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Nucleic Acid Related Compounds. 116. Nonaqueous Diazotization of Aminopurine Nucleosides. Mechanistic Considerations and Efficient Procedures with *tert*-Butyl Nitrite or Sodium Nitrite[†,1]

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Nonaqueous diazotization−dediazoniation of two types of aminopurine nucleoside derivatives has been investigated. Treatment of 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2-amino-6-chloropurine (**1**) with $SbCl_3/CH_2Cl_2$ was examined with benzyltriethylammonium (BTEA) chloride as a soluble halide source and *tert*-butyl nitrite (TBN) or sodium nitrite as the diazotization reagent. Optimized yields (>80%) of the 2,6-dichloropurine derivative were obtained with $SbCl_3$. Combinations with $SbBr_3/CH_2Br_2$ gave the 2-bromo-6-chloropurine product (>60%), and SbI_3/CH_2I_2/THF gave the 2-iodo-6-chloropurine derivative (>45%). Antimony trihalide catalysis was highly beneficial. Mixed combinations ($SbX_3/CH_2X'_2$; X/X′ = Br/Cl) gave mixtures of 2-(bromo, chloro, and hydro)-6-chloropurine derivatives that were dependent on reaction conditions. Addition of iodoacetic acid (IAA) resulted in diversion of purine radical species into a 2-iodo-6-chloropurine derivative with commensurate loss of other radical-derived products. This allowed evaluation of the efficiency of SbX_3-promoted cation-derived dediazoniations relative to radical-derived reactions. Efficient conversions of adenosine, 2′-deoxyadenosine, and related adenine nucleosides into 6-halopurine derivatives of current interest were developed with analogous combinations.

Introduction

The versatility of halopurines[2] as intermediates for nucleoside synthesis was recognized by Fischer a century ago.[2a] Nucleophilic aromatic substitution reactions[3] and palladium-catalyzed cross-coupling processes[4] with 2-, 6-, and 8-halopurines and nucleosides provide convenient means for manipulation of base substituents. Such approaches have recently been used for synthesis of analogues of nitrous acid-mediated DNA cross-links,[5] DNA−carcinogen adducts,[6] and preparation of oligonucleotides with site-specific base modifications.[7] Continuing interest in the modification of purines is reflected in recent reports of synthesis and screening of purine libraries and nucleoside analogues.[4g,i]

Diazotization of electron-deficient heterocyclic amines is problematic,[8−12] and coupling of radical species derived from putative diazo intermediates with arenes gave

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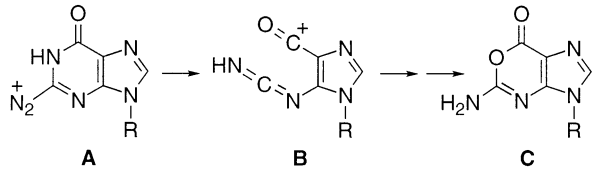

FIGURE 1. Proposed intermediate structure **B**[14b] for conversion of a putative purine 2-diazonium ion **A** into the oxazine ring of an isolated oxanosine derivative[17] **C**.

variable yields of aryl derivatives.[11,12] Nonaqueous diazotization is useful for incorporation of halogens at the (2 or 6)-positions of purine nucleosides,[4b,13] but purinediazonium ions and their fragmentations have not been investigated in detail. Experimental[10] and theoretical studies[14] indicate that purinediazonium species have very short lifetimes and lose N_2 much more readily than common arenediazonium ions.[15] In fact, purinediazonium ions have not been observed directly.[10,14] Glaser et al. proposed a ring-opened ketene−carbodiimide species[14b] (Figure 1) to rationalize formation of the 2′-deoxyoxanosine that results from nitrous acid-mediated dediazoniation[16] of 2′-deoxyguanosine. Isolation of this rearrangement product[17] and theoretical analyses[14b] indicate that multiple decomposition pathways are possible for transient purinediazonium species.

White and co-workers presented arguments for predominance of heterolytic decomposition pathways[18,19] resulting from protonation of 9-methylpurine-6-diazoate salts[19] with acetic acid in $CHCl_3$ or deuteriobenzene. Products of 6-(acetoxy, chloro, hydro, and hydroxy)-dediazoniation[16] were detected with $CHCl_3$, and 6-(acetoxy, hydroxy, and phenyl)purine derivatives were formed in C_6D_6.[19] Chloro-dediazoniation might occur via formation of a purine carbocation, which might abstract chloride via a chloronium ion species[18] (Figure 2) rather than by radical mechanisms. Product analysis cannot distinguish between homolytic and heterolytic processes,[15,20] and radical abstraction of chlorine from solvent might also have occurred. Hydro-dediazoniation is thought to occur by homolytic processes, except in strongly alkaline media or with sodium borohydride.[20] In solvents of low electron-donating ability ($CHCl_3$ or C_6D_6) and in the absence of an exogenous source of electrons, high levels of homolytic dediazoniation products are not expected.[15,20]

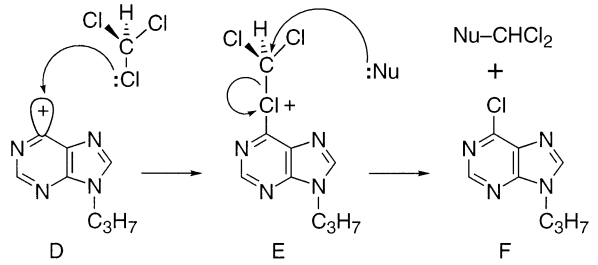

FIGURE 2. Conversion of a purine-6-cation species **D** into the 6-chloropurine product **F** via a solvent-derived chloronium intermediate[18,19] **E**.

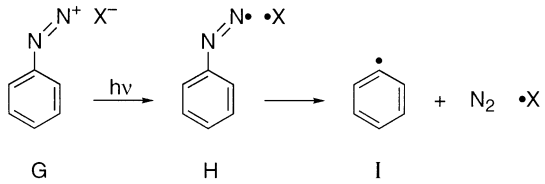

FIGURE 3. Generation of an aryl radical **I** via electron transfer (**G** → **H**) from an anion (X^-) with an appropriate redox potential to a (photoexcited) diazonium ion.[15,22]

Nair et al.[21] studied dediazoniation with aminopurine derivatives. They employed pentyl nitrite in THF or halocarbon solvents with both photoactivation and thermal activation for hydro- or halo-dediazoniation of 6-aminopurine derivatives.[21a,b] Purinyl radicals were detected (ESR) during photolysis of 6-iodo-9-ethylpurine,[21c] and it was postulated that homolysis of purinediazonium intermediates was followed by abstraction of hydrogen or halogen atoms from solvent.[21b] However, photolytic cleavage of a carbon−iodine bond to form a purinyl radical is quite different from photochemical activation for dediazoniation. Evidence exists that photoinitiated dediazoniation proceeds via electron transfer from a counterion to a photoexcited arenediazonium ion within a charge-transfer complex, followed by homolytic cleavage of an arenediazenyl radical[15,22] (Figure 3). Photoirradiation was not used in later procedures for hydro- and halo-dediazoniation.[21d,e] We and others[23] have observed ∼50% of protected inosine derivatives (hydroxy-dediazoniation characteristic of carbocationic processes) upon halo-dediazoniation[21b] of acetylated adenosine derivatives with alkyl nitrites in halocarbon solvents, and product analysis cannot exclude halide abstraction by a cationic mechanism[18] such as that illustrated in Figure 2.

We observed mixtures of 2-(chloro and fluoro)purine nucleoside derivatives upon treatment of protected 2-amino precursors with TBN and BF_3·OEt_2 in $CHCl_3$ or CH_2Cl_2.[13a] Montgomery and co-workers[24] had reported 2-(chloro and fluoro) substitution with diazotization of a 2-aminopurine nucleoside derivative in 48% HBF_4/H_2O// $CHCl_3$. They detected minor quantities of a 2-chloro

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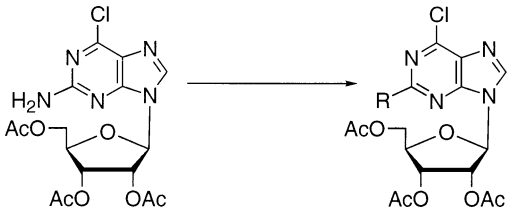
product upon diazotization of a 2-aminopurine derivative in concentrated HCl/H_2O,[25] and Gerster and Robins synthesized 2-chloropurine nucleoside derivatives from 2-amino precursors with concentrated HCl/H_2O.[26] Shapiro and Pohl had isolated 2-nitroinosine from treatment of guanosine with nitrous acid and excess nitrite in an acetate buffer.[27]

Electron-deficient nucleobase analogues should give diazonium ions with high reduction potentials, which would facilitate electron transfer and homolytic cleavage.[15,20] However, the low electron-donating potential of halohydrocarbon solvents would favor heterolytic fragmentation mechanisms.[15,20] Interplay between these factors could make halo-dediazoniation of purine nucleosides particularly sensitive to changes in reaction conditions. Ionic catalysis of aryl halo-dediazoniation is known, and in situ generation of NOBr or NOCl from Br^- or Cl^- can occur.[15] Electron transfer also might facilitate dediazoniation. Galli has noted that electron transfer to benzenediazonium salts can occur from substrates with appropriate redox potentials, and electron transfer from iodide is well-known.[28] Increased yields of 2-iodopurine nucleosides were obtained from iodo-dediazoniation of 2-aminopurine nucleosides with isoamyl nitrite in CH_3CN when both I^- and CuI were added.[4a] Bromide is a borderline case, and might transfer an electron to an arenediazonium ion with a compatible reduction potential.[28,29] Nitrite also can transfer an electron to electron-deficient arenediazonium ions to give aryl radicals and a nitrogen dioxide radical.[15,20] Effects of different sources of halide and nitrite on product distributions resulting from nonaqueous dediazoniation of purines have not been studied systematically.

Antimony trichloride has been employed for stibono-dediazoniation of diazonium salts.[30] Our introduction of $SbCl_3$ and $SbBr_3$ for nonaqueous halo-dediazoniation of 2-aminopurine nucleoside derivatives provided high yields of 2-halo products, and no 2-(hydro, hydroxy, or stibono)-dediazoniation byproducts were detected.[13a,31] These procedures have been used for preparation of 2-halopurine[9,31] and related nucleosides,[32] and a recent application of our $SbBr_3$ catalysis for syntheses of some 2-bromonucleoside analogues has been reported.[5] We observed both 2-(bromo and chloro)-dediazoniation products upon treatment of acetylated 2-amino-6-chloropurine nucleosides with $SbX_3/CH_2X'_2$ mixtures.[13a] We now report studies on dediazoniation of (2 and 6)-aminopurine nucleosides with different antimony trihalides, nitrite and halide salts, and solvents at different temperatures.

SCHEME 1



1

2 R = Cl
3 R = Br
4 R = I
5 R = H

Results and Discussion

Halopurine nucleosides are valuable synthetic intermediates.[2−9] Conflicting opinions on the S_NAr reactivity of 6-(bromo versus chloro)purine compounds have appeared recently.[3d,4d] We undertook a systematic study of reagents and reaction conditions to provide reliable and convenient procedures for introduction of halogens at the 2- and/or 6-positions of purine nucleosides. There is uncertainty regarding the intermediacy of cation versus radical (and other) intermediates in dediazoniation reactions of electron-deficient rings such as purines.[14,15,19−21] Iodoacetic acid (IAA) has been reported[33] to be a selective trapping agent for radical species, and detection of aryl iodide products provides evidence for the transient presence of aryl radicals. Concomitant decreases in yields of products otherwise derived from aryl radicals occur as IAA diverts these species into iodo products.[33]

We first examined product distributions resulting from dediazoniation of 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-amino-6-chloropurine[34,35] (**1**) with *tert*-butylnitrite (TBN) and benzyltriethylammonium (BTEA) bromide at ambient temperature in CH_2Cl_2 for 3 h with or without IAA (Scheme 1). Ratios of 2-[chloro (**2**), bromo (**3**), and iodo (**4**)]purine nucleosides were determined by ^1H NMR analysis of purified dediazoniation mixtures [H8 signals at δ 8.27 (**2**), 8.25 (**3**), and 8.18 (**4**)]. Products were separated by TLC (radial, RTLC, Chromatotron) or preparative thin-layer chromatography (PTLC). Yields were quantitated by UV spectroscopy, and structures were confirmed by MS. The hydro-dediazoniation product **5** was isolated (PTLC or RTLC) and quantitated (UV), and its structure was verified (MS and NMR). Results are summarized in Table 1, entries 1 and 2.

No **5** was detected with IAA present, which indicated that **5** had been derived from a purinyl radical. Yields of **3** were markedly diminished with IAA present, which suggested that purinyl radicals had been diverted from **3** into iodo compound **4**. The **3** (24%) observed with IAA indicated that heterolytic bromo-dediazoniation occurred, and the amounts of chloro-dediazoniation product **2** were similar with or without IAA (11 or 8%). It has been noted that radicals usually abstract hydrogen much more rapidly than chlorine.[19] Our observation that IAA effectively interrupted hydrogen atom abstraction without

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TABLE 1. Products from Dediazoniation Reactions of 1

			products (yield %)			
entry	(reagents/solvents)	IAA	**2**	**3**	**4**	**5**
1	(BTEA-Br/TBN/CH_2Cl_2)	−	8	58		4
2	(BTEA-Br/TBN/CH_2Cl_2)	+	11	24	52	
3	(BTEA-Cl/TBN/CH_2Br_2)	−	22	30		8
4	(BTEA-Cl/TBN/CH_2Br_2)	+	<1	21	28	5
5	($SbBr_3$/TBN/CH_2Cl_2)	−	40	30		
6	($SbBr_3$/TBN/CH_2Cl_2)	+	43	25	2	
7	($SbCl_3$/TBN/CH_2Br_2)	−	48	35		
8	($SbCl_3$/TBN/CH_2Br_2)	+	46	32	4	
9	(BTEA-Br/$SbBr_3$/TBN/CH_2Cl_2)	−	4	44		1
10	(BTEA-Br/$SbBr_3$/$NaNO_2$/DCA/CH_2Cl_2)	−	29	40		<1
11	(BTEA-Cl/$SbCl_3$/TBN/CH_2Br_2)	−	32	28		2
12	(BTEA-Cl/$SbCl_3$/$NaNO_2$/DCA/CH_2Br_2)	−	33	27		1
13[a]	(BTEA-Cl/$SbCl_3$/$NaNO_2$/DCA/CH_2Cl_2)	−	>80			
14[a]	(BTEA-Br/$SbBr_3$/$NaNO_2$/DCA/CH_2Br_2)	−		>60		
15[a]	(SbI_3/TBN/CH_2I_2/THF)	−			>45	
16[a]	($NaNO_2$/DCA/THF)	−				>80

[a] See the Results and Discussion and Experimental Section for conditions for preparative scale reactions.

significant alteration in yields of the chloro-dediazoniation product is consistent with White's suggestion that overall abstraction of Cl^- from solvent might occur by a heterolytic process[18] (Figure 2). Our results are compatible with competing homolytic and heterolytic dediazoniation at ambient temperature.

Product distributions resulting from dediazioniation of **1** with CH_2Br_2 as solvent with or without IAA were next determined (Table 1, entries 3 and 4). Marked reductions in yields of **2** occurred with IAA. Diminished yields of solvent-derived **3** (30 → 21%) and **5** (8 → 5%) occurred with IAA, and these results are similar to those for dediazoniation of **1** with CH_2Cl_2. Stabilities of the 2-[chloro (**2**), bromo (**3**), or iodo (**4**)]purine nucleosides were evaluated by their treatment with TBN (20 equiv) and BTEA-Cl (2 equiv) in CH_2Br_2 at ambient temperature for 3 h with or without IAA (2 equiv). Only minor decomposition was observed (recovered **2**, **3**, or **4**, 90−99%). No apparent differences were seen in reactions with or without IAA, and no nucleobase or nucleoside byproducts were detected. However, treatment of **2** or **3** with TBN (20 equiv) plus BTEA-Br and IAA (2 equiv each) in CH_2Cl_2 at reflux for 3 h resulted in significant glycosyl bond cleavage and other decomposition processes (∼33% loss of either **2** or **3**).

The effect of ionic halide on dediazonation at elevated temperature was probed by treatment of **1** with excess TBN plus IAA and BTEA-Br (2 equiv each) in CH_2Cl_2 at reflux for 15 min. Combined yields of 57% of 2-[chloro (**2**, 2%), bromo (**3**, 21%), and iodo (**4**, 34%)]purine dediazoniation products were obtained, but **5** was not detected. Competition between homolytic and heterolytic dediazoniation mechanisms apparently occurs also at ∼40 °C.

We observed that halo-dediazoniation of **1** with TBN and SbX_3 at reduced temperature (−10 °C) eliminated formation of 2-(hydro and hydroxy)-dediazoniation products. Halo-dediazoniation of **1** with TBN and $SbBr_3$/CH_2Cl_2 or $SbCl_3$/CH_2Br_2 at ambient temperature with IAA (2 equiv) proceeded rapidly [**1** was not detected (TLC) after 15−30 min]. The results with SbX_3 (Table 1, entries 5−8) differed markedly from those with BTEA-X salts (entries 1−4). Yields of radical-derived products were drastically reduced with SbX_3, and the hydro-dediazoniation compound **5** was not detected with or without IAA (entries 5−8). Only minor quantities of the 2-iodo product **4** were generated with IAA/$SbBr_3$ (2%, entry 6) or IAA/$SbCl_3$ (4%, entry 8), in contrast with the reactions with BTEA-Br (52%, entry 2) or BTEA-Cl (28% entry 4). Ratios of **2**/**3** (SbX_3 to solvent-derived halo-dediazoniation products) were within experimental error for entries 5 and 6, or 7 and 8. With SbX_3 present, purinediazonium ion decompositions depart from radical pathways.

Because $SbCl_3$ induces DNA damage and is toxic,[36] we evaluated BTEA-Cl[37] versus $SbCl_3$ for chloro-dediazoniation of **1** with TBN in CH_2Cl_2. One equivalent of BTEA-Cl or $SbCl_3$ was added to **1** and TBN in CH_2Cl_2 at ambient temperature. Reactions proceeded rapidly, and starting material was absent after 10 min. However, chloro-dediazoniation of **1** with BTEA-Cl resulted in a significantly reduced yield of **2** (46%) relative to the reaction with $SbCl_3$ (70%), and byproduct **5** (7%) was formed with BTEA-Cl. Compounds **2** and **5** are difficult to separate. Treatment of **1** with excess TBN and BTEA-Cl (10 equiv) in CH_2Cl_2 at −10 °C increased the yield of **2** from ∼50 to 62%, but did not eliminate formation of **5** (∼4%). Addition of 20 mol % of $SbCl_3$ to **1**/TBN/BTEA-Cl (1 equiv each) in CH_2Cl_2 at −10 °C did not diminish formation of **5**. Equimolar $SbCl_3$ and BTEA-Cl resulted in lower yields of **2** (42%), and did not suppress formation of **5**. Clearly, BTEA-Cl was not a viable substitute for $SbCl_3$.

Heterolytic dediazoniation is known to be favored under acidic conditions,[15,39] and acetic acid has been used for enhancement of diazotization of heteroaromatic amines.[40] We next probed addition of organic acids and alternative sources of nitrite. Sodium nitrite is inexpensive and a safer alternative to the potentially hazardous[41] TBN. Experiments were performed with addition of an equimolar amount of acetic, chloroacetic, dichloroacetic, or trichloroacetic acid (or Dowex 50 [H^+] resin) to **1**,

(36) Huang, H.; Shu, S. C.; Shih, J. H.; Kuo, C. J.; Chiu, I. D. *Toxicology* **1998**, *129*, 113−123.
(37) BTEA-X salts are easier to use than Et_4NX[35] or Me_4NX. BTEA-X has been used previously in halodedizoniation procedures.[38]
(38) Lee, J. G.; Cha, H. T. *Tetrahedron Lett.* **1992**, *33*, 3167−3168.
(39) Broxton, T. J.; Bunnett, J. F.; Paik, C. H. *J. Org. Chem.* **1977**, *42*, 643−649.
(40) Butler, R. N. *Chem. Rev.* **1975**, *75*, 241−257.
(41) Lopez, F. *Chem. Eng. News* **1992**, *70* (51), 2.

excess $NaNO_2$, and BTEA-Cl (10 equiv) in CH_2Cl_2. Only the experiment with dichloroacetic acid (DCA) gave significant amounts of **2**.

Treatment of **1** with either TBN (20 equiv) or excess powdered $NaNO_2$, BTEA-Br and $SbBr_3$ (1 equiv each) in CH_2Cl_2 (or BTEA-Cl and $SbCl_3$ in CH_2Br_2), and DCA (1.5 equiv) at ambient temperature for 3 h was examined (Table 1, entries 9−12). Unfavorable interaction(s) among TBN/$SbBr_3$/BTEA-Br/CH_2Cl_2 (entry 9) resulted in reduced yields of **2** + **3** (48% combined), but the yield of **5** was reduced to ∼1%. Addition of DCA to such a mixture (DCA/$NaNO_2$/$SbBr_3$/BTEA-Br/CH_2Cl_2) (entry 10) gave **2** + **3** (69% combined) with <1% of **5**. Analogous treatment of **1** with $SbCl_3$/BTEA-Cl/CH_2Br_2 gave the same combined yields (60%) and proportions of **2** and **3** with either TBN or DCA/$NaNO_2$ (entries 11 and 12).

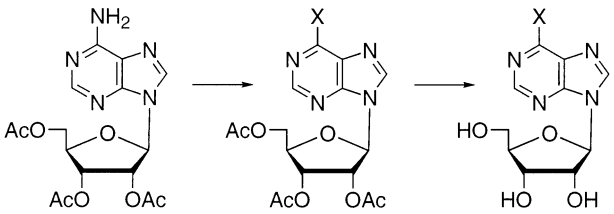
Effects of reagent proportions, temperature, and concentration were evaluated with **1**. DCA (1.5 equiv), $NaNO_2$ (20 equiv), and BTEA-Cl (1 equiv) in CH_2Cl_2 at ambient temperature for 3 h were held constant. Optimum yields were obtained with ∼1 equiv of $SbCl_3$. Yields of **2** declined with >1 equiv, and **5** was detected in addition to diminished yields of **2** with <0.5 equiv of $SbCl_3$. Amounts of DCA used impacted quantities of **5** produced. Treatment of **1** with $NaNO_2$ (20 equiv) plus $SbCl_3$ and BTEA-Cl (1 equiv each) in CH_2Cl_2 at ambient temperature for 6 h with variable amounts of DCA (0−2 equiv) gave optimum yields of **2** (>80%) with ∼1.5 equiv of DCA. Lower quantities of DCA (0.1−1 equiv) resulted in increasing amounts of **5**. Best yields were obtained with 2 equiv of DCA in ∼3.5 h, 1.5 equiv in 3.5−6 h, or 1−1.5 equiv in ≥12 h (reactions did not proceed with <0.1 equiv). Treatment of **1** with excess $NaNO_2$ plus $SbCl_3$ and BTEA-Cl (1 equiv each) in CH_2Cl_2 at ambient temperature with increasing amounts of HOAc (1.5−20 equiv) resulted in negligible suppression of the formation of **5**, and required extended reaction times. The acidic properties of DCA were most effective for reactions with **1**.

Inversion of the order of addition of $SbCl_3$ and DCA produced dramatic changes. Addition of DCA to the reaction mixture prior to the addition of $SbCl_3$ resulted in reduced yields of **2**, extended reaction times, a shift in the optimum ratio from 1 (39%) to 2 equiv (87%) of $SbCl_3$, formation of **5** at the higher ratio of $SbCl_3$, and an increase in the quantities of polar decomposition products. Addition of DCA after the addition of $SbCl_3$ gave higher yields of **2** in shorter times with lower ratios of SbX_3, and resulted in less byproduct formation.

Treatment of **1** with excess $NaNO_2$ plus $SbCl_3$ and BTEA-Cl (1 equiv each) and DCA (1.5 equiv) in CH_2Cl_2 gave **2** at ambient temperature (82%), 0 °C (77%), and −15 to −20 °C (61%). No **5** was detected at these three temperatures. The same reagent ratios at concentrations of **1**/CH_2Cl_2 of 0.033 M (1.0 mmol/30 mL), 0.025 M (1.0 mmol/40 mL), and 0.017 M (1.0 mmol/60 mL) gave crystalline **2** (56, 74, and 64%, respectively). Nucleoside concentrations of 0.025 M in CH_2X_2 at ambient temperature were subsequently employed. It is clear that SbX_3 has a pronounced positive effect on these halo-dediazoniations. Yields of halopurine products were increased substantially, and byproduct formation was suppressed.

SbX_3 compounds hydrolyze to form white precipitates that produce emulsions during extraction workup.[13a] This problem was eliminated by addition of diatomaceous earth (Celite) to the reaction mixtures followed by rapid filtration of the suspensions with a short column of silica gel layered with activated charcoal and Celite, and yields comparable to our prior results[13a] were obtained. Optimized conditions for chlorodediazoniation of **1** (Table 1, entry 13) were applied to bromo-dediazoniation with analogous bromine reagents. Brief examination of $SbBr_3$ and BTEA-Br ratios, solvent volume, and temperature showed that good yields of **3** (>60%) were obtained with **1** (0.025 M), DCA (1.5 equiv), excess $NaNO_2$, and $SbBr_3$/BTEA-Br (1 equiv each) in CH_2Br_2 (entry 14). SbI_3/TBN/CH_2I_2/THF (45%, dark-colored reaction mixture, not optimized) was used for conversion of **1** → **4**.

SCHEME 2



6 **5** X = Cl, **7** X = Br, **8** X = I, **9** X = H, **10** X = OH; **5a** X = Cl, **7a** X = Br, **8a** X = I, **9a** X = H

Effects of SbX_3 on product distributions from halodediazoniations at C6 of purine nucleosides were evaluated (Scheme 2). Treatment of 2′,3′,5′-tri-*O*-acetyladenosine (**6**) with excess TBN/CH_2Cl_2 and 2 equiv each of $SbBr_3$ and IAA (or without IAA) at ambient temperature gave products which were separated (TLC), quantitated (UV), and verified by NMR and MS. Ratios of the 6-[chloro (**5**), bromo (**7**), and iodo (**8**)] compounds in dedizoniation mixtures were determined by ^{1}H NMR [H8 singlets at δ 8.76 (**5**), 8.71 (**7**), and 8.62 (**8**)]. The hydroxydediazoniation product [2′,3′,5′-tri-*O*-acetylinosine (**10**)] also was quantitated (Table 2, entries 1 and 2), but no hydro-dediazoniation product [2′,3′,5′-tri-*O*-acetylnebularine (**9**)] was detected. Ratios of **7**/**5** were similar with or without IAA, as were yields of **10** (6 or 4%, respectively). Formation of **8** and **9** was suppressed to very low levels with $SbBr_3$, as was observed with analogous reactions of **1** at C2 (Scheme 1, Table 1). Treatment of **6** with excess TBN/CH_2Cl_2, BTEA-Br (1 equiv) with or without $SbBr_3$ (1 equiv) at ambient temperature resulted in ∼20-fold enhancement of bromo- (**7**, 79%) relative to chloro- (**5**, 5%) dediazoniation with $SbBr_3$ and BTEA-Br or with BTEA-Br only [**7** (61%), **5** (3%)] (Table 2, entries 3 and 4). A higher yield of **7** (79 versus 61%) was obtained with the $SbBr_3$/BTEA-Br combination, but hydroxydediazoniation to give **10** (6%) also occurred. Treatment of **6** with excess TBN/CH_2Br_2 and $SbBr_3$ (2 equiv) at reflux significantly increased yields of **7**, and suppressed formation of even traces of **9**. Analogous treatment of **11** or **13** also gave good yields of the protected arabino, **12**, or 3′-deoxy, **14**, 6-bromopurine nucleosides (Scheme 3).

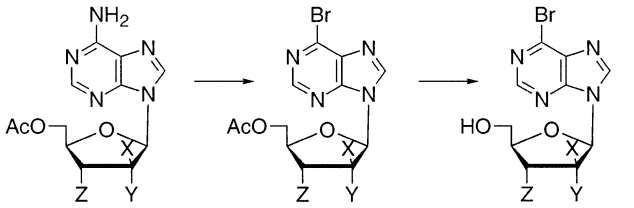
$NaNO_2$/DCA also was an effective reagent combination. Treatment of **6** with $SbBr_3$ and BTEA-Br (1 equiv each), $NaNO_2$ (20 equiv), and DCA (1.5 equiv) in CH_2Br_2 at ambient temperature for 18 h gave **7** (69%), whereas dediazoniation of **6** with TBN/CH_2Br_2 and $SbBr_3$ (2 equiv) was not complete after 72 h. Addition of DCA (1.5 equiv)

TABLE 2. Products from Dediazoniation Reactions of 6

			products (yield %)			
entry	(reagents/solvents)	IAA	**5**	**7**	**8**	**10**
1	($SbBr_3$/TBN/CH_2Cl_2)	−	20	32		4
2	($SbBr_3$/TBN/CH_2Cl_2)	+	11	17	1	6
3	(BTEA-Br/TBN/CH_2Cl_2)	−	3	61		7
4	(BTEA-Br/$SbBr_3$/TBN/CH_2Cl_2)	−	5	79		6
5[a]	(BTEA-Br/$SbBr_3$/$NaNO_2$/DCA/CH_2Br_2)	−		>70		*b*
6[a]	($SbBr_3$/TBN/CH_2Br_2/Δ)	−		>60		*b*
7[a]	(SbI_3/TBN/CH_2I_2/THF/Δ)	−			>45	*b*

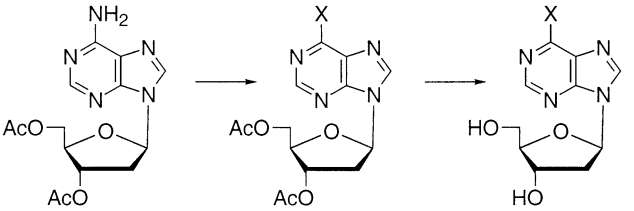
[a] See the Results and Discussion and Experimental Section for conditions for preparative scale reactions. [b] Trace quantities (<10%).

SCHEME 3



11 X = Z = OAc, Y = H **12** X = Z = OAc, Y = H **12a** X = Z = OH, Y = H
13 X = Z = H, Y = OAc **14** X = Z = H, Y = OAc **14a** X = Z = H, Y = OH

SCHEME 4



15 **16** X = Br **16a** X = Br
17 X = I **17a** X = I

to **6**/$SbBr_3$/TBN/CH_2Br_2 at ambient temperature did not enhance the yield of **7**. Dediazoniations with $NaNO_2$/DCA/$SbBr_3$/BTEA-Br proceeded equally well at ambient temperature or ∼60 °C (CH_2Br_2 at reflux), whereas lower temperatures (−10 °C) retarded reaction rates. Efficient bromo-dediazoniations at C6 were parallel with those at C2 except lower ratios of DCA were required. Constant proportions of $SbBr_3$, BTEA-Br, $NaNO_2$, and CH_2Br_2 gave better yields of **7** (72%) with ∼0.5 equiv than with 1 (62%) or 1.5 (58%) equiv of DCA.

Substitution of HOAc (0.5 equiv) for DCA allowed efficient bromo-dediazoniation of the acid-labile 2′-deoxy derivative. Treatment of **15** (Scheme 4) with $SbBr_3$, BTEA-Br, $NaNO_2$, and HOAc in CH_2Br_2 under optimized conditions gave **16** (74%). An alternative method with SbX_3 (2 equiv), TBN, and CH_2X_2 gave **16** (60%) or its 6-iodo analogue **17** (47%).

Finally, treatment of **1** (Scheme 1) with DCA and powdered $NaNO_2$ (15 equiv each) in THF at ambient temperature for 2 h gave high yields of **5** (82%) (Table 1, entry 16). This demonstrated that hydro-dediazoniation at C2 of **1** can be enhanced dramatically by alteration of acid and nitrite reagents. This procedure provides efficient access to the 6-chloropurine derivative **5** starting from guanosine, a naturally occurring 2-aminopurin-6-one nucleoside.

Deacylation of 6-halopurine nucloside derivatives can be problematic, because liberated oxygen nucleophiles on the sugar can effect S_NAr displacement of 6-halo substituents to produce insoluble polymers. Dilute solutions in alcoholic ammonia at −5 to 0 °C or dilute solutions in 0.01 M NaOH/H_2O gave good yields (61−92%) of the analytically pure deacetylated products.

In summary, our results are consistent with fragmentations of purinediazonium species at C2 or C6 via competing homolytic and heterolytic processes. Antimony trihalides are efficient catalysts. Nonaqueous halo-dediazoniation of 2-amino-6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine (**1**) with SbX_3/BTEA-X/$NaNO_2$ gave good yields (>70%) of 2-(bromo or chloro)-6-chloropurine products. The 6-chloro-2-iodopurine compound **4** (45%) was obtained with SbI_3, and 6-chloropurine derivative **5** (82%) was prepared by hydro-dediazoniation of **1**. Bromo-dediazoniations at C6 of 2′,3′,5′-tri-*O*-acetyladenosine (**6**) and analogues were effected in good yields (>60%). A modified procedure gave the 6-bromopurine 2′-deoxynucleoside **16** (74%) from 3′,5′-di-*O*-acetyl-2′-deoxyadenosine (**15**). Analogous SbI_3 catalysis gave the 6-iodopurine analogue **17** (47%), and mild deacetylation conditions were employed to provide crystalline 6-(bromo or iodo)purine 2′-deoxynucleosides (88%). Optimized procedures are noted in the general material of the Experimental Section.

Experimental Section

Uncorrected melting points were determined with a hot-stage apparatus. UV spectra were recorded with solutions in MeOH unless otherwise indicated. ^{1}H NMR spectra (solutions in TMS/DMSO-d_6) were recorded at 100 or 200 MHz unless otherwise indicated. "Apparent" peak shapes are in quotation marks when first-order splitting should be more complex, or when peaks were poorly resolved. High-resolution mass spectra (MS) were determined with FAB (glycerol) or CI (CH_4). All chemicals and solvents were of reagent quality. THF, CH_2Cl_2, and CH_2Br_2 were dried by reflux over and distillation from CaH_2. $SbCl_3$ (Fisher Scientific) and $SbBr_3$ (Alfa Inorganics) were commercially available; SbI_3 was prepared as described;[42] antimony trihalides were purified by sublimation (90 °C, 50 mmHg). Benzyltriethylammonium bromide (BTEA-Br) was prepared from BTEA-Cl by ion exchange [Dowex 1 × 2 (Br^-)]. Column chromatography was performed with silica gel (230−400 mesh). Radial TLC (Chromatotron) was performed with silica gel (Merck, TLC grade 7749 with gypsum binder). Substrates **1**,[35] **6**,[43] and **15**[3b] were prepared as described.

Methods 1 (SbX_3/BTEA-X/$NaNO_2$/HOAc/CH_2X_2), **2** (SbX_3/BTEA-X/$NaNO_2$/DCA/CH_2X_2), and **3** (SbX_3/TBN/CH_2X_2) are described for conversions of **15** → **16**. Analogous treatment

(42) Schenk, P. W. In *Handbook of Preparative Inorganic Chemistry*; Brauer, G., Ed.; Academic: New York, 1963; Vol. 1, p 614.
(43) Bredereck, H.; Martini, A. *Chem. Ber.* **1947**, *80*, 401−405.

with equivalent molar proportions of other nucleosides gave the indicated products and quantities. "Column A" (7-cm diameter) contained (top to bottom) silica gel (10 g), decolorizing carbon (0.4 g), Celite filter aid (0.4 g), and silica gel (20 g). Protected nucleosides were deacetylated by methods 4 or 5. **Method 4:** The acetylated nucleoside (~1 mmol) was dissolved in NH_3/MeOH (50 mL, saturated at 0 °C) and the solution was stored at −5 to 0 °C for 18−24 h. Volatiles were evaporated under reduced pressure (0−5 °C), and 98% EtOH was added to and evaporated from the residue. The residue was recrystallized (from 98% EtOH or MeOH), filtered, washed with cold EtOH, and dried over Drierite ($CaSO_4$). **Method 5:** The acetylated nucleoside (~1 mmol) was dissolved in CH_2Cl_2 (100 mL) in a 2000-mL round-bottom flask, and volatiles were evaporated to give a thin, dilute film (this procedure retards polymerization/decomposition). NaOH/H_2O (0.01 M, 380 mL, 3.8 mmol) was added, and the solution was stirred at ambient temperature for 1−2 h (TLC, $CHCl_3$/MeOH, 9:1). The solution was transferred to a clean flask, the 2000-mL flask was rinsed with H_2O (3 × 10 mL), and Amberlite XAD-4 resin (145 mL) was added to the combined aqueous solution. The mixture was stirred for 10 min at ambient temperature (UV of the supernatant indicated that product was adsorbed), and the resin was filtered and washed with H_2O (2 × 100 mL). The resin was then suspended in CH_3CN (100 mL), the mixture was stirred for 10 min at ambient temperature, and the resin was filtered. This extraction was repeated (CH_3CN, 2 × 100 mL), and volatiles were evaporated (0−5 °C) from the combined CH_3CN filtrates. The residue was lyophilized (oil pump), dried Et_2O was added and evaporated (3 × 5 mL), and the solid was dried over Drierite ($CaSO_4$) at ambient temperature. Drying some samples over P_2O_5 caused decomposition.

9-(2,3,5-Tri-*O*-acetyl-*β*-D-ribofuranosyl)-2,6-dichloropurine (2). Treatment of **1** (428 mg, 1.0 mmol) by method 2 gave **2** (329 mg, 74%) as slightly yellow crystals (from BuOH) with mp 161−163 °C (lit.[26] mp 158 °C); UV (H_2O, pH ~7) max 273 nm (ε 10 100); ^{1}H NMR (200 MHz; $CDCl_3$) δ 2.07, 2.13, 2.15 (3 × s, 3 × 3H), 4.38 ("d", J = 3.4 Hz, 2H), 4.44−4.48, 5.53−5.58 (2 × m, 2 × 1H), 5.77 ("t", J = 5.5 Hz, 1H), 6.20 (d, J = 5.6 Hz, 1H), 8.27 (s, 1H); LRMS (CI) m/z 447 (MH^+ [$C_{16}H_{17}{}^{35}Cl_2N_4O_7$] = 447).

9-(2,3,5-Tri-*O*-acetyl-*β*-D-ribofuranosyl)-2-bromo-6-chloropurine (3). Treatment of **1** (428 mg, 1.0 mmol) by method 2 gave **3** (308 mg, 63%) as white needles (from EtOH) with mp 162−163 °C (lit.[21d] mp 155−156 °C); UV max 275 nm (ε 9100); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.08, 2.13, 2.15 (3 × s, 3 × 3H), 4.42 ("d", J = 3.4 Hz, 2H), 4.41−4.50, 5.56−5.61 (2 × m, 2 × 1H), 5.79 ("t", J = 5.5 Hz, 1H), 6.22 (d, J = 5.4 Hz, 1H), 8.25 (s, 1H); LRMS (FAB) m/z 491 (MH^+ [$C_{16}H_{17}{}^{79}Br{}^{35}ClN_4O_7$] = 491).

9-(2,3,5-Tri-*O*-acetyl-*β*-D-ribofuranosyl)-6-chloro-2-iodopurine (4). TBN (9.5 mL, 8.2 g, 80 mmol) was added with stirring at ambient temperature to a solution of **1** (1.71 g, 4.0 mmol) and SbI_3 (4 g, 8 mmol) in a mixture of dried THF (15 mL) and CH_2I_2 (35 mL). Reaction was complete after 2 h (TLC; MeOH/$CHCl_3$, 9:91), and volatiles were evaporated under reduced pressure. The residue was diluted ($CHCl_3$), and the solution was washed (5% $NaHSO_3$/H_2O and then H_2O) and dried ($MgSO_4$). Volatiles were evaporated, and the residue was diluted ($CHCl_3$) and chromatographed (silica gel, 100 mL, $CHCl_3$). Volatiles were evaporated, the residual oil was dissolved ($CHCl_3$/PrOH), and the solution was concentrated to a small volume and cooled (~4 °C) overnight. Light yellow crystals were filtered and washed (PrOH) to give **4** (965 mg, 45%) with mp 182−183 °C (lit.[21d] mp 181−183 °C); UV max 255, 281 nm (ε 5700, 8800); ^{1}H NMR δ 2.03, 2.08, 2.14 (3 × s, 3 × 3H), 4.24−4.44 (m, 3H), 5.66 (dd, 1H), 5.92 (t, 1H), 6.33 (d, 1H), 8.86 (s, 1H); MS m/z 539.9717 (M^+ [^{37}Cl] = 539.9722). Anal. Calcd for $C_{16}H_{16}ClIN_4O_7$: C, 35.68; H, 2.99; N, 10.40. Found: C, 35.99; H, 3.08; N, 10.35.

9-(2,3,5-Tri-*O*-acetyl-*β*-D-ribofuranosyl)-6-chloropurine (5). Procedure A: Powdered $NaNO_2$ (1.04 g, 15 mmol) and **1** (488 mg, 1.0 mmol) were added to dried THF (40 mL) in a 250-mL round-bottom flask stirred with a heavy magnetic stirring bar or a mechanical stirrer. Dichloroacetic acid (1.25 mL, 1.93 g, 15 mmol) was added, and the flask was flushed with dried N_2 and sealed. The mixture was stirred *vigorously*, and a thick gel was formed. This became a thick slurry after stirring for 1.5−2 h (TLC; MeOH/$CHCl_3$, 1:9, indicated conversion of **1** into a major and a minor product). The slurry was transferred (dropwise with a large-bore pipet) from the flask into a vigorously stirred mixture of saturated $NaHCO_3$/H_2O (200 mL) and $CHCl_3$ (200 mL) that was cooled in an ice−water bath. The phases were separated, and the organic layer was washed [H_2O (100 mL) and then brine (100 mL)], dried ($MgSO_4$), and filtered. The filtrate was passed through a layer of silica gel (20 g) in a fritted-glass funnel, and product was eluted with MeOH/$CHCl_3$ (0.1:99.9, 1 L). Volatiles were evaporated to give a slightly yellow oil. Dried Et_2O was added and evaporated several times to give **5** (327 mg, 82%) as a slightly yellow TLC-homogeneous solid foam. UV and NMR data were in agreement with published values.[21b] **Procedure B:** Treatment of **6** (1.97 g, 5.0 mmol) by method 3 gave **5** (965 mg, 47%) as a light-yellow oil with TLC migration and spectral data the same as product from procedure A.

6-Chloro-9-(*β*-D-ribofuranosyl)purine (5a). Treatment of **5** by method 4 gave **5a** (61%) (two crops from EtOH) with mp 193−195 °C dec (lit.[44] mp 180−182 °C dec); UV max 265 nm (ε 8700); ^{1}H NMR δ 3.67 (m, 2H), 4.01 (m, 1H), 4.22 (q, 1H), 4.62 (q, 1H), 5.10 (t, 1H), 5.26 (d, 1H), 5.58 (d, 1H), 6.08 (d, 1H), 8.86, 9.00 (2 × s, 2 × 1H); MS m/z 286.0463/288.0420 (M^+ ($^{35/37}$Cl) = 286.0468/288.0439). Anal. Cacd for $C_{10}H_{11}ClN_4O_4$: C, 41.90; H, 3.87; N, 19.54. Found: C, 42.14; H, 4.12; N, 19.45.

9-(2,3,5-Tri-*O*-acetyl-*β*-D-ribofuranosyl)-6-bromopurine (7). Treatment of **6** (393 mg, 1.0 mmol) by method 2 gave **7**[21b] (331 mg, 72%) as a white solid foam with ^{1}H NMR δ 2.02, 2.06, 2.14 (3 × s, 3 × 3H), 4.10−4.50 (m, 3H), 5.65 ("dd", 1H), 6.03 ("t", J = 5.0 Hz, 1H), 6.37 (d, J = 5.0 Hz, 1H), 8.80, 8.90 (2 × s, 2 × 1H); MS m/z 456.0281/458.0268 (M^+ [$C_{16}H_{17}{}^{79/81}BrN_4O_7$] = 456.0281/458.0260). Treatment of **6** (1.97 g, 5.0 mmol) by method 3 gave **7** (1.33 g, 58%) as a white solid foam with TLC migration and spectral data the same as the product from method 2.

6-Bromo-9-(*β*-D-ribofuranosyl)purine (7a). Treatment of **7** by method 4 gave **7a** (65%) (from EtOH) with mp 192 °C dec (lit.[34] mp 181−182 °C); UV max 267 nm (ε 9800); ^{1}H NMR δ 3.62 (q, 1H), 3.68 (m, 2H), 4.01 (m, 1H), 4.22 (q, 1H), 5.09 (t, 1H), 5.25 (d, 1H), 5.57 (d, 1H), 6.07 (d, 1H), 8.81, 9.00 (2 × s, 2 × 1H); MS m/z 329.9950 (M^+ [^{79}Br] = 329.9963). Anal. Calcd for $C_{10}H_{11}BrN_4O_4$: C, 36.27; H, 3.35; N, 16.92. Found: C, 36.44; H, 3.52; N, 17.07. Treatment of **7** by method 5 gave **7a** (69%) (from EtOH) with the same TLC migration and spectral data as the product from method 4.

6-Iodo-9-(*β*-D-ribofuranosyl)purine (8a). TBN (11.9 mL, 10.3 g, 100 mmol) was added to a stirred solution of **6** (1.97 g, 5.0 mmol) and SbI_3 (5.0 g, 10 mmol) in CH_2I_2/THF (1:1, 100 mL) at 60 °C (oil bath temperature), and stirring was continued for 10 min. Volatiles were evaporated, and the residue was diluted ($CHCl_3$). The solution was washed (5% $NaHSO_3$/H_2O and then H_2O) and dried ($MgSO_4$). Volatiles were evaporated, and a small volume of $CHCl_3$ was added. Chromatography (silica gel, 100 mL, $CHCl_3$) gave 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-6-iodopurine[21b] (**8**) as a light-yellow oil (1.16 g, 46%) with ^{1}H NMR δ 2.02, 2.06, 2.14 (3 × s, 3 × 3H), 4.29 (m, 1H), 4.43 (m, 2H), 5.66 (dd, 1H), 6.04 (t, 1H), 6.34 (d, 1H), 8.70, 8.88 (2 × s, 2 × 1H); MS m/z 504.0158 (M^+ [$C_{16}H_{17}IN_4O_7$] = 504.0142).

Treatment of **8** by method 4 gave **8a** (76%) (from EtOH) with mp 173−175 °C (lit.[34] mp 173 °C dec); UV max 276 nm (ε 10 800); ^{1}H NMR δ 3.62 (q, 1H), 3.67 (m, 2H), 4.01 (m, 1H),

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4.22 (q, 1H), 5.09 (t, 1H), 5.25 (d, 1H), 5.56 (d, 1H), 6.03 (d, 1H), 8.70, 8.95 (2 × s, 2 × 1H); MS *m*/*z* 377.9825 (M^+ [$C_{10}H_{11}IN_4O_4$] = 377.9824).

9-(β-D-Ribofuranosyl)purine (Nebularine) (9a). TBN (23.8 mL, 20.6 g, 200 mmol) was added to a stirred solution of **6** (3.94 g, 10 mmol) in dried THF (120 mL) at 60 °C (oil bath temperature). After 20 min, TLC (MeOH/$CHCl_3$, 9:91) showed the less polar 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine (**9**) and more polar 2′,3′,5′-tri-*O*-acetylinosine (**10**). Volatiles were evaporated, and the residue was dissolved ($CHCl_3$) and chromatographed (silica gel, $CHCl_3$) to give **9**[21b] (1.16 g, 31%) as a light-yellow oil with ^{1}H NMR δ 2.02, 2.06, 2.14 (3 × s, 3 × 3H), 4.20−4.60 (m, 3H), 5.70 (dd, 1H), 6.10 (t, 1H), 6.40 (d, 1H), 8.86, 9.04, 9.28 (3 × s, 3 × 1H); MS *m*/*z* 378.1155 (M^+ [$C_{16}H_{18}N_4O_7$] = 378.1175).

Treatment of **9** by method 4 gave **9a** (65%) (from EtOH) with mp 178−180 °C (lit.[45] mp 176−178 °C); UV (H_2O, pH ∼7) max 262 nm (ε 5600); ^{1}H NMR δ 3.21 (q, 1H), 3.65 (m, 2H), 3.66 (q, 1H), 4.00 (m, 1H), 5.10 (t, 1H), 5.25 (d, 1H), 5.55 (d, 1H), 6.08 (d, 1H), 8.89, 9.00, 9.24 (3 × s, 3 × 1H); MS *m*/*z* 252.0862 (M^+ = 252.0859). Anal. Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.64; H, 4.98; N, 22.14.

2′,3′,5′-Tri-*O*-acetylinosine (10). TBN (11.9 mL, 10.3 g, 100 mmol) was added to a stirred solution of **6** (1.97 g, 5.0 mmol) in DME/H_2O (1:1, 100 mL) preheated to 60 °C (oil bath temperature). After 15 min, the solution was concentrated to one-half volume, neutralized ($NaHCO_3$/H_2O), and extracted ($CHCl_3$, 3 × 50 mL). Volatiles were evaporated from the combined organic phase, and the residue was recrystallized (from EtOH) to give **10** (1.36 g, 69%) with mp 239−243 °C (lit.[43] mp 241 °C); UV max 244 (ε 11 500); ^{1}H NMR δ 2.03, 2.05, 2.12 (3 × s, 3 × 3H), 4.10−4.50 (m, 3H), 5.55 (dd, 1H), 5.91 (t, 1H), 6.20 (d, 1H), 8.11, 8.32 (2 × s, 2 × 1H), 12.48 (br, 1H).

9-(β-D-Arabinofuranosyl)-6-bromopurine (12a). Treatment of **11**[46] (4.0 g, 10 mmol) by method 3 gave 9-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-6-bromopurine (**12**) (2.9 g, 63%) as a slightly yellow oil with ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93, 2.18, 2.22 (3 × s, 3 × 3H), 4.32 ("dt", *J* = 6.0, 4.5 Hz, 1H), 4.50 (2 × dd, *J* = 12.0, 6.0, 4.5 Hz, 2H), 5.48 (dd, *J* = 4.5, 3.5, Hz, 1H), 5.56 (dd, *J* = 4.5, 3.5 Hz, 1H), 6.67 (d, *J* = 4.5 Hz, 1H), 8.37, 8.76 (2 × s, 2 × 1H); MS *m*/*z* 456.0277/458.0264 (M^+ [$C_{16}H_{17}{}^{79/81}BrN_4O_7$] = 456.0281/458.0261).

Treatment of **12** by method 4 gave **12a** (80%) (from MeOH) with mp >350 °C dec; UV max 266 nm (ε 11 000); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.71 (m, *J* = 12.0, 5.0 Hz, 2H), 3.85 (q, *J* = 5.0 Hz, 1H), 4.18 (q, *J* = 5.0 Hz, 1H), 4.27 (q, *J* = 5.0 Hz, 1H), 5.15 (t, *J* = 5.0 Hz, 1H), 5.61, 5.67, 6.42 (3 × d, 3 × 1H), 8.77, 8.80 (2 × s, 2 × 1H). Anal. Calcd for $C_{10}H_{11}BrN_4O_4$: C, 36.27; H, 3.35; Br, 24.13; N, 16.92. Found: C, 36.42; H, 3.42; Br, 24.19; N, 16.95.

6-Bromo-9-(3-deoxy-β-D-*erythro*-pentofuranosyl)purine (14a). Treatment of **13**[47] (5.0 g, 15 mmol) by method 3 gave 9-(2,5-di-*O*-acetyl-3-deoxy-β-D-*erythro*-pentofuranosyl)-6-bromopurine (**14**) (3.7 g, 61%) as a slightly yellow oil with ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.98, 2.13 (2 × s, 2 × 3H), 2.28 (ddd, *J* = 14.0, 6.0, 1.0 Hz, 1H), 2.64 (ddd, *J* = 14.0, 10.5, 6.0 Hz, 1H), 4.22 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.30 (dd, *J* = 12.0, 3.0 Hz, 1H), 4.58 (m, 1H), 5.76 (br d, 1H), 6.30 (d, *J* = 1.5 Hz, 1H), 8.81, 8.86 (2 × s, 2 × 1H); MS *m*/*z* 398.0214/400.0204 (M^+ [$C_{14}H_{15}{}^{79/81}BrN_4O_5$] = 398.0227/400.0207).

Treatment of **14** by method 4 gave **14a** (92%) (from MeOH) with mp 155−156 °C; UV max 266 nm (ε 11 200); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.90, (ddd, *J* = 13.5, 9.5, 2.5 Hz, 1H), 2.24 (ddd, *J* = 13.5, 6.0, 5.5 Hz, 1H), 3.55 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.74 (dd, *J* = 12.0, 3.5 Hz, 1H), 4.42 (m, 1H), 4.62 (m, 1H), 5.08 (t, *J* = 5.5 Hz, 1H), 5.75 (d, *J* = 4.0 Hz, 1H), 6.01 (d, *J* = 1.5 Hz, 1H), 8.75, 8.94 (2 × s, 2 × 1H); MS *m*/*z* 315.0098/317.0077 (MH^+ [$C_{10}H_{12}{}^{79/81}BrN_4O_3$] = 315.0094/317.0073). Anal. Calcd for $C_{10}H_{11}BrN_4O_3$: C, 38.11; H, 3.52; Br, 25.36; N, 17.78. Found: C, 38.11; H, 3.54; Br, 25.19; N, 17.85.

9-(3,5-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-bromopurine (16). Method 1: $SbBr_3$ (361 mg, 1.0 mmol) in CH_2Br_2 (4.5 mL) was added to a solution of **15** (335 mg, 1.0 mmol), BTEA-Br (272 mg, 1.0 mmol), and $NaNO_2$ (1.4 g, 20 mmol) in CH_2Br_2 (40 mL). AcOH (29 μL, 30 mg, 0.50 mmol) was added, and the flask was flushed with dried N_2 and sealed. The mixture was stirred *vigorously* with a heavy magnetic stirring bar or mechanical stirrer at ambient temperature (25 ± 5 °C) until **15** had been converted into a major and minor product (∼3 days; TLC, MeOH/$CHCl_3$, 1:9). Celite (3 g) and $CHCl_3$ (120 mL) were added, and the suspension was stirred for 10 min. The mixture was applied to "column A" and product was eluted (MeOH/$CHCl_3$, 0.2:100, ∼600 mL). Volatiles were evaporated, and dried Et_2O was added and evaporated several times to give **16**[3d] (294 mg, 74%) as a yellow glass with UV (EtOH) max 267 nm (ε 7300); ^{1}H NMR) δ 1.97, 2.09 (2 × s, 2 × 3H), 2.53−2.67, 3.09−3.22 (2 × m, 2 × 1H), 4.15−4.32 (m, 3H), 5.42−5.45 (m, 1H), 6.49 ("t", *J* = 7.0 Hz, 1H), 8.76, 8.89 (2 × s, 2 × 1H); LRMS (CI) *m*/*z* 399/401 (MH^+ [$^{79/81}$Br] = 399/401). Anal. Calcd for $C_{14}H_{15}BrN_4O_5$: C, 42.12; H, 3.79; N, 14.04. Found: C, 42.15; H, 4.06; N, 14.23.

Method 2: $SbBr_3$ (361 mg, 1.0 mmol) in CH_2Br_2 (4.5 mL) was added to a mixture of **15** (335 mg, 1.0 mmol), BTEA-Br (272 mg, 1.0 mmol), and $NaNO_2$ (1.4 g, 20 mmol) in CH_2Br_2 (40 mL). Cl_2CHCO_2H (41 μL, 64 mg, 0.5 mmol) was added, and the flask was flushed with dried N_2 and sealed. The mixture was stirred at ambient temperature until nearly all of **15** was converted into a major and three minor products (∼2 days, TLC, MeOH/$CHCl_3$, 1:9). Celite (3 g) and $CHCl_3$ (120 mL) were added, and the suspension was stirred for 10 min. The mixture was applied to "column A" and product was eluted (MeOH/$CHCl_3$, 0.2:100, ∼500 mL). Volatiles were evaporated, and dried Et_2O was added and evaporated several times to give **16** (264 mg, 66%) as a yellow glass that had the same TLC migration and spectral data as the product from method 1.

Method 3: A stirred solution of **15** (1.8 g, 5.3 mmol) and $SbBr_3$ (3.84 g, 10.6 mmol) in CH_2Br_2 (100 mL) was heated at 60 °C for 15 min. TBN (12.6 mL, 10.9 g, 106 mmol) was added, and heating was continued for 20 min. Volatiles were evaporated (to half the original volume), and this solution was washed (5% $NaHCO_3$/H_2O and then H_2O) and dried ($MgSO_4$). Volatiles were evaporated, and the residual oil was chromatographed (100 mL silica gel, $CHCl_3$). TLC-homogeneous fractions were combined and volatiles were evaporated. Dried Et_2O was added and evaporated several times to give **16** (1.3 g, 60%) as a slightly yellow solid foam with ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.13, 2.14 (2 × s, 2 × 3H), 2.66 (ddd, *J* = 14.5, 6.5, 3.0 Hz, 1H), 3.21 ("quint", *J* = ∼6.5 Hz, 1H), 4.26 (dd, *J* = 12.5, 7.5 Hz, 1H), 4.33 (m, 1H), 4.34 (dd, *J* = 4.5, 3.0 Hz, 1H), 5.49 ("quint", *J* = ∼3.5 Hz, 1H), 6.54 (t, *J* = 6.5 Hz, 1H), 8.83, 8.96 (2 × s, 2 × 1H); MS *m*/*z* 398.0221/400.0189 (M^+ [$^{79/81}$Br] = 398.0227/400.0207). Anal. Calcd for $C_{14}H_{15}BrN_4O_5$: C, 42.12; H, 3.79; Br, 20.01; N, 14.04. Found: C, 42.28; H, 3.90; Br, 19.71; N, 13.98.

6-Bromo-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine (16a). Treatment of **16** by method 4 gave **16a** (78%) (from MeOH/EtOAc) with mp 150−151 °C; UV max 266 nm (ε 10 700); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.39 (ddd, *J* = 13.5, 6.5, 4.5 Hz, 1H), 2.78 ("quint", *J* = 6.5 Hz, 1H), 3.55 (dd, *J* = 12.0, 4.5 Hz, 1H), 3.63 (dd, *J* = 12.0, 4.5 Hz, 1H), 3.91 ("q", *J* = 4.5 Hz, 1H), 4.47 (m, 1H), 4.99 (t, *J* = 6.5 Hz, 1H), 5.39 (d, *J* = 4.5 Hz, 1H), 6.54 ("t", *J* = 6.5 Hz, 1H), 8.83, 8.96 (2 × s, 2 × 1H); LRMS (CI) *m*/*z* 315/317 (MH^+ [$^{79/81}$Br] = 315/317). Anal. Calcd for $C_{10}H_{11}BrN_4O_3$: C, 38.11; H, 3.52; Br, 25.36; N, 17.78. Found: C, 38.00; H, 3.55; Br, 25.51; N, 18.04.

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Treatment of **16** by method 5 gave **16a** (88%) (from MeOH/EtOAc) with mp 150 °C. Its TLC migration and spectral data were the same as the product from method 4.

9-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-6-iodopurine (17a). TBN (1.2 mL, 1.04 g, 10 mmol) was added to a stirred solution of **15** (167 mg, 0.5 mmol) and SbI_3 (0.5 g, 1.0 mmol) in CH_2I_2/THF (1:1, 10 mL) at 60 °C (oil bath temperature), and stirring was continued for 10 min. Volatiles were evaporated, and the residue was diluted ($CHCl_3$). The solution was washed (5% $NaHSO_3$/H_2O and then H_2O) and dried ($MgSO_4$). Volatiles were evaporated, and a small volume of $CHCl_3$ was added. Chromatography (silica gel, 15 mL, $CHCl_3$) gave 9-(3,5-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-iodopurine (**17**) as a white solid foam (105 mg, 47%) with UV max 275 nm (ε 10 400); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.98, 2.10 (2 × s, 2 × 3H), 2.60 (ddd, J = 14.7, 6.6, 3.3 Hz, 1H), 3.18 ("quint", J = 7.2 Hz, 1H), 4.26 (m, 3H), 5.44 ("quint", J = 3.3 Hz, 1H), 6.47 (dd, J = 6.9, 7.2 Hz, 1H), 8.66, 8.85 (2 × s, 2 × 1H).

Treatment of **17** by method 4 gave **17a**[3c] (89%) (from EtOH) with mp 152−153 °C; UV max 275 nm (ε 10 200); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.36 (m, 1H), 2.76 ("quint", J = 6.6 Hz, 1H), 3.52 (m, 1H), 3.60 (m, 1H), 3.89 ("q", J = 4.2 Hz, 1H), 4.44 (m, 1H), 4.99 (m, 1H), 5.39 (m, 1H), 6.43 ("t", J = 6.6 Hz, 1H), 8.63, 8.86 (2 × s, 2 × 1H); LRMS m/z 362 (M^+ = 362). Anal. Calcd for $C_{10}H_{11}IN_4O_3$: C, 33.17; H, 3.06; N, 15.47. Found: C, 33.17; H, 3.12; N, 15.30.

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