

# Nucleic Acid Related Compounds. 86. Nucleophilic Functionalization of Adenine, Adenosine, Tubercidin, and Formycin Derivatives via Elaboration of the Heterocyclic Amino Group into a Readily Displaced 1,2,4-Triazol-4-yl Substituent<sup>1</sup>

Robert W. Miles, Vicente Samano,<sup>†</sup> and Morris J. Robins\*

Contribution from the Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602

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**Abstract:** Treatment of 9-methyladenine and hydroxyl-protected derivatives of adenosine and 2'-deoxyadenosine with 1,2-bis[(dimethylamino)methylene]hydrazine and/or its dihydrochloride at elevated temperatures in appropriate solvents resulted in elaboration of the 6-amino group into a 6-(1,2,4-triazol-4-yl) substituent in excellent yields. Analogous functionalization of the amino groups of tubercidin {4-amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine} and formycin {7-amino-3-(β-D-ribofuranosyl)pyrazolo[4,3-d]pyrimidine} gave the respective 4- and 7-(1,2,4-triazol-4-yl) derivatives. Nucleophilic replacement of the triazole moiety gave the respective 6-, 4-, and 7-substituted purine, pyrrolo[2,3-d]pyrimidine, and pyrazolo[4,3-d]pyrimidine products. This first general method for "direct" nucleophilic replacement of an amino group on these nitrogen heterocycles also provides a new class of compounds for potential postsynthetic modifications after incorporation into oligonucleotides.

## Introduction

The synthesis of nucleoside and nucleotide analogues with unnatural bases is important due to the biological and medicinal significance of these compounds. Two frequently used methods for their synthesis are (i) base synthesis and base-sugar coupling and (ii) base modification of intact nucleosides.<sup>2</sup> Of the two, coupling offers greater flexibility in base structures. However, these reactions often suffer from poor yields and lack of isomeric selectivity. Nucleoside modifications minimize reaction steps and avoid isomeric separations by employing readily available, chiral starting materials.

Naturally occurring oxo functions often can be converted into leaving groups and displaced by nucleophiles. Such procedures for pyrimidines begin with uracil compounds,<sup>3</sup> and guanosine and inosine derivatives are used for purine nucleosides.<sup>4</sup> However, no convenient, efficient procedures have been

developed for analogous transformations beginning with amino nucleosides. Approaches reported with cytosine and adenine nucleosides have involved inconvenient methodologies, poor to moderate yields, and/or noxious reagents.<sup>5,6</sup> A two-stage approach has employed enzymatic deamination followed by transformation of the resulting oxo function.<sup>7</sup>

Requirements of a general methodology for conversion of a heterocyclic amine into a suitable leaving group include the following: (i) the NH<sub>2</sub> group must be activated by R/R' substituents that markedly diminish its pK<sub>a</sub> (i.e., to generate a viable leaving group under mild displacement conditions); (ii) this intermediate cannot be so reactive that displacement of the NRR' group occurs during generation or isolation; (iii) nucleophiles must attack at the carbon atom of the parent heterocyclic

<sup>†</sup> Present address: Division of Organic Chemistry, Burroughs Wellcome Co., 3030 Cornwallis Road, Research Triangle Park, NC 27709.

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ring and not at the NR/R' terminus. Certain potential activating groups have failed the latter requirement.<sup>8</sup>

Divakar and Reese treated uracil nucleosides with phosphoryl chloride/1,2,4-triazole and obtained 4-(1,2,4-triazol-1-yl)pyrimidin-2-one derivatives via in situ replacement of 4-*O*-phosphorylated intermediates. The triazole moiety, in turn, was readily displaced from these compounds by other nucleophiles.<sup>3a</sup> Attempted analogous conversions of purin-6-one nucleosides via 6-(triazol-1-yl) and 6-(nitrotriazol-1-yl) intermediates have been reported, but displacement data are sketchy.<sup>9</sup>

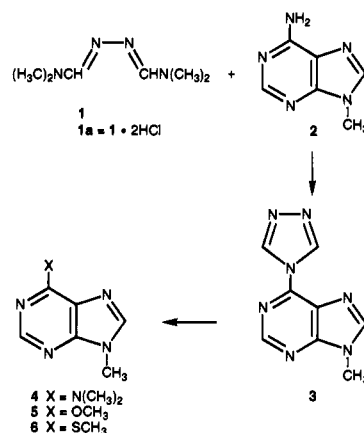
We reasoned that isomeric 6-(1,2,4-triazol-4-yl)purine compounds should be promising candidates to fulfill the above requirements. Thermodynamic leaving group ability (triazole  $pK_a \sim 10$ )<sup>10a</sup> and kinetic activation of nucleophilic attack at C6 of the purine ring (suppression of purine amidine resonance stabilization involving the amino lone-pair electrons) would be expected. Enhanced "aromaticity" in azole rings should retard undesired nucleophilic attack on the triazole ring.<sup>10b</sup> Bartlett and Humphrey prepared 1,2-bis[(dimethylamino)methylene]hydrazine (**1**) and its dihydrochloride (**1a**) from *N,N'*-diformylhydrazine and thionyl chloride in DMF and reported cyclizations of **1** with amines to give 4-*N*-substituted-1,2,4-triazoles.<sup>11a</sup> Alternative preparations of **1** and analogous azines are available.<sup>11</sup> We recently demonstrated that this reaction can be applied to adenine compounds to generate 6-(1,2,4-triazol-4-yl) derivatives which give 6-substituted purines in high to excellent yields upon treatment with nucleophiles.<sup>1</sup> We have explored other applications and convenient new methodology and now report an expanded generality with additional amino heterocyclic nucleoside analogues.

## Results and Discussion

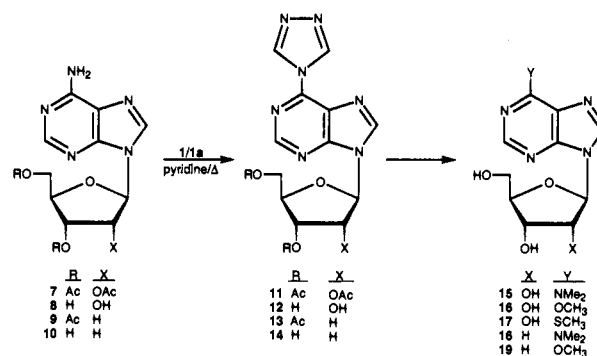
Relatively few elaborations of amines into triazoles with azine **1/1a** have been reported, and in several cases, problems such as the need for a large excess of reagent, long reaction times, and moderate yields were encountered.<sup>12</sup> No examples of this cyclization had been noted with compounds as acid- and heat-sensitive or with amines as weakly basic as adenine nucleosides (adenosine  $pK_a \sim 3.5$ ).<sup>13</sup> Therefore, 9-methyladenine (**2**; Scheme 1) was chosen as a robust model system.

We heated **2** and **1a** in DMF at reflux for 18 h followed by addition of **1a** and heating for 2 days to give 9-methyl-6-(1,2,4-triazol-4-yl)purine (**3**, 85%). Three representative nucleophiles

## Scheme 1



## Scheme 2



were employed to test the reactivity of **3** toward nucleophilic aromatic substitution. Treatment of **3** with 40% aqueous dimethylamine for 1 h at ambient temperature gave 9-methyl-6-(dimethylamino)purine (**4**, 99% after chromatography). Sodium methoxide in methanol/DMF at ambient temperature gave 6-methoxy-9-methylpurine (**5**, 97% recrystallized). Displacement with sodium thiomethoxide in DMF gave 9-methyl-6-(methylthio)purine (**6**, 84% recrystallized).

Efforts next were focused on more challenging nucleoside systems. Attempted application of the above conditions with **1a** and adenosine (**8**; Scheme 2) resulted in significant base-sugar cleavage. The more stable tri-*O*-acetyl analogue (**7**) required long reaction times and multiple additions of **1a** to give moderate yields of the desired product. Since protonation of the purine ring would be expected to deactivate the 6-amino group, attempts were made to neutralize excess acid without serious deactivation of the electrophilic reagent **1a**. Pyridine was a good base/solvent, and treatment of **7** with **1a** in anhydrous pyridine for 20 h at 100 °C gave 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6-(1,2,4-triazol-4-yl)purine (**11**, 88%).

Treatment of **11** with 40% HNMe<sub>2</sub>/H<sub>2</sub>O at ambient temperature gave 6-(dimethylamino)-9-(β-D-ribofuranosyl)purine (**15**, 99.8%). Slow passage of a methanolic solution of **11** through a column of Dowex 1 × 2 (OH<sup>-</sup>) resin (presoaked with MeOH) gave 6-methoxy-9-(β-D-ribofuranosyl)purine (**16**, 89% recrystallized). Treatment of a solution of **11** in DMF with sodium thiomethoxide in DMF gave 6-(methylthio)-9-(β-D-ribofuranosyl)purine (**17**, 94%).

Minor cleavage of adenosine occurred under the less acidic cyclization conditions with pyridine. However, the transient protection methodology of Jones<sup>14</sup> with the sugar hydroxyl groups converted into trimethylsilyl ethers conferred enhanced

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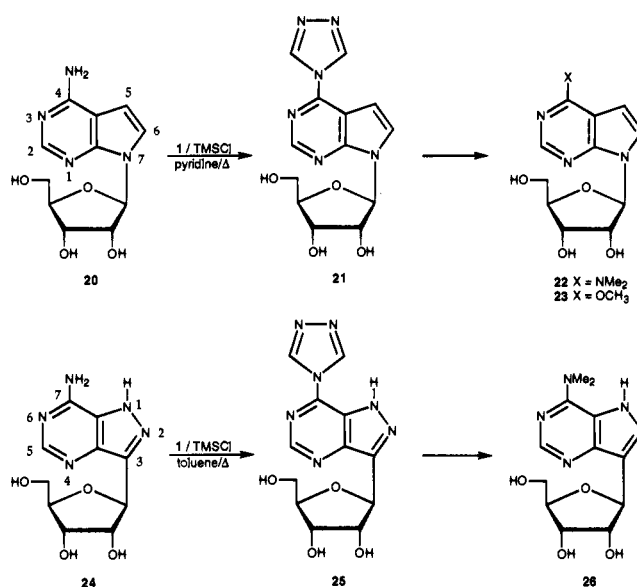
glycosyl bond stability.<sup>15</sup> Treatment of adenosine with TMSCl and **1a** in anhydrous pyridine at 100 °C for 24 h followed by deprotection with MeOH gave 9-( $\beta$ -D-ribofuranosyl)-6-(1,2,4-triazol-4-yl)purine (**12**, 94%). Treatment of **12** with 40% HNMe<sub>2</sub>/H<sub>2</sub>O gave 6-(dimethylamino)-9-( $\beta$ -D-ribofuranosyl)purine (**15**, 92%), and 1 M NaOMe/MeOH converted **12** into 6-methoxy-9-( $\beta$ -D-ribofuranosyl)purine (**16**, 98%).

Treatment of the acid- and heat-sensitive 3',5'-di-*O*-acetyl-2'-deoxyadenosine (**9**) with **1a** in pyridine at 100 °C resulted in ~50% glycosyl cleavage by the time **9** was consumed. Attempted application of the transient protection conditions with 2'-deoxyadenosine (**10**), TMSCl, and **1a** in pyridine at 100 °C resulted in nearly quantitative glycosyl bond cleavage in <2 h, but ~50% cyclization to the 6-(1,2,4-triazol-4-yl)purine had occurred. Attempts to reduce glycosyl cleavage by addition of various bases severely impeded the cyclization reaction. A buffer system of azine **1** and its dihydrochloride **1a** (a rough titration of **1** showed pK<sub>a(1)</sub> ~2.4 and pK<sub>a(2)</sub> ~7.7) was found to effectively retard glycosyl cleavage and retain adequate electrophilic reactivity for efficient cyclization. Variation of the ratio of **1/1a** allowed fine tuning of acidity in order to favor cyclization over cleavage (a more convenient method for the preparation of **1**<sup>11a</sup> was developed, see the Experimental Section). Thus, **9/1a** (~2:9:1) was heated at 100 °C in pyridine with TMSCl for 48 h to give 9-(3,5-di-*O*-acetyl-2'-deoxy- $\beta$ -D-erythro-pentofuranosyl)-6-(1,2,4-triazol-4-yl)purine (**13**, 83%). Treatment of **13** with 40% HNMe<sub>2</sub>/H<sub>2</sub>O gave 9-(2-deoxy- $\beta$ -D-erythro-pentofuranosyl)-6-(dimethylamino)purine (**18**, 97%). The **1/1a** buffer also was generated *in situ* with 2'-deoxyadenosine (**10**), TMSCl (for protection/glycosyl bond stabilization and HCl formation) and enough **1** to give a proper balance for cyclization. Treatment of **10** with TMSCl and 4 equiv of **1** in pyridine at 100 °C for 24 h gave 9-(2-deoxy- $\beta$ -D-erythro-pentofuranosyl)-6-(1,2,4-triazol-4-yl)purine (**14**, 88%) after processing. Treatment of **14** with 40% HNMe<sub>2</sub>/H<sub>2</sub>O gave **18** (96%), and **14** was converted into 9-(2-deoxy- $\beta$ -D-erythro-pentofuranosyl)-6-(methoxy)purine (**19**, 96%) by application to a column of Dowex 1  $\times$  2 (OH<sup>-</sup>) resin (presoaked with MeOH).

Tubercidin,<sup>16a</sup> 4-amino-7-( $\beta$ -D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**20**; Scheme 3), was the first example of a series of naturally occurring analogues containing this ring system and is an antibiotic<sup>16</sup> with diverse biological activity. Coupling methods usually have been employed to obtain substituted tubercidin derivatives.<sup>17</sup> The 4-chloro compound derived from its 4-oxo analogue served as a prior substrate for nucleophilic substitution reactions.<sup>18</sup>

Application of the cyclization conditions developed for adenosine converted tubercidin to its triazole derivative. However, 5–20% of the starting material persisted after 24 h. The enhanced basicity of tubercidin (pK<sub>a</sub> ~ 5.2; adenosine, pK<sub>a</sub> ~ 3.5)<sup>13</sup> apparently resulted in amplified protonation of this heterocyclic nucleophile. Therefore, the less acidic conditions developed for 2'-deoxyadenosine were employed. Treatment of tubercidin (**20**) with **1** and TMSCl at 100 °C for 24 h gave

Scheme 3



7-( $\beta$ -D-ribofuranosyl)-4-(1,2,4-triazol-4-yl)pyrrolo[2,3-*d*]pyrimidine (**21**, 95%).

Nucleophilic displacements with pyrrolo[2,3-*d*]pyrimidines are known to be more difficult than with their purine counterparts.<sup>18</sup> Complete displacement of the triazole group from **21** with 40% HNMe<sub>2</sub>/H<sub>2</sub>O at ambient temperature required 7 h (vs ~10 min for the purine analogue), and a major byproduct was detected (~20%, TLC). Pyridine as cosolvent eliminated this byproduct formation but also diminished the reaction rate. Thus, **21** was stirred with pyridine/40% HNMe<sub>2</sub>/H<sub>2</sub>O for 3 days at ambient temperature to give 4-(dimethylamino)-7-( $\beta$ -D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**22**, 96%). In contrast, treatment of **21** with 1 M NaOMe/MeOH for 1 h at ambient temperature gave 4-methoxy-7-( $\beta$ -D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**23**, 86%).

The nucleoside antibiotic formycin<sup>16b</sup> (**24**; Scheme 3) contains a pyrazolo[4,3-*d*]pyrimidine ring. Prior methods for introduction of functionality at C7 involved multistep ring elaborations or conversions of 7-oxo to 7-chloro derivatives.<sup>19</sup> Application of our triazole methodology to formycin required modified conditions. Owing to the acidic proton at N1, 7-substituted formycin derivatives undergo replacement sluggishly with strongly basic nucleophiles. However, they react readily with less basic nucleophiles. Treatment of **24** with **1a** in pyridine, or **1/TMSCl**/pyridine, resulted in extensive conversion to 7-(dimethylamino)-3-( $\beta$ -D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidine (**26**) by a secondary reaction of the triazole intermediate with dimethylamine evolved during ring closure. However, the use of toluene as solvent rendered the dimethylammonium chloride byproduct insoluble without hindering the cyclization reaction. Treatment of **24** with **1** and TMSCl in toluene at 70 °C for 15 h gave 3-( $\beta$ -D-ribofuranosyl)-7-(1,2,4-triazol-4-yl)pyrazolo[4,3-*d*]pyrimidine (**25**, 76%). Quantitative conversion to fluorescent **25** was observed (TLC), but significant quantities of product were lost during aqueous workup. Treatment of **25** with excess Me<sub>2</sub>NH·HCl in pyridine at 57 °C gave **26** quantitatively. Excess Me<sub>2</sub>NH·HCl was removed by chromatography [Dowex 1  $\times$  2 (OH<sup>-</sup>), 0.1 N HOAc], and the displaced triazole was removed by sublimation.

In summary, we have shown that the 1,2,4-triazole ring can be elaborated readily onto the 6-amino group of adenosine as well as *O*-acetyl derivatives of adenosine and 2'-deoxyadenosine with

(15) Protection of sugar hydroxyls with electron-withdrawing groups stabilizes the glycosidic bond of nucleosides.<sup>7a</sup> The electron-withdrawing effect of silyl ethers (Bassindale, A. R.; Taylor, P. G. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1989; Part I, pp 809–827) is a possible explanation for the present observation.

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Table 1. <sup>1</sup>H NMR Spectral Data<sup>a,b</sup>

compd	H1' <sup>c</sup> (J <sub>1'-2'</sub> )	H2' <sup>d</sup> (J <sub>2'-3'</sub> )	H3' <sup>d</sup> (J <sub>3'-4'</sub> )	H4' <sup>d</sup> (J <sub>4'-5',5''</sub> )	H5',5'' <sup>e,f</sup> (J <sub>5'-5''</sub> )	H2 <sup>g</sup>	H8 <sup>g</sup>	HT <sup>g</sup>	OH5' <sup>h</sup> ( <sup>3</sup> J <sub>HO-CH<sub>2</sub></sub> )	OH3' <sup>c</sup> ( <sup>3</sup> J <sub>HO-CH</sub> )	OH2'/H2'' <sup>c</sup> ( <sup>3</sup> J <sub>HO-CH</sub> )	others <sup>g</sup>
3						8.94	8.78	9.66				3.92 (CH <sub>3</sub> )
11	6.44 (5.1)	6.08 <sup>i</sup> (5.6)	5.69 <sup>i</sup> (5.4)	4.25-4.47 <sup>e</sup>	4.25-4.47	8.99	9.02	9.64				2.02, 2.06, 2.14 (Ac's)
12	6.12 (5.2)	4.64 (5.1)	4.23 (3.7)	4.02 (3.5, 3.9)	3.55-3.79 (3.76, 3.65) <sup>ij</sup> (12.2)	8.96	9.07	9.66	5.14 (5.5)	5.30 (5.2)	5.62 (5.9)	
13	6.58 <sup>i</sup> (7.6) (6.4) <sup>j</sup>	3.23 (7.0) (14.3) <sup>m</sup>	5.48	4.19-4.37 <sup>e</sup>	4.19-4.37	8.97	9.01	9.65			2.67 <sup>d</sup> (3.0) <sup>k</sup>	2.01, 2.12 (Ac's)
14	6.54 <sup>i</sup> (6.8) (6.4) <sup>j</sup>	2.81 (6.0) (13.3) <sup>m</sup>	4.44-4.52 <sup>e</sup> (2.6)	3.93 (4.3, 4.5)	3.50-3.72 (3.67, 3.6) <sup>ij</sup> (11.8)	8.94	9.01	9.64	5.02 (5.5)	5.41 (4.2)	2.42 <sup>d</sup> (3.9) <sup>k</sup>	
15	5.91 (5.9)	4.58 (4.9)	4.15 (3.2)	3.96 (3.6, 3.5)	3.34-3.73 (3.68, 3.55) <sup>ij</sup> (12.2)	8.22	8.38	—	5.38 <sup>i</sup> (4.6, 6.8)	5.20 (4.7)	5.46 (6.0)	3.34-3.73 <sup>e</sup> (NMe <sub>2</sub> ) 3.46 <sup>ij,n</sup> (NMe <sub>2</sub> )
16	6.00 (5.8)	4.60 (4.8)	4.18 (3.6)	3.98 (3.6, 3.9)	3.51-3.75 (3.68, 3.57) <sup>ij</sup> (12.2)	8.57	8.64	—	5.16 (5.5)	5.25 (4.8)	5.53 (6.0)	4.11 (OMe)
17	6.00 (5.6)	4.60 (5.0)	4.18 (3.5)	3.97 (3.8, 4.0)	3.51-3.75 (3.70, 3.58) <sup>ij</sup> (12.2)	8.71	8.76	—	5.13 (5.6)	5.25 (4.9)	5.54 (5.9)	2.68 (SMe)
18	6.37 <sup>i</sup> (7.6) (6.1) <sup>j</sup>	2.69 (5.7) (13.2) <sup>m</sup>	4.41 <sup>e</sup> (2.6)	3.88 (3.9, 4.3)	3.46-3.70 (3.62, 3.52) <sup>ij</sup> (12.1)	8.21	8.36	—	5.21 (5.7)	5.32 (4.0)	2.26 <sup>d</sup> (3.0) <sup>k</sup>	3.46-3.70 <sup>e</sup> (NMe <sub>2</sub> ) 3.41 <sup>ij,n</sup> (NMe <sub>2</sub> )
19	6.44 <sup>i</sup> (7.3) (6.2) <sup>j</sup>	2.74 (5.9) (13.3) <sup>m</sup>	4.43 <sup>e</sup> (2.7)	3.89 (4.5, 4.7)	3.44-3.70 (3.63, 3.53) <sup>ij</sup> (11.8)	8.55	8.60	—	5.04 (5.6)	5.36 (4.0)	2.32 <sup>d</sup> (3.4) <sup>k</sup>	4.10 (OMe)

compd	H1' <sup>c</sup> (J <sub>1'-2'</sub> )	H2' <sup>d</sup> (J <sub>2'-3'</sub> )	H3' <sup>d</sup> (J <sub>3'-4'</sub> )	H4' <sup>d</sup> (J <sub>4'-5',5''</sub> )	H5',5'' <sup>e,f</sup> (J <sub>5'-5''</sub> )	H2 <sup>g</sup>	H6 <sup>c</sup>	H5 <sup>c</sup> (J <sub>5-6</sub> )	HT <sup>g</sup>	OH5' <sup>h</sup> ( <sup>3</sup> J <sub>HO-CH<sub>2</sub></sub> )	OH3' <sup>c</sup> ( <sup>3</sup> J <sub>HO-CH</sub> )	OH2' <sup>c</sup> ( <sup>3</sup> J <sub>HO-CH</sub> )	others <sup>g</sup>
21	6.30 (5.9)	4.46 (4.9)	4.16 (3.3)	3.97 (4.0, 4.0)	3.53-3.74 (3.68, 3.58) <sup>ij</sup> (12.0)	8.82	8.12	7.26 (3.9)	9.52	5.10 (5.4)	5.23 (4.9)	5.44 (6.2)	
22	6.08 (6.2)	4.39 (5.0)	4.08 (3.3)	3.89 (3.4, 3.8)	3.46-3.68 (3.62, 3.53) <sup>ij</sup> (12.2)	8.13	7.42	6.72 (3.8)	—	5.10-5.30 <sup>e</sup>	5.10-5.30 <sup>e</sup>	5.10-5.30 <sup>e</sup>	3.30 (NMe <sub>2</sub> )
23	6.15 (6.2)	4.43 <sup>ij</sup> (5.2)	4.12 <sup>ij</sup> (3.1)	3.95 <sup>j</sup> (3.7, 4.0)	(3.62, 3.58) <sup>ij</sup> (12.0)	8.44	7.68	6.60 (3.7)	—	5.0-5.4 <sup>o</sup>	5.0-5.4 <sup>o</sup>	5.0-5.4 <sup>o</sup>	4.05 (OMe)

compd	H1' <sup>e</sup> (J <sub>1'-2'</sub> )	H2' <sup>d</sup> (J <sub>2'-3'</sub> )	H3' <sup>d</sup> (J <sub>3'-4'</sub> )	H4' <sup>d</sup> (J <sub>4'-5',5''</sub> )	H5',5'' <sup>if</sup> (J <sub>5'-5''</sub> )	H5 <sup>g</sup>	—	—	HT <sup>g</sup>	OH5' <sup>e</sup>	OH3' <sup>e</sup>	OH2' <sup>e</sup>	others
25	5.07-5.21 5.18 <sup>ej</sup> (6.9)	4.61 (5.2)	4.13 (3.6)	3.95 (4.2, 4.6)	3.67, 3.53 (12.0)	8.96	—	—	9.59	5.07-5.21	5.07-5.21	5.07-5.21	(NH not observed)
26	4.91-5.10 5.00 <sup>ej</sup> (7.4)	4.47 <sup>ij</sup> (5.0)	4.09 <sup>ij</sup> (2.7)	3.95 <sup>ej</sup> (2.9, 3.2)	(3.64, 3.54) <sup>j</sup> (12.2)	8.14	—	—	—	4.91-5.10	4.91-5.10	4.91-5.10	3.43 <sup>n</sup> (NMe <sub>2</sub> ) (NH not observed)

<sup>a</sup> Chemical shifts ( $\delta$ ) in Me<sub>2</sub>SO-*d*<sub>6</sub> at 200 MHz unless noted otherwise. <sup>b</sup> "Apparent" first-order coupling constants (Hz, in parentheses). <sup>c</sup> Doublet unless noted otherwise. <sup>d</sup> Doublet of doublets of doublets unless noted otherwise. <sup>e</sup> Multiplet unless noted otherwise. <sup>f</sup> Upfield resonance assigned to H5'' (*pro-R*). <sup>g</sup> Singlet unless noted otherwise. <sup>h</sup> Triplet unless noted otherwise. <sup>i</sup> Doublet of doublets unless noted otherwise. <sup>j</sup> After D<sub>2</sub>O exchange. <sup>k</sup> (*J*<sub>2'-3'</sub>). <sup>l</sup> (*J*<sub>1'-2'</sub>). <sup>m</sup> (*J*<sub>2'-2''</sub>). <sup>n</sup> Broad singlet. <sup>o</sup> Unresolved.

inexpensive, readily available reagents. This cyclization also can be performed with unprotected adenosine, 2'-deoxyadenosine, tubercidin, and formycin (with transient trimethylsilyl protection of the hydroxyl groups). Amines used in previously reported cyclizations were quite basic, and the unprotonated azine was generally employed. Formation of triazoles from the less basic amines used in the present study required more electrophilic (protonated) forms of the azine.

The triazole ring is readily displaced by common nucleophiles from these respective 6-, 4-, and 7-(1,2,4-triazol-4-yl) derivatives of purine, pyrrolo[2,3-*d*]pyrimidine, and pyrazolo[4,3-*d*]pyrimidine nucleosides. The (1,2,4-triazol-4-yl)nucleoside intermediates are easily purified (transient protection procedures normally give analytically pure products after extraction and deprotection/filtration), and the isolated solids appear to be stable indefinitely at room temperature under normal laboratory conditions. They should be amenable to mild oligonucleotide synthesis procedures and provide new monomeric units for postsynthetic modifications in nucleic acid chemistry.

## Experimental Section

Uncorrected melting points were determined with a capillary tube apparatus. UV spectra were determined with solutions in MeOH unless otherwise noted. NMR spectra were obtained with solutions in Me<sub>2</sub>SO-*d*<sub>6</sub> (Me<sub>4</sub>Si internal), <sup>1</sup>H at 200 MHz (Table 1) and <sup>13</sup>C at 50.3 MHz (Table 2) unless otherwise noted. Mass spectra were determined by direct probe introduction at 20 eV. TLC was performed with Whatman Al Sil G/UV 254 plates. Reagent grade chemicals were used. TMSCl and reaction solvents except toluene were distilled before use. Pyridine was dried by reflux over and distillation from CaH<sub>2</sub>. Cyclization reactions were conducted under an atmosphere of N<sub>2</sub> or Ar with a leak-proof Teflon sleeve on the ground-glass joint of the condenser. Volatile materials were flash evaporated at <35 °C under water aspirator or mechanical oil pump vacuum. Solid products were dried in vacuo over P<sub>4</sub>O<sub>10</sub> for ≥1 day, and stable compounds were dried at elevated temperatures. "Diffusion crystallization" was performed as described.<sup>20</sup> Yields can suffer markedly if the optimized

Table 2. <sup>13</sup>C NMR Spectral Data<sup>a,b</sup>

compd	C2	C4	C5	C6	C8	C1'	C2'	C3'	C4'	C5'	C (triazole)	others
3 <sup>c</sup>	151.64	142.22	121.77	154.04	148.24						140.77	29.97 (CH <sub>3</sub> )
11 <sup>d</sup>	153.25	144.10	123.60	154.05	144.46	87.32	73.51	70.83	80.98	63.23	141.34	20.57, 20.72, 20.97 (Ac); 170.03, 170.19, 170.86 (Ac)
12	152.32	143.03	122.85	153.75	146.21	88.32	74.24	70.35	86.04	61.28	141.19	
13 <sup>d</sup>	152.89	143.88	123.57	153.83	144.19	83.47	38.16	74.70	85.66	64.02	141.25	21.27, 21.38 (Ac); 170.65, 170.72 (Ac)
14	152.14	142.84	122.83	153.44	146.15	84.45	e	70.59	88.26	61.49	141.19	
15	151.96	150.00	119.99	154.55	138.81	88.02	73.62	70.65	85.95	61.67		(NMe <sub>2</sub> ) <sup>e</sup>
16 <sup>f</sup>	151.87	151.99	121.32	160.67	142.63	87.99	73.89	70.48	85.89	61.45		54.37 (OMe)
17 <sup>f</sup>	151.85	148.10	131.40	160.74	143.32	87.92	73.89	70.41	85.88	61.38		11.46 (SMe)
18	151.91	149.58	119.79	154.46	138.42	84.18	e	71.02	87.87	61.86		(NMe <sub>2</sub> ) <sup>e</sup>
19	151.73	151.89	121.37	160.59	142.52	84.13	e	70.94	88.26	61.87		54.22 (OMe)

compd	C2	C7a	C4a	C4	C6	C1'	C2'	C3'	C4'	C5'	C (triazole)	others
21	150.78	145.03	107.70	153.62	129.20	87.31	74.58	70.78	85.66	61.70	141.32	100.03 (C5)
22	150.51	150.84	103.37	157.14	121.83	87.49	73.79	70.71	85.08	61.83		102.89 (C5); (NMe <sub>2</sub> ) <sup>e</sup>
23	150.84	152.16	98.94	162.54	125.19	87.40	74.30	70.84	85.40	61.87		105.44 (C5); 53.76 (OMe)

compd	C5	C3a	C7a	C7	C3	C1'	C2'	C3'	C4'	C5'	C (triazole)	others
24 <sup>g,h</sup>	148.71	137.53 <sup>i</sup>	131.87	154.40	140.48 <sup>i</sup>	78.00	74.83	71.51	84.60	61.87		
25 <sup>h,j</sup>	146.25	140.66 <sup>i</sup>	131.25	143.87	141.22 <sup>i</sup>	77.22	74.49	71.21	84.60	61.57	141.54	
26 <sup>g,h</sup>	148.56	137.85 <sup>i</sup>	133.30	154.14	139.79 <sup>i</sup>	77.86	74.68	71.48	84.60	61.78		43.68 (NMe <sub>2</sub> )

<sup>a</sup> Chemical shifts ( $\delta$ ) in Me<sub>2</sub>SO-*d*<sub>6</sub> at 50.3 MHz unless noted otherwise. <sup>b</sup> Proton-decoupled singlets. <sup>c</sup> At 125.7 MHz in Me<sub>2</sub>SO-*d*<sub>6</sub>. <sup>d</sup> At 50.3 MHz in CDCl<sub>3</sub>. <sup>e</sup> Obscured by solvent resonance. <sup>f</sup> Chenon, M.-T.; Pugmire, R. J.; Grant, D. M.; Panzica, R. P.; Townsend, L. B. *J. Am. Chem. Soc.* **1975**, *97*, 4627–4636. <sup>g</sup> At 125.7 MHz in NaOD/D<sub>2</sub>O, pD ~ 11. <sup>h</sup> Diffuse peaks in Me<sub>2</sub>SO-*d*<sub>6</sub> or neutral D<sub>2</sub>O. <sup>i</sup> Assignments might be reversed. <sup>j</sup> At 50.3 MHz in NaOD/D<sub>2</sub>O, pD ~ 11.

conditions described are altered for the concentrated triazole cyclization reactions, ice-cold workup temperatures, etc.

**1,2-Bis[(dimethylamino)methylene]hydrazine (1).** Dihydrochloride **1a**<sup>11a</sup> (4.33 g, 20.1 mmol) was stirred with NaOH/H<sub>2</sub>O (1 M, 70 mL) and extracted with CHCl<sub>3</sub> (3 × 50 mL). The combined organic phase was washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered through a small layer of Na<sub>2</sub>SO<sub>4</sub>, and evaporated. EtOAc was added to the residue and evaporated (2×), and the solid was dried (0.5 h under water aspirator vacuum, since the compound sublimes) to give **1** (2.67 g, 94%); mp 75.5–77.5 °C (lit.<sup>11a</sup> mp 79–81 °C); <sup>1</sup>H NMR  $\delta$  2.72 (s, 6, NMe<sub>2</sub>), 7.69 (s, 2, N=CH).

**9-Methyl-6-(1,2,4-triazol-4-yl)purine (3).** A suspension of **1a** (2.54 g, 11.8 mmol) and 9-methyladenine (**2**; 1.33 g, 8.9 mmol) in DMF (250 mL) was refluxed for 18 h. Additional **1a** was added (1.47 g, 6.8 mmol), and heating was continued for 2 days. Volatiles were evaporated, and the residue was coevaporated (MeOH, 3×). The solid was suspended in MeOH, filtered, and dried to give **3** (1.53 g, 85%). A small analytical sample was recrystallized (MeOH) to give **3**: mp 292.5–294 °C; UV max 276 nm ( $\epsilon$  13 300), min 235 nm ( $\epsilon$  2200); MS *m/z* 201 (90, M<sup>+</sup>). Anal. Calcd for C<sub>8</sub>H<sub>7</sub>N<sub>7</sub> (201.2): C, 47.76; H, 3.51; N, 48.73. Found: C, 47.91; H, 3.46; N, 48.66.

**9-Methyl-6-(dimethylamino)purine (4).** A solution of **3** (80.3 mg, 0.40 mmol) in 40% HNMe<sub>2</sub>/H<sub>2</sub>O (3 mL) was stirred for 1 h at ambient temperature. Volatiles were evaporated, and the residue was purified by chromatography [Dowex 1 × 2 (OH<sup>-</sup>), H<sub>2</sub>O] and dried to give analytically pure **4** (70.3 mg, 99%); mp 113.5–115 °C (lit.<sup>21</sup> mp 114–115 °C); <sup>1</sup>H NMR spectrum agreed with literature values.<sup>22</sup> Anal. Calcd for C<sub>8</sub>H<sub>11</sub>N<sub>5</sub> (177.2): C, 54.22; H, 6.26; N, 39.52. Found: C, 54.10; H, 6.21; N, 39.53.

**6-Methoxy-9-methylpurine (5).** A solution of **3** (201 mg, 1.0 mmol) in DMF (4 mL) was treated with NaOMe/MeOH (1 M, 5 mL) for 30 min at ambient temperature and neutralized with HOAc. Volatiles were evaporated, the residue was dissolved in H<sub>2</sub>O, and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (1 mL, 10–15×). The combined organic phase was evaporated, and the residue was dried and "diffusion crystallized" (MeOH/Et<sub>2</sub>O) to give **5** (159 mg, 97%). This material was dried at 110 °C in vacuo (which caused loss of product by sublimation) to yield **5** (140 mg, 85%); mp 149–150 °C (lit.<sup>23</sup> mp 150–151 °C); <sup>1</sup>H NMR spectrum agreed with literature values.<sup>23</sup>

**9-Methyl-6-(methylthio)purine (6).** A deoxygenated solution of NaSMe (109 mg, 1.6 mmol) in DMF (6 mL) was added to **3** (201 mg, 1.0 mmol) under N<sub>2</sub> and stirred for 1.5 h. The mixture was neutralized

(HOAc), volatiles were evaporated, and the residue was partitioned [H<sub>2</sub>O (3 mL)/CH<sub>2</sub>Cl<sub>2</sub> (1 mL)]. The aqueous layer was extracted (CH<sub>2</sub>Cl<sub>2</sub>) until product was removed, and the combined organic layer was washed (1 M HCl/H<sub>2</sub>O, 1 mL). The acid layer was extracted (CHCl<sub>3</sub>), and the combined organic layers were washed [saturated NaHCO<sub>3</sub>/H<sub>2</sub>O (3 mL) and brine (3 mL)], dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. The crude product (165 mg) was "diffusion crystallized" (CH<sub>2</sub>Cl<sub>2</sub>/hexane) to give **5** (151 mg, 84%); mp 166.5–168 °C (lit.<sup>24</sup> mp 171–172 °C); <sup>1</sup>H NMR spectrum agreed with literature values.<sup>22</sup>

**9-(2,3,5-Tri-*O*-acetyl- $\beta$ -D-ribofuranosyl)-6-(1,2,4-triazol-4-yl)purine (11).** **Method A.** A suspension of 2',3',5'-tri-*O*-acetyladenosine (**7**; 106 mg, 0.27 mmol) and **1a** (205 mg, 0.95 mmol) in pyridine (0.5 mL) was heated at 100 °C with stirring for 20 h. Volatiles were evaporated, and the residue was partitioned [H<sub>2</sub>O (8 mL)/EtOAc (8 mL)] (3×). The organic layer was washed (brine), dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated, and the residue was purified by centrifugal chromatography (Chromatotron, 1-mm rotor thickness, EtOAc) to give **11** (106.3 mg, 88%). A small portion was recrystallized to give **11**: mp 136.5–137 °C; UV max 274, 256 nm ( $\epsilon$  12 700, 8200), min 259, 231 nm ( $\epsilon$  8100, 2000); MS *m/z* 445 (6, M<sup>+</sup>), 386 (10, M – OAc), 326 (6, M – 2 OAc). Anal. Calcd for C<sub>18</sub>H<sub>19</sub>N<sub>7</sub>O<sub>7</sub> (445.4): C, 48.54; H, 4.30; N, 22.01. Found: C, 48.45; H, 4.38; N, 21.83.

**Method B.** A cold, stirred suspension of **12** (1.014 g, 3.18 mmol) in pyridine (6 mL) was treated with Ac<sub>2</sub>O (1.04 mL, 11 mmol) and stirred for 17.5 h at 5 °C. MeOH (5 mL) was added, stirring was continued for 30 min at ambient temperature, and volatiles were evaporated. The residue was dissolved in cold CH<sub>2</sub>Cl<sub>2</sub> (80 mL), and this solution was washed [brine/2 M HCl/H<sub>2</sub>O (1:1, 10 mL); brine/saturated NaHCO<sub>3</sub>/H<sub>2</sub>O (1:1, 40 mL)], dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. Gentle heating of the solid foam in Et<sub>2</sub>O (75–100 mL) resulted in formation of a fine white solid suspension. Volatiles were evaporated, and the residue was dried to give analytically pure **11** (1.40 g, 99%); mp 135.5–136 °C; <sup>1</sup>H NMR spectrum identical to that from method A.

**9-( $\beta$ -D-Ribofuranosyl)-6-(1,2,4-triazol-4-yl)purine (12).** Dried pyridine was added to adenosine (**8**; 543 mg, 2.0 mmol) and **1a** (1.53 g, 7.1 mmol), and the mixture was evaporated. Pyridine (3 mL) and TMSCl (1.02 mL, 8.0 mmol) were added, the mixture was heated at 100 °C (24 h), and volatiles were evaporated. The residue was dissolved in ice-cold CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed {[brine (30 mL) + H<sub>2</sub>O (18 mL)] and [brine (30 mL) + HCl/H<sub>2</sub>O (2 M, 6 mL)]}, filtered through Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The residue was dissolved in MeOH (30 mL), stirred (2 h), and concentrated (to ~20%), and the white precipitate was filtered off. This solid was washed [MeOH (5 mL) and Et<sub>2</sub>O (4 mL)], and a second crop was collected from the mother

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liquors. Both crops were dried to give **12** (609 mg, 94%): mp ~223 °C (variable); UV max 275 nm ( $\epsilon$  13 500), min 236 nm ( $\epsilon$  2900). Anal. Calcd for  $C_{12}H_{13}N_7O_4$  (319.3): C, 45.14; H, 4.10; N, 30.71. Found: C, 44.97; H, 4.08; N, 30.72.

**9-(3,5-Di-O-acetyl-2-deoxy- $\beta$ -D-erythro-pentofuranosyl)-6-(1,2,4-triazol-4-yl)purine (13).** Dried pyridine was added to 3',5'-di-O-acetyl-2'-deoxyadenosine (**9**; 139 mg, 0.41 mmol), **1a** (45 mg, 0.21 mmol), and **1** (267 mg, 1.88 mmol), and the mixture was evaporated. Pyridine (1 mL) and TMSCl (0.21 mL, 1.7 mmol) were added, the mixture was heated at 100 °C (45 h), additional TMSCl ("1 drop") was added, and heating was continued for 3 h. Volatiles were evaporated, the residue was dissolved in  $CH_2Cl_2$  (20 mL), and the solution was washed [brine (10 mL) + HCl/H<sub>2</sub>O (2 M, 7 mL)]. The organic layer was dried ( $Na_2SO_4$ ) and concentrated to half-volume, an equal volume of EtOAc was added, and the solution was evaporated. The white solid was dried to give 149 mg (93%) of crude product which was recrystallized (EtOAc) to give **13** (132 mg, 82%): mp 179–179.5 °C; UV max 275 nm ( $\epsilon$  13 900), shoulder 258 nm ( $\epsilon$  9100), min 232 nm ( $\epsilon$  3000); MS *m/z* 387 (6, M<sup>+</sup>). Anal. Calcd for  $C_{16}H_{17}N_7O_5$  (387.4): C, 49.61; H, 4.42; N, 25.31. Found: C, 49.73; H, 4.53; N, 25.46.

**9-(2-Deoxy- $\beta$ -D-erythro-pentofuranosyl)-6-(1,2,4-triazol-4-yl)purine (14).** Dried pyridine was added to 2'-deoxyadenosine (**10**; 845 mg, 3.4 mmol) and **1** (1.91 g, 13.4 mmol), and the mixture was evaporated (3 $\times$ ). Pyridine (8 mL) and TMSCl (0.85 mL, 6.7 mmol) were added, and the mixture was heated at 100 °C (24 h). After cooling, TMSCl (0.34 mL) was added, the mixture was stirred (15 min), and volatiles were evaporated. The residue was dissolved in ice-cold  $CH_2Cl_2$  (85 mL), and the solution was washed {with cold brine (34 mL) + saturated  $NaHCO_3/H_2O$  (17 mL) and then [brine (34 mL) + HCl/H<sub>2</sub>O (1 M, 12 mL)] (2 $\times$ )}. The solution was dried ( $Na_2SO_4$ ) and evaporated, and the residue was dissolved in MeOH (10 mL) and stirred overnight. The resulting suspension was evaporated, and the residue was dried, suspended in  $CH_2Cl_2/MeOH$  (9:1, 7 mL), and filtered. The white solid was dried to give **14** (895 mg, 88%): mp ~180 °C, softening, ~274 °C dec (variable); UV max 275 nm ( $\epsilon$  13 200), min 234 nm ( $\epsilon$  2700); MS *m/z* 304 (2, M<sup>+</sup>). Anal. Calcd for  $C_{12}H_{13}N_7O_3$  (303.3): C, 47.52; H, 4.32; N, 32.33. Found: C, 47.32; H, 4.60; N, 32.06.

Excess azine **1** was recovered by treatment of the combined aqueous washes (~125 mL) with NaOH/H<sub>2</sub>O (2 M, 15 mL) and extraction with  $CHCl_3$  (3  $\times$  50 mL). Volatiles were evaporated, and crude **1** was purified by chromatography [Dowex 1  $\times$  2 (OH<sup>-</sup>), H<sub>2</sub>O]. The eluate was evaporated, EtOAc was added and evaporated (3 $\times$ ), and the solid was dried to give **1** (1.19 g, 83% recovery).

**6-(Dimethylamino)-9-( $\beta$ -D-ribofuranosyl)purine (15).** Method A. A solution of **11** (118.2 mg, 0.27 mmol) in 40%  $HNMe_2/H_2O$  (5 mL) was stirred at ambient temperature for 40 min. The solution was concentrated (~1 mL) and chromatographed [Dowex 1  $\times$  2 (OH<sup>-</sup>); H<sub>2</sub>O (50 mL), H<sub>2</sub>O/MeOH (1:1, 10 mL), and MeOH (50 mL)]. Pooled fractions were evaporated,  $CH_3CN$  was added and evaporated (4 $\times$ ), and the fine white solid was dried to give analytically pure **15** (78.2 mg, 99.8%): mp 182–183.5 °C (lit.<sup>25</sup> mp 183–184 °C); <sup>1</sup>H NMR spectrum agreed with literature values.<sup>26</sup> Anal. Calcd for  $C_{12}H_{17}N_5O_4$  (295.3): C, 48.81; H, 5.80; N, 23.72. Found: C, 48.91; H, 5.78; N, 23.55.

Method B. A solution of **12** (75.7 mg, 0.24 mmol) in 40%  $HNMe_2/H_2O$  (3 mL) was stirred at ambient temperature and processed as in method A. After chromatography, the residue was dried to give **15** (64.8 mg, 93%): mp 181.5–183 °C.

**6-Methoxy-9-( $\beta$ -D-ribofuranosyl)purine (16).** Method A. A solution of **11** (173 mg, 0.39 mmol) in MeOH was applied to a column of Dowex 1  $\times$  2 (OH<sup>-</sup>) [prewashed with H<sub>2</sub>O, H<sub>2</sub>O/MeOH (1:1), and MeOH] and allowed to stand overnight. The product was eluted (MeOH), volatiles were evaporated, and the residue was "diffusion crystallized" (MeOH/Et<sub>2</sub>O) to give **16** (98.2 mg, 90%): mp 138.5–140 °C (lit.<sup>27</sup> mp 144–146 °C).

Method B. A solution of **12** (55.5 mg, 0.17 mmol) in pyridine (~0.5 mL) was stirred with NaOMe/MeOH (1 M, 0.5 mL) for 2.5 h at ambient

temperature and neutralized (HOAc, "six drops"). Volatiles were evaporated, and the residue was chromatographed [Dowex 1  $\times$  2 (OH<sup>-</sup>); H<sub>2</sub>O, H<sub>2</sub>O/MeOH (1:1), MeOH]. Product fractions were evaporated, EtOAc was added (the suspension was heated) and evaporated (2 $\times$ ), and the resulting white solid was dried to give **16** (48 mg, 98%): mp 140–143 °C.

**6-(Methylthio)-9-( $\beta$ -D-ribofuranosyl)purine (17).** To a solution of **11** (116 mg, 0.26 mmol) in DMF (2 mL) under Ar was added a deoxygenated solution of NaSMe (72.7 mg, 1.04 mmol) in DMF (3 mL), and stirring was continued for 15 min at ambient temperature. The solution was sparged (Ar), neutralized with  $NH_4Cl$  (65 mg, 1.2 mmol), and evaporated, and the residue was stirred with  $NH_3/MeOH$  (6 mL) for 3 days. Volatiles were evaporated, and the residue was treated with pyridine (1 mL) and TMSCl (0.2–0.3 mL) and sonicated to give a white solid suspension. Volatiles were evaporated, and the residue was partitioned {ice-cold  $CH_2Cl_2$  (14 mL)/[brine (4 mL) + 1 M HCl/H<sub>2</sub>O (2 mL)]}. The organic layer was washed [brine (4 mL) + saturated  $NaHCO_3/H_2O$  (2 mL)], passed through a layer of  $Na_2SO_4$ , and evaporated. The residue was stirred with MeOH (3 mL) for 4 days at ambient temperature, and the solution was evaporated. Addition and evaporation of  $CH_3CN$  (2 $\times$ ) gave a white solid which was dried to give analytically pure **17** (73 mg, 94%): mp 125–126 °C, softening, 161.5–163 °C (lit.<sup>4h</sup> mp 163–164 °C); <sup>1</sup>H NMR spectrum agreed with literature values.<sup>28</sup> Anal. Calcd for  $C_{11}H_{14}N_4O_4S$  (298.3): C, 44.29; H, 4.73; N, 18.78. Found: C, 44.41; H, 4.76; N, 18.79.

**9-(2-Deoxy- $\beta$ -D-erythro-pentofuranosyl)-6-(dimethylamino)purine (18).** Method A. A suspension of **13** (49.8 mg, 0.13 mmol) in pyridine (1 mL) was stirred with 40%  $HNMe_2/H_2O$  (1 mL) for 4 h, and volatiles were evaporated. The residue was purified by chromatography at 5 °C for enhanced adsorption [Dowex 1  $\times$  2 (OH<sup>-</sup>): washed with H<sub>2</sub>O (14 mL), eluted with H<sub>2</sub>O/MeOH (1:1, 2 mL) and MeOH (8 mL)]. The eluate was evaporated,  $CH_3CN$  was added and evaporated (2 $\times$ ), and the white solid was dried to give **18** (35.1 mg, 98%): mp 171.5–173 °C (lit.<sup>29</sup> mp 177.5–179 °C); UV (MeOH) max 274 nm ( $\epsilon$  18 600) min 235 nm ( $\epsilon$  1800); MS *m/z* 279 (29, M<sup>+</sup>).

Method B. A cold (5 °C) suspension of **14** (40.6 mg, 0.13 mmol) was stirred with cold 40%  $HNMe_2/H_2O$  (2 mL) for 15 min, concentrated to half-volume, and chromatographed ["cold" Dowex 1  $\times$  2 (OH<sup>-</sup>): H<sub>2</sub>O (~5 mL), H<sub>2</sub>O/MeOH (1:1, ~1 mL), MeOH (~5 mL)]. The eluate was evaporated,  $CH_3CN$  was added and evaporated (2 $\times$ ), and the white solid was dried to give **18** (35.8 mg, 96%): mp 170–172 °C. A sample was recrystallized (MeOH/Et<sub>2</sub>O) to give **18**; mp 171.5–173 °C.

**9-(2-Deoxy- $\beta$ -D-erythro-pentofuranosyl)-6-methoxypurine (19).** A sample of **14** (51.8 mg, 0.17 mmol) was applied to a column of Dowex 1  $\times$  2 (OH<sup>-</sup>) resin (1  $\times$  2 cm, presoaked with MeOH) and allowed to stand, and the product was eluted with MeOH. Fractions were combined and evaporated to give a colorless glass which was "diffusion crystallized" (MeOH/Et<sub>2</sub>O) and dried to give **19**<sup>30</sup> (38.9 mg) as its hemihydrate. Mother liquors were evaporated, heated/sonicated with Et<sub>2</sub>O, evaporated, and dried to give a white solid (6.2 mg; total yield 45.1 mg, 96%): UV (MeOH) max 248 nm ( $\epsilon$  11 300), min 220 nm ( $\epsilon$  2300); MS *m/z* 266 (6, M<sup>+</sup>). Anal. Calcd for  $C_{11}H_{14}N_4O_4 \cdot 0.5(H_2O)$  (275.3): C, 48.00; H, 5.49; N, 20.35. Found: C, 48.06; H, 5.57; N, 20.14.

**7-( $\beta$ -D-Ribofuranosyl)-4-(1,2,4-triazol-4-yl)pyrrolo[2,3-d]pyrimidine (21).** A suspension of tubercidin (**20**; 285 mg, 1.1 mmol) and **1** (307 mg, 2.2 mmol) in pyridine (1.6 mL) was heated with TMSCl (0.27 mL, 2.1 mmol) at 100 °C for 24 h. The cooled mixture was treated with TMSCl (0.3 mL), stirred for 15 min, and evaporated. The residue was dissolved in ice-cold  $CH_2Cl_2$  (30 mL), and the solution was washed {with brine (11 mL) + saturated  $NaHCO_3/H_2O$  (6 mL) and [brine (11 mL) + HCl/H<sub>2</sub>O (1 M, 3 mL)] (2 $\times$ )}. The organic layer was dried ( $Na_2SO_4$ ) and filtered, MeOH (5 mL) was added, and the solution was stirred overnight. Volatiles were evaporated, the residue was dissolved in MeOH (7 mL), and the solution was stirred for 2 h and evaporated. The residue was dried, suspended in  $CH_2Cl_2/MeOH$  (93:7, 2 mL), filtered, and dried to give **21** (322 mg, 95%): mp 206.5–208 °C; UV (MeOH) max 227, 299 nm ( $\epsilon$  25 500, 6400), min 248 nm ( $\epsilon$  1200);

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MS  $m/z$  319 (5,  $M^+$ ). Anal. Calcd for  $C_{13}H_{14}N_6O_4$  (318.3): C, 49.06; H, 4.43; N, 26.40. Found: C, 49.17; H, 4.27; N, 26.63.

**4-(Dimethylamino)-7-( $\beta$ -D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (22).** A solution of **21** (27 mg, 0.085 mmol) in pyridine (1 mL) was stirred with 40%  $HNMe_2/H_2O$  (1 mL) for 3 days at ambient temperature. Volatiles were evaporated, and the residue was chromatographed [Dowex 1  $\times$  2 ( $OH^-$ ):  $H_2O$ ,  $H_2O/MeOH$  (1:1), MeOH]. The eluate was evaporated,  $CH_3CN$  was added, heated, and evaporated (2 $\times$ ), and the white solid was dried to give **22** (24 mg, 96%): mp  $\sim 159$ – $160$  °C, softening,  $190$ – $193$  °C (lit.<sup>18</sup> mp  $192$ – $195$  °C); UV (MeOH) max 283 nm ( $\epsilon$  15 000) min 246 nm ( $\epsilon$  2500); MS  $m/z$  294 (22,  $M^+$ ). Anal. Calcd for  $C_{13}H_{18}N_4O_4$  (294.3): C, 53.05; H, 6.16; N, 19.04. Found: C, 53.29; H, 6.14; N, 18.83.

**4-Methoxy-7-( $\beta$ -D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (23).** A suspension of **21** (24.9 mg, 0.078 mmol) in MeOH ( $\sim 0.25$  mL) was stirred with NaOMe/MeOH (1 M, 0.5 mL) for 1 h. Volatiles were evaporated, and the residue was chromatographed [Dowex 1  $\times$  2 ( $OH^-$ ):  $H_2O$  (5 mL),  $H_2O/MeOH$  (1:1, 1 mL), MeOH (11 mL)]. The eluate was evaporated,  $CH_3CN$  was added and evaporated (3 $\times$ ), and the white solid was dried and recrystallized (acetone) to give **23** (19.2 mg, 87%): mp  $156.5$ – $157.5$  °C (lit.<sup>18</sup> mp  $158$ – $160$  °C); UV max 262 nm ( $\epsilon$  7500), min 235 nm ( $\epsilon$  2700); MS  $m/z$  281 (11,  $M^+$ ). Anal. Calcd for  $C_{12}H_{13}N_3O_5$  (281.3): C, 51.24; H, 5.38; N, 14.94. Found: C, 51.10; H, 5.43; N, 14.78.

**3-( $\beta$ -D-Ribofuranosyl)-7-(1,2,4-triazol-4-yl)pyrazolo[4,3-*d*]pyrimidine (25).** A suspension of formycin (**24**; 148 mg, 0.55 mmol) and **1** (246 mg, 1.7 mmol) in toluene (25 mL) was heated with  $TMSCl$  (0.22 mL, 1.7 mmol) at  $70$  °C for 15 h. Volatiles were evaporated, and the residue was partitioned with cold solvents ( $5$  °C) [ $H_2O$  (10 mL)/ $CH_2Cl_2$  (90 mL)]. The organic phase was filtered through a layer of  $Na_2-$

$SO_4$ , evaporated, and stirred with  $CH_3CN$  (15 mL) +  $H_2O$  (3.5 mL) + 5% HOAc ("two drops") for 4 days. Volatiles were evaporated, and the residue was suspended in  $CH_3CN$  and filtered. The solid was dried to give **25** (135 mg, 76%): mp  $202$ – $205$  °C (coloration); UV (MeOH) max 265, 273, 323 nm ( $\epsilon$  3300, 3100, 6500), min 256, 271, 280 nm ( $\epsilon$  3000, 3100, 2700); MS  $m/z$  319 (2,  $M^+$ ). Anal. Calcd for  $C_{12}H_{13}N_7O_4$  (319.3): C, 45.14; H, 4.10; N, 30.71. Found: C, 45.00; H, 4.26; N, 30.55.

**7-(Dimethylamino)-3-( $\beta$ -D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidine (26).** A solution of **25** (9.6 mg, 0.03 mmol) and  $Me_2NH \cdot HCl$  (11 mg, 0.13 mmol) in pyridine (0.5 mL) was heated at  $57$  °C for 22 h. Volatile materials were evaporated and the residue was applied to a column of Dowex 1  $\times$  2 ( $OH^-$ ) (0.5  $\times$  2 cm) at  $5$  °C. The column was washed ( $H_2O$ ), and product was eluted (0.1 N HOAc/ $H_2O$ ). The eluate was evaporated, and the resulting glass was heated in  $CH_3CN$  and evaporated (2 $\times$ ). The solid glass was dried and then heated in  $CH_3CN$ , evaporated to give a powder, and dried to give **26**<sup>31</sup> (quantitative): mp  $\sim 181$ – $184$  °C (variable); UV (MeOH) max 242, 305 nm ( $\epsilon$  4300, 14 500), min 234, 260 nm ( $\epsilon$  4100, 3400), shoulders 312, 325 nm ( $\epsilon$  13 600, 7100), UV (0.1 M HCl/ $H_2O$ ) max 307, 317 nm [lit.<sup>31</sup> UV (0.1 M HCl/ $H_2O$ ) max 307, 316 nm]; MS  $m/z$  295 (4,  $M^+$ ).

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