H, H-4′), 3.74 (m, 1H, H-5′), 3.62 (m, 1H, H-5′). ^{13}C NMR (125 MHz, THF-d_8 + 4 drops of DMSO-d_6): δ 155.5, 152.7, 148.5, 147.2, 146.0, 131.6, 129.8, 129.3, 126.9, 124.7, 121.2, 90.4, 87.7, 76.5, 71.9, 62.6. HRMS (ESI): calcd for $C_{18}H_{18}N_7O_4$ $[M + H]^+$ 396.1415, found 396.1416.

6-[4-(4-Methylphenyl)-1,2,3-triazol-1-yl]-9-(β-D-ribofuranosyl)purine (7b). Desilylation of **5b** (112.8 mg, 0.15 mmol) with $Et_3N \cdot 3HF$ (0.12 mL, 0.75 mmol) and chromatographic purification as for **7a** afforded **7b** as a white solid (59.2 mg, 96% yield). R_f (silica gel, 10% MeOH in CH_2Cl_2) = 0.28. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.56 (s, 1H, Ar-H), 9.08 (s, 1H, Ar-H), 9.04 (s, 1H, Ar-H), 7.96 (d, 2H, Ar-H, J = 7.8 Hz), 7.33 (d, 2H, Ar-H, J = 7.8 Hz), 6.15 (d, 1H, H-1′, J = 4.9 Hz), 5.62 (d, 1H, OH, J = 5.8 Hz), 5.28 (d, 1H, OH, J = 5.1 Hz), 5.14 (t, 1H, OH, J = 5.3 Hz), 4.65 (m, 1H, H-2′), 4.24 (m, 1H, H-3′), 4.02 (m, 1H, H-4′), 3.74 (m, 1H, H-5′), 3.62 (m, 1H, H-5′), 2.37 (s, 3H, CH_3). ^{13}C NMR (125 MHz, THF-d_8 + 4 drops of DMSO-d_6): δ 155.5, 152.7, 148.6, 147.1, 145.9, 139.0, 130.4, 128.8, 126.8, 124.7, 120.7, 90.5, 87.7, 76.4, 71.9, 62.6, 21.5. HRMS (ESI): calcd for $C_{19}H_{20}N_7O_4$ $[M + H]^+$ 410.1571, found 410.1572.

6-[4-(4-Methoxyphenyl)-1,2,3-triazol-1-yl]-9-(β-D-ribofuranosyl)purine (7c). Desilylation of **5c** (115.2 mg, 0.150 mmol) with $Et_3N \cdot 3HF$ (0.12 mL, 0.75 mmol) and chromatographic purification as for **7a** afforded **7c** as a white solid (51.3 mg, 81% yield). R_f (silica gel, 10% MeOH in CH_2Cl_2) = 0.30. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.51 (s, 1H, Ar-H), 9.07 (s, 1H, Ar-H), 9.04 (s, 1H, Ar-H), 8.01 (d, 2H, Ar-H, J = 8.8 Hz), 7.08 (d, 2H, Ar-H, J = 8.8 Hz), 6.15 (d, 1H, H-1′, J = 5.4 Hz), 4.65 (t, 1H, H-2′, J = 5.0 Hz), 4.23 (t, 1H, H-3′, J = 4.5 Hz), 4.03 (app q, 1H, H-4′, $J_{app} \approx 4.9$ Hz), 3.83 (s, 3H, OCH_3), 3.74 (dd, 1H, H-5′, J = 3.9, 11.7 Hz), 3.62 (dd, 1H, H-5′, J = 3.9, 11.7 Hz). ^{13}C NMR (125 MHz, THF-d_8 + 4 drops of DMSO-d_6): δ 161.2, 155.5, 152.7, 148.5, 147.2, 145.9, 128.2, 124.6, 124.0, 120.1, 115.3, 90.3, 87.6, 76.5, 71.8, 62.5, 55.8. HRMS (ESI): calcd for $C_{19}H_{20}N_7O_5$ $[M + H]^+$ 426.1520, found 426.1521.

6-[4-(Fluorophenyl)-1,2,3-triazol-1-yl]-9-(β-D-ribofuranosyl)-purine (7d). Desilylation of **5d** (113.4 mg, 0.15 mmol) with $Et_3N \cdot 3HF$ (0.12 mL, 0.75 mmol) and chromatographic purification as for **7a** afforded **7d** as a white solid (44.0 mg, 71% yield). R_f (silica gel, 10% MeOH in CH_2Cl_2) = 0.26. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.63 (s, 1H, Ar-H), 9.08 (s, 1H, Ar-H), 9.05 (s, 1H, Ar-H), 8.13 (dd, 2H, Ar-H, $J_{H,H}$ = 8.9 Hz, $J_{F,H}$ = 5.5 Hz), 7.37 (t, 2H, Ar-H, $J_{H,H} = J_{F,H}$ = 8.9 Hz), 6.15 (d, 1H, H-1′, J = 5.1 Hz), 5.62 (d, 1H, OH, J = 5.8 Hz), 5.28 (d, 1H, OH, J = 5.3 Hz), 5.14 (t, 1H, OH, J = 5.3 Hz), 4.65 (m, 1H, H-2′), 4.24 (m, 1H, H-3′), 4.03 (m, 1H, H-4′), 3.74 (m, 1H, H-5′), 3.62 (m, 1H, H-5′). ^{13}C NMR (125 MHz, THF-d_8 + 4 drops of DMSO-d_6): δ 163.7 (d, $^1J_{C,F}$ = 246.3 Hz), 155.6, 152.7, 147.6, 147.3, 145.8, 128.9 (d, $^3J_{C,F}$ = 8.2 Hz), 128.0 (d, $^4J_{C,F}$ = 3.2 Hz), 124.7, 121.2, 116.7 (d, $^2J_{C,F}$ = 21.8 Hz), 90.4, 87.7, 76.5, 71.8, 62.5. HRMS (ESI): calcd for $C_{18}H_{17}FN_7O_4$ $[M + H]^+$ 414.1321, found 414.1319.

6-[4-(*N*-Phthalimidomethyl)-1,2,3-triazol-1-yl]-9-(β-D-ribofuranosyl)purine (7e). Desilylation of **5e** (115.0 mg, 0.15 mmol) with $Et_3N \cdot 3HF$ (0.12 mL, 0.75 mmol) and chromatographic purification as for **7a** afforded **7e** as a white solid (61.7 mg, 85% yield). R_f (silica gel, 10% MeOH in CH_2Cl_2) = 0.26. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.22 (s, 1H, Ar-H), 9.05 (s, 1H, Ar-H), 8.99 (s, 1H, Ar-H), 7.94−7.91 (m, 2H, Ar-H), 7.89−7.86 (m, 2H, Ar-H), 6.12 (d, 1H, H-1′, J = 5.1 Hz), 5.03 (s, 2H, NCH_2), 4.60 (t, 1H, H-2′, J = 5.2 Hz), 4.21 (t, 1H, H-3′, J = 4.3 Hz), 4.01 (app q, 1H, H-4′, $J_{app} \approx 3.8$ Hz), 3.72 (dd, 1H, H-5′, J = 3.6, 12.0 Hz), 3.60 (dd, 1H, H-5′, J = 3.8, 12.0 Hz). ^{13}C NMR (125 MHz, THF-d_8 + 4 drops of DMSO-d_6): δ 168.3, 155.5, 152.7, 147.3, 145.7, 144.5, 135.2, 133.5, 124.6, 124.5, 124.1, 90.2, 87.6, 76.5, 71.8, 62.5, 33.8. HRMS (ESI): calcd for $C_{21}H_{19}N_8O_6$ $[M + H]^+$ 479.1422, found 479.1432.

6-(4-Ferrocenyl-1,2,3-triazol-1-yl)-9-(β-D-ribofuranosyl)purine (7f). Desilylation of **5f** (126.9 mg, 0.15 mmol) with $Et_3N \cdot 3HF$ (0.12 mL, 0.75 mmol) and chromatographic purification as for **7a** afforded **7f** as an orange solid (73.4 mg, 97% yield). R_f (silica gel, 10% MeOH in CH_2Cl_2) = 0.28. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.23 (s, 1H, Ar-H), 9.07 (s, 1H, Ar-H), 9.02 (s, 1H, Ar-H), 6.14 (d, 1H, H-1′, J = 5.1 Hz), 4.95 (br t, 2H, ferrocenyl-H), 4.64 (t, 1H, H-2′, J = 4.9 Hz), 4.41 (br t, 2H, ferrocenyl-H), 4.23 (t, 1H, H-3′, J = 4.4 Hz), 4.10 (s, 5H, ferrocenyl-H), 4.03 (app q, 1H, H-4′, $J_{app} \approx 3.9$ Hz), 3.74 (dd, 1H, H-5′, J = 3.9, 11.8 Hz), 3.62 (dd, 1H, H-5′, J = 3.9, 11.8 Hz). ^{13}C NMR (125 MHz, THF-d_8 + 4 drops of DMSO-d_6): δ 155.5, 152.7, 148.0, 147.1, 145.8, 124.5, 120.0, 90.4, 87.6, 76.5, 76.3, 71.8, 70.5, 69.7, 62.5. HRMS (ESI): calcd for $C_{22}H_{22}FeN_7O_4$ $[M + H]^+$ 504.1077, found 504.1060.

6-[4-(1-Butyl)-1,2,3-triazol-1-yl]-9-(β-D-ribofuranosyl)purine (7g). Desilylation of **5g** (107.7 mg, 0.15 mmol) with $Et_3N \cdot 3HF$ (0.12 mL, 0.75 mmol) and chromatographic purification as for **7a** afforded **7g** as a white solid (53.5 mg, 95% yield). R_f (silica gel, 10% MeOH in CH_2Cl_2) = 0.28. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.03 (s, 1H, Ar-H), 8.99 (s, 1H, Ar-H), 8.97 (s, 1H, Ar-H), 6.12 (d, 1H, H-1′, J = 5.1 Hz), 5.60 (br s, 1H, OH), 5.27 (br s, 1H, OH), 5.12 (br s, 1H, OH), 4.63 (t, 1H, H-2′, J = 4.7 Hz), 4.22 (t, 1H, H-3′, J = 4.2 Hz), 4.01 (app q, 1H, H-4′, $J_{app} \approx 3.8$ Hz), 3.72 (dd, 1H, H-5′, J = 3.4, 11.7 Hz), 3.61(dd, 1H, H-5′, J = 3.2, 11.7 Hz), 2.80 (t, 2H, butyl-CH_2, J = 7.6 Hz), 1.70 (quint, 2H, butyl-CH_2, J = 7.5 Hz), 1.39 (sextet, 2H, butyl-CH_2, J = 7.4 Hz), 0.94 (t, 3H, butyl-CH_3, J = 7.3 Hz). ^{13}C NMR (125 MHz, THF-d_8 + 4 drops of DMSO-d_6): δ 155.3, 152.7, 149.2, 146.9, 146.0, 124.4, 122.4, 90.4, 87.7, 76.4, 71.9, 62.6, 32.4, 26.1, 23.3, 14.4. HRMS (ESI): calcd for $C_{16}H_{22}N_7O_4$ $[M + H]^+$ 376.1728, found 376.1731.

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Supporting Information Available: General experimental details, materials, and methods for antiproliferative tests and the results, ORTEP of **4b**, copies of ^{1}H and ^{13}C NMR spectra of **2c**, **2d**, **3a**−**f**, **4a**−**g**, **4f′**, **5a**−**g**, **5a′**, **5c′**−**f′**, **6a**−**6g**, and **7a**−**7g**. This information is available free of charge via the Internet at http://pubs.acs.org.