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Unusual Deoxygenation and Reactivity Studies Related to O^6-(Benzotriazol-1-yl)inosine Derivatives

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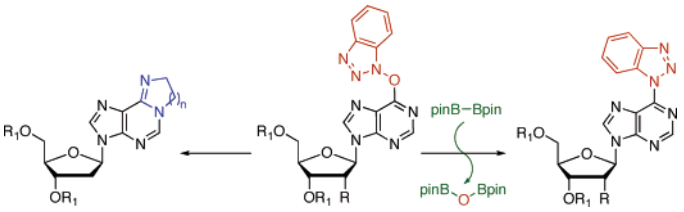

New and unusual developments related to the chemistry of O^6-(benzotriazol-1-yl)inosine derivatives are reported. First, a simple, scalable method for their syntheses via the use of PPh_3/I_2/HOBt has been developed and has been mechanistically investigated by $^{31}P\{^1H\}$ NMR. Studies were then conducted into a unique oxygen transfer reaction between O^6-(benzotriazol-1-yl)inosine nucleosides and bis-(pinacolato)diboron (pinB-Bpin) leading to the formation of C-6 (benzotriazol-1-yl)purine nucleoside derivatives and pinB-O-Bpin. This reaction has been investigated by $^{11}B\{^1H\}$ NMR and compared to pinB-O-Bpin obtained by oxidation of pinB-Bpin. The structures of the C-6 (benzotriazol-1-yl)purine nucleosides have been unequivocally established via Pd-mediated C−N bond formation between bromo purine nucleosides and 1*H*-benzotriazole. Finally, short and extremely simple synthesis of 1,N^6-ethano- and 1,N^6-propano-2′-deoxyadenosine are reported in order to demonstrate the synthetic versatility of the O^6-(benzotriazol-1-yl)inosine nucleoside derivatives for the assembly of relatively complex compounds.

Introduction

On the basis of the known reactivity of hypoxanthine nucleosides with phosphonium salts,[1,2] we have recently described the synthesis of O^6-(benzotriazol-1-yl)inosine nucleosides via reaction of silylated inosine nucleosides with 1*H*-benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP).[3] In studying the mechanism of this reaction, we showed by $^{31}P\{^1H\}$ NMR that hexamethylphosphonium salts of the nucleosides are formed as intermediates, and in the absence of an added nucleophile, these lead to the formation of the O^6-(benzotriazol-1-yl)inosine derivatives by reaction with 1-hydroxybenzotriazole (HOBt) that is formed in situ.[3] These new derivatives are extremely versatile compounds that can be converted to a large assortment of nucleoside analogues via reaction with nucleophiles, and postsynthetic DNA modification was also possible (Scheme 1).[3]

We have now developed a second generation, cost-economical synthesis of these versatile, reactive nucleosides. In order to expand the synthetic utility of these compounds, we have attempted metal-mediated transformations. During the course of these investigations we have discovered a highly unusual *deoxygenation* of the O^6-(benzotriazol-1-yl)inosine derivatives in the presence of bis(pinacolato)diboron (pinB-Bpin). We have explored this transformation chemically and spectroscopically by ^1H as well as $^{11}B\{^1H\}$ NMR, and have unequivocally confirmed the structures of the products by independent synthesis. Finally, as a continued demonstration of the synthetic versatility of these reactive nucleosides we have developed an exceptionally facile synthesis of 1,N^6-ethano- and 1,N^6-propano-2′-deoxyadenosine analogues.

Results and Discussion

By analogy to BOP we began our investigation via the use of hexamethylphosphorus triamide (HMPT)/I_2. Reaction of silylated nucleoside **1** with HMPT (1.1−1.5 mol equiv), I_2 (1.1−1.5 mol equiv), and HOBt (1.5 mol equiv) was tested in the presence of $(i\text{-Pr})_2$NEt (DIPEA, 4 mol equiv) in CH_2Cl_2 at room

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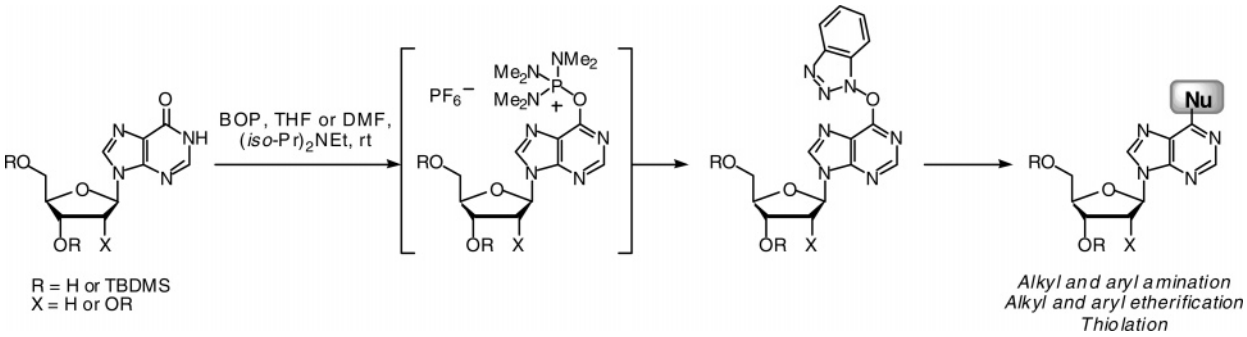
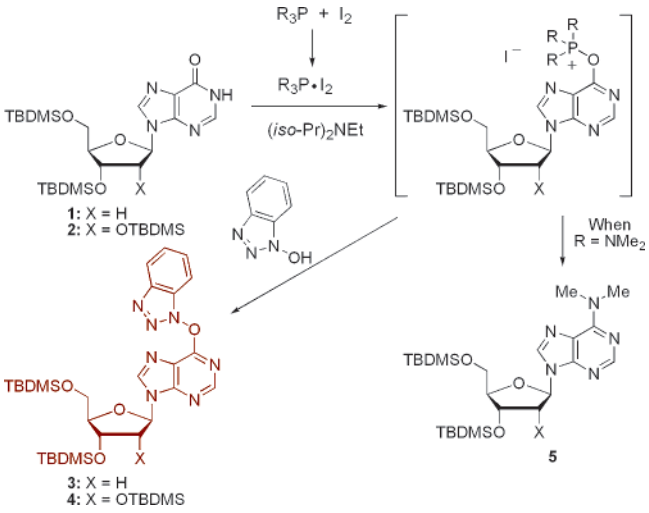
SCHEME 1. Synthesis and Reactions of O^6-(Benzotriazol-1-yl)inosine Nucleosides



SCHEME 2. Reaction of 3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine with R_3P/I_2/HOBt



temperature. These reactions led to the formation of the desired O^6-(benzotriazol-1-yl)inosine derivative **3**, but this was accompanied by the *N*,*N*-dimethylamino derivative **5** (Scheme 2 as well as Table 1, entries 1 and 2). Although **5** was not observed in small-scale reactions of **1** and **2** with BOP, we have occasionally detected its formation upon scale up.

The fact that **5** was observed in the reactions involving HMPT was not entirely surprising since *N*,*N*-dimethylaminoadenosine has been reported to form in the halogenation reaction of 2′,3′,5′-tri-*O*-acetylinosine with HMPT and CCl_4 or CBr_4.[4] Also, competitive formation of *N*,*N*-dimethylamides has been observed in the conversion of 2,2,2-trihaloethyl esters to amides, mediated by HMPT.[5]

On the basis of the above observations, we decided to investigate the synthesis of **3** and **4** via the use of PPh_3/I_2/HOBt (Table 1, entries 3−12). At room temperature in DMF, a reaction with 1.5 mol equiv each of PPh_3, I_2, and HOBt and 4 mol equiv of DIPEA showed incomplete consumption of **1** and no formation of **3** (entry 3). In 1,2-dichloroethane (DCE) use of 3 mol equiv each of PPh_3 and I_2 and 8 mol equiv of DIPEA was also unsatisfactory even at 83 °C (entry 4). Although consumption of **1** occurred, no formation of **3** was observed. Use of THF as solvent provided an improvement although reactions were still incomplete (entries 5 and 6). The use of CH_2Cl_2 proved to be superior (entry 7): with just 1.5 mol equiv each of PPh_3, I_2, and HOBt and 4 mol equiv of DIPEA, **3** was obtained in 82% yield. However, this reaction was also incomplete, but upon increasing the amount of PPh_3 and I_2 to 3.0 mol equiv and DIPEA to 8.0 mol equiv, an excellent 96% yield of **3** was obtained at room temperature (entry 8).

Entries 9−12 are also quite instructive. It is clear from entries 9 and 10 that the reactions are scalable, and that both the 2′-deoxyriboside **3** as well as the riboside **4** can be readily synthesized on the 0.5 g scale. Entries 11 and 12 indicate that when all components were present in the reaction mixture right at the beginning, the reactions were inefficient, and that best results are obtained when the conversion is conducted as a 2-step, 1-pot process.

Although formation of nucleoside phosphonium salts was proposed in prior studies,[1,2] we had previously shown,[3] for the first time, the presence of such an intermediate in the reaction of **1** with BOP. The phosphonium intermediate then underwent conversion to **3** in the absence of an added nucleophile. In the present case, the nucleoside phosphonium salt formed in situ (from the reaction of $Ph_3P{\cdot}I_2$ and **1**) should undergo a nucleophilic displacement by HOBt with loss of $Ph_3P{=}O$ (Scheme 2). To obtain mechanistic insight into the reaction $^{31}P\{^1H\}$ NMR was utilized to monitor the progress of the reaction (Figure 1).

As shown in panel A of Figure 1, Ph_3P appeared at δ −4.25 ppm. Addition of 3.0 mol equiv of I_2 (1:1 stoichiometry of I_2/PPh_3) resulted in the disappearance of the free phosphine signal and appearance of a new resonance at δ −15.77 ppm, presumably due to $Ph_3P{\cdot}I_2$ (panel B). The reaction of PPh_3 and I_2 can be quite complex, dependent upon solvent and stoichiometry.[6,7] Thus, although we cannot speculate about the exact nature of the complex, the upfield chemical shift observed upon addition of I_2 to PPh_3 was comparable to what has been reported.[7] Upon adding DIPEA (8.0 mol equiv) and **1** (1.0 mol equiv), disappearance of the signal at δ −15.77 ppm was observed with concomitant formation of a new resonance at δ 66.25 ppm, ascribed to the nucleoside phosphonium salt (panel C). A small amount of $Ph_3P{=}O$ was also seen to form (δ 30.60 ppm) probably due to reaction with water present in the NMR solvent. Addition of HOBt (1.5 mol equiv) resulted in a rapid decrease in the signal intensity at δ 66.25 ppm and an increase in the resonance corresponding to $Ph_3P{=}O$ (panel D). Finally, the signal at δ 30.60 ppm corresponding to $Ph_3P{=}O$ was the only persisting resonance after 38 h (panel E). In a separate

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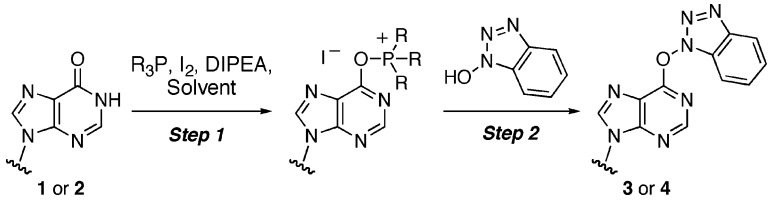
TABLE 1. Analysis of Optimal Reaction Conditions for the Formation of the O^6-(Benzotriazol-1-yl)inosine Derivatives



entry	substrate, mol equiv	R_3P, mol equiv	I_2, mol equiv	DIPEA, mol equiv	HOBt, mol equiv	solvent	conditions step 1 step 2	result
1	**1**, 1.0	HMPT, 1.1	1.1	4.0	1.5	CH_2Cl_2	1: rt, 2 h 2: rt, 20 h	complete **3**:**5** 4:1[a]
2	**1**, 1.0	HMPT, 1.5	1.5	4.0	1.5	CH_2Cl_2	1: rt, 0.5 h 2: rt, 18 h	complete **3**:**5** 11:1[b]
3	**1**, 1.0	PPh_3, 1.5	1.5	4.0	1.5	DMF	1: rt, 20 h 2: rt, 30 h	**3** not formed[c]
4	**1**, 1.0	PPh_3, 3.0	3.0	8.0	1.5	DCE	1: 83 °C, 2 h 2: 83 °C, 25 h	**3** not formed[d]
5	**1**, 1.0	PPh_3, 1.5	1.5	4.0	1.5	THF	1: rt, 2 h 2: 67 °C, 66 h	incomplete **1**:**3** ~1:1[e]
6	**1**, 1.0	PPh_3, 1.5	1.5	4.0	1.5	THF	1: rt, 2 h 2: rt, 66 h	incomplete ~73% **3**[f]
7	**1**, 1.0	PPh_3, 1.5	1.5	4.0	1.5	CH_2Cl_2	1: rt, 8 h then 40 °C, 4 h 2: 67 °C, 66 h	incomplete 82% **3**[g]
8	**1**, 1.0	PPh_3, 3.0	3.0	8.0	1.5	CH_2Cl_2	1: rt, 20 h 2: rt, 30 h	96% **3**[h]
9	**1**, 1.0 (0.5 g)	PPh_3, 3.0	3.0	8.0	1.5	CH_2Cl_2	1: rt, 26 h 2: rt, 22 h	93% **3**[h]
10	**2**, 1.0 (0.5 g)	PPh_3, 3.0	3.0	8.0	1.5	CH_2Cl_2	1: rt, 26 h 2: rt, 22 h	90% **4**[h]
11	**1**, 1.0	PPh_3, 3.0	3.0	8.0	1.5	CH_2Cl_2	rt, 68 h	incomplete ~49% **3**[f]
12	**2**, 1.0	PPh_3, 3.0	3.0	8.0	1.5	CH_2Cl_2	rt, 68 h	incomplete ~21% **4**[f]

[a] Yield ~67%, ratio determined by ^{1}H NMR. [b] Yield ~86%, ratio determined by ^{1}H NMR. [c] TLC indicated presence of **1** but **3** was not observed. [d] TLC indicated consumption of **1** but **3** was not observed. [e] Reaction was incomplete, analyzed by TLC. [f] Reaction was incomplete, analyzed by ^{1}H NMR of the crude reaction mixture. [g] Reaction incomplete, isolated yield of **3**. [h] Isolated yield.

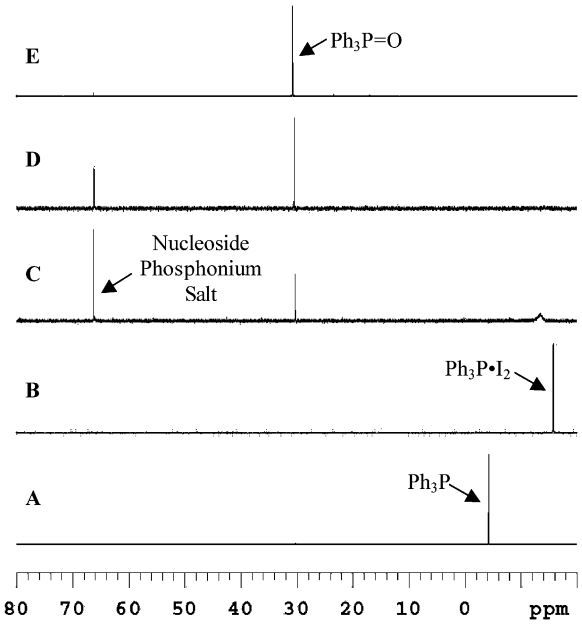


FIGURE 1. Monitoring the progress of the reaction between PPh_3, I_2, **1**, and HOBt in the presence of DIPEA by $^{31}P\{^1H\}$ NMR in $CDCl_3$: (A) PPh_3; (B) 10 min after addition of a stoichiometric amount of I_2 at rt; (C) 1.5 h after addition of DIPEA and **1** at rt; (D) 10 min after addition of HOBt at rt; (E) same as D after 38 h at rt.

experiment, a mixture of PPh_3/I_2/DIPEA/**1** produced by the sequential addition described above, was left to stand in the NMR tube for 18 h at room temperature. The $^{31}P\{^1H\}$ NMR spectrum of this mixture was essentially identical with that shown in panel C except that a slightly greater amount of $Ph_3P{=}O$ was detected along with some other minor phosphorus species. This experiment indicated the longevity of the nucleoside phosphonium salt in solution in the absence of a nucleophile. The isolated yield of **3** from one of these NMR studies was about 67% indicating the predominant pathway to the product.

Since HOBt underwent reaction with the nucleoside phosphonium salt, we queried whether an alcohol would react in a similar manner, as this would provide an alternative to the Mitsunobu etherification.[8] However, reaction of **1** (1.0 mol equiv) with Ph_3P (3.0 mol equiv), I_2 (3.0 mol equiv), EtOH (20 mol equiv), and DIPEA (8 mol equiv) in CH_2Cl_2 led only to recovery of the starting nucleoside. Thus, it appears that the reaction of HOBt with the nucleoside phosphonium salts is rather unique and that simple alcohols do not undergo comparable reactions under the conditions. Nevertheless, this is not a limitation, since we have shown that the O^6-(benzotriazol-1-yl)inosine derivatives undergo facile etherification reactions.[3]

An Unusual Rearrangement of the O^6-(Benzotriazol-1-yl)-inosine Nucleosides 3 and 4. Next, we decided to investigate the utility of **3** and **4** for Pd-catalyzed C−C bond-forming reactions. This was based on our recent success with facile C−C

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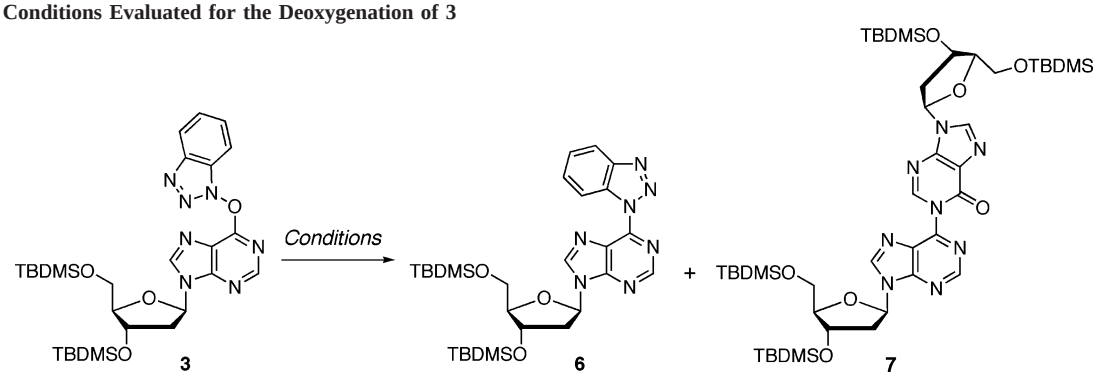
TABLE 2. Conditions Evaluated for the Deoxygenation of 3



entry	conditions	result
1	$Pd(OAc)_2$, 2-(dicyclohexylphosphino)-1,1′-biphenyl, $PhB(OH)_2$, K_3PO_4, PhMe, 6 h at rt, then 16 h at 100 °C	**3** consumed, **6**:**7** ca. 3:2[a]
2	$PhB(OH)_2$, Cs_2CO_3, PhMe, 100 °C, 24 h	**3** unconsumed[b]
3	Cs_2CO_3, PhMe, 100 °C, 15 h	∼80% **3** left and 13% **7**[b]
4	pinB-Bpin, Cs_2CO_3, PhMe, 100 °C, 4 h	**3** consumed, 81% yield of **6**[c]
5	pinB-Bpin, PhMe, 100 °C, 28 h	no reaction[a]
6	(a) pinB-Bpin, Cs_2CO_3, PhMe, rt, 28 h (b) then mixture was heated at 40 °C, 22 h	(a) trace of **6**[a] (b) **3** consumed, predominant formation of **6**[b]

[a] As observed by TLC. [b] Estimated by integration of the H-1′ resonances in the crude product mixture. [c] Yield of isolated, purified product.

bond-forming reactions of 2′-deoxyguanosine and thymidine O^4-arylsulfonates.[9,10] Since these metal-catalyzed reactions of the nucleoside sulfonates involve a C−O bond scission, we wondered whether the excellent leaving group ability of BtO^- would translate to a C−O bond cleavage in **3** and **4** via oxidative addition to Pd. Thus, **3** was exposed to a catalytic complex comprised of $Pd(OAc)_2$ (10 mol %)/2-(dicyclohexylphosphino)-1,1′-biphenyl (20 mol %)/K_3PO_4 (2.0 mol equiv) and $PhB(OH)_2$ (2.0 mol equiv) in toluene. Complete consumption of **3** was observed with the formation of two products in a ∼3:2 ratio (TLC analysis, entry 1 in Table 2). The major product was identified as the *deoxygenated* 6-(1,2,3-benzotriazol-1-yl) nucleoside **6** and the minor product was the previously described unsymmetrical C-6, N-1 dimer **7**.[3] The formation of **7** is likely due to hydrolysis of **3** to the silyl-protected deoxyinosine **1** that then reacts further with **3**. The fact that **6** was the unsymmetrical 1,2,3-benzotriazol-1-yl and not the 1,2,3-benzotriazol-2-yl derivative was obvious from the ^{1}H NMR data that showed four different aromatic protons for the benzotriazolyl moiety. This deoxygenation reaction was probed further to gain greater insight into the transformation, and these experiments and their results are summarized in Table 2.

Bis(pinacolato)diboron (pinB-Bpin) has been utilized as an oxygen atom acceptor in the Cu-catalyzed reduction of CO_2 to CO, resulting in the formation of pinB-O-Bpin.[11] Further, oxidation of pinBH with phosphine oxides and amine oxides has been shown to produce pinB-O-Bpin.[12] Similarly, bis(catecholato)diboron (catB-Bcat) has been shown to undergo conversion to the catB-O-Bcat in the presence of wet bis(triphenylphosphoranylidine)ammonium acetate, possibly by insertion of an oxygen atom from water.[13]

On the basis of the previous observations, we conducted an experiment utilizing pinB-Bpin as the oxygen acceptor (entry 4). In this case complete consumption of **3** was observed within 4 h and resulted in a 81% yield of the deoxygenated product **6**. Since deoxygenation was observed, a subsequent experiment was conducted without Cs_2CO_3 (entry 5). However, in this case no conversion occurred, indicating a synergistic effect of Cs_2CO_3 and pinB-Bpin in this transformation. Although the basis for this is presently unclear, it is possible that coordination of soluble carbonate to the boron center(s) is important. The transformation did not proceed efficiently at room temperature, although consumption of **3** and formation of **6** was observed upon raising the temperature to 40 °C (entry 6). The transformation of **3** to **6** is very clean and can be readily monitored by ^{1}H NMR (Figure 2).

Not only did **3** undergo conversion to **6** but under identical conditions **4** also underwent smooth conversion to the corresponding ribose derivative **8**. To confirm the structures of products **6** and **8**, these were independently synthesized via C−N bond formation between bromo nucleosides **9**[14] and **10**[14] and 1*H*-benzotriazole, catalyzed by $Pd(OAc)_2$/Xantphos/Cs_2CO_3, a system we have recently disclosed as being effective for amination of nucleosides with azolyl nitrogen atoms.[14] Consistent with our previous observations, the products from the Pd-catalyzed reaction were the unsymmetrical 1,2,3-benzotriazol-1-yl products.[14] Scheme 3 shows these two complementary approaches that also confirmed the structures of the deoxygenated products **6** and **8**.

To gain further insight into the unusual deoxygenation reaction, we undertook ^{11}B{^{1}H} NMR experiments (using BF_3·Et_2O as an external standard). For this reason pinB-O-Bpin needed to be independently synthesized. In analogy to the

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(14) Lagisetty, P.; Russon, L. M.; Lakshman, M. K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3660−3663. For the synthesis of the bromo nucleosides please see the Supporting Information.

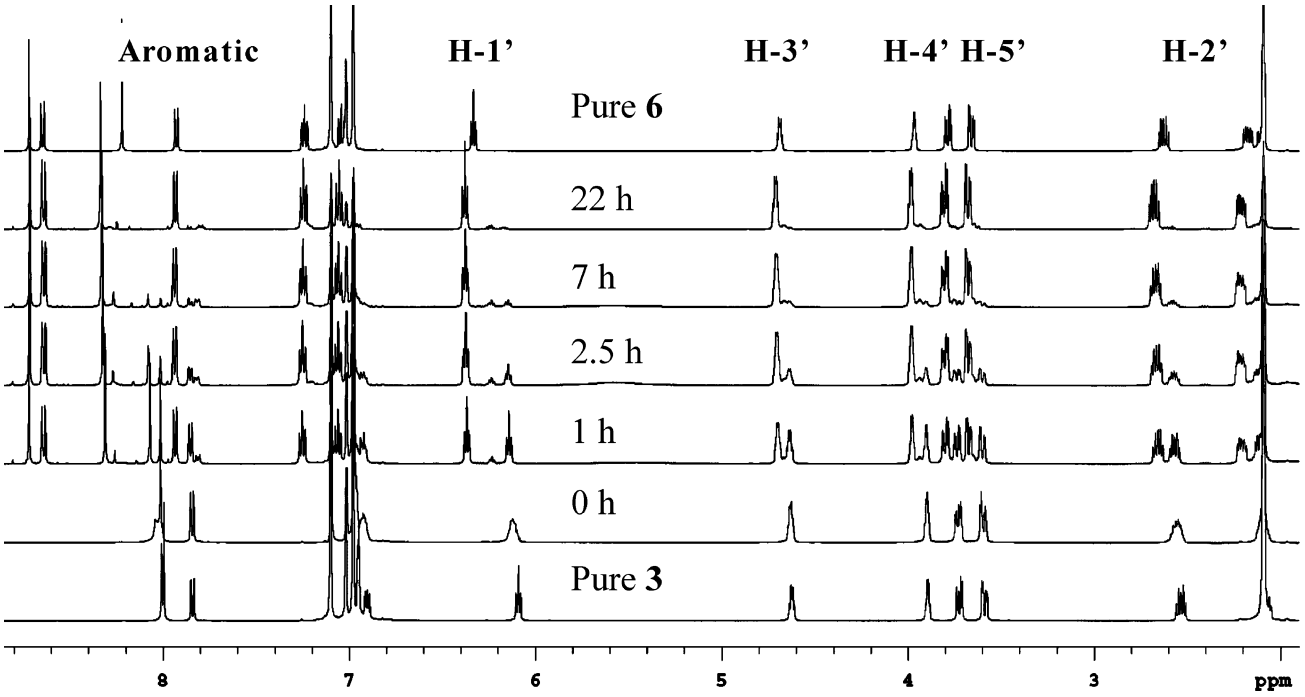
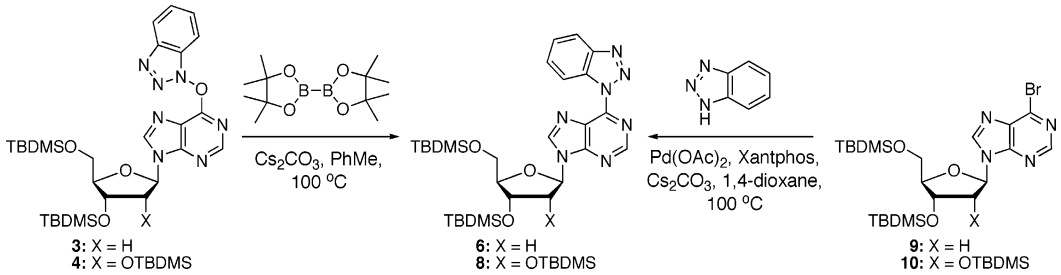


FIGURE 2. Monitoring the conversion of **3** to **6** with pinB-Bpin and Cs_2CO_3 in toluene-d_8 at 100 °C by ^{1}H NMR.

SCHEME 3. Synthesis of the C-6 1,2,3-Benzotriazol-1-yl Nucleosides via Deoxygenation and Pd-Catalyzed C−N Bond Formation



oxidation of pinB-H, oxidation of pinB-Bpin was conducted in toluene at room temperature (see Figure 1 in the Supporting Information).[12] The ^{11}B signal of pinB-Bpin in toluene-d_8 appeared at δ 31.36 ppm and that of pinB-O-Bpin appeared at δ 22.91 ppm.[11,12] With these data in hand the next set of experiments were aimed at understanding the transformation of **3**→**6** using ^{11}B{^{1}H} NMR.

Table 3 shows the nucleoside H-1′, the ^{1}H resonances of pinB-Bpin and pinB-O-Bpin, as well as the ^{11}B resonance as a function of various reaction conditions. As shown in entry **A** of Table 3, no thermal change was observed in the ^{1}H or ^{11}B resonances of pinB-Bpin (a minor resonance pinB-O-Bpin was evident even in the commercial sample of pinB-Bpin). Use of K_2CO_3 instead of Cs_2CO_3 in the reaction did not produce any transformation [entry **B**(a)]. However, addition of Cs_2CO_3 [entry **B**(b)] led to complete formation of **6** within 20 h as seen from the disappearance of the H-1′ resonance of **3** and appearance of the H-1′ corresponding to **6**. Heating pinB-Bpin and Cs_2CO_3 in toluene-d_8 resulted in no formation of pinB-O-Bpin [entry **C**(a)] indicating that Cs_2CO_3 was not the source of the oxygen atom for the oxidation. However, addition of excess **3** led to the appearance of H-1′ corresponding to **6** accompanied by a shift in the methyl resonances of the pinacol moiety and complete formation of pinB-O-Bpin [entry **C**(b)]. Replacement of Cs_2CO_3 with KOAc again led to no reaction [entry **D**].

These collective results indicate a synergism between Cs_2CO_3 and pinB-Bpin for the deoxygenation of O^6-(benzotriazol-1-yl)inosine derivatives, and other bases such as K_2CO_3 and KOAc are ineffective under the conditions tested. It also becomes clear that the oxygen atom for oxidation of pinB-Bpin arises from the (benzotriazol-1-yl)oxy unit of the nucleoside.

In a mechanistic alternative to a one-step process, the deoxygenation could occur via formation of even low amounts of benzotriazolate (BtO^-) from the O^6-(benzotriazol-1-yl) nucleosides (see, for example, Scheme 4).[15] Formation of BtO^- from **3** or **4** followed by an oxygen transfer to pinB-Bpin would produce a resonance-stabilized benzotriazolide that could then cause S_NAr displacement of BtO^- from **3** or **4**. In such a process the actual oxidation of pinB-Bpin would occur by the formed BtO^- and will continue until either the O^6-(benzotriazol-1-yl) nucleoside or pinB-B-pin is completely consumed. To test for the possibility of such an operative mechanism, a series of experiments were conducted. HOBt (2 mol equiv) was exposed to pinB-Bpin (1 mol equiv) in the presence of Cs_2CO_3 (2 mol equiv) in toluene at 100 °C, and this was monitored by ^{11}B-{^{1}H} NMR. The pinB-Bpin resonance disappeared and a new signal appeared at the region where the pinB-O-Bpin resonance

(15) We thank a reviewer for comments that led us to additional investigations of the possible mechanism.

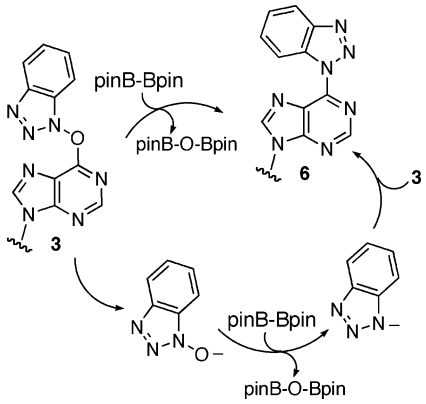
TABLE 3. Monitoring the Conversion of 3→6 and pinB-Bpin→pinB-O-Bpin by ^{1}H and ^{11}B{^{1}H} NMR in Toluene-d_8[a]

entry	conditions	H-1′ of Nucleoside	pinB-Bpin and/or pinB-O-Bpin ^{1}H NMR (CH_3)[b]	pinB-Bpin and/or pinB-O-Bpin ^{11}B{^{1}H} NMR[c]
A	pinB-Bpin, 100 °C, 36 h	None		
B	(a) pinB-Bpin (2 mol eq), **3** (1 mol eq), K_2CO_3 (2 mol eq), 100 °C, 24 h	**3**		
	(b) then Cs_2CO_3 (2 mol eq), 100 °C, 20 h	**6**		
C	(a) pinB-Bpin (1 mol eq), Cs_2CO_3 (2 mol eq), 100 °C, 24 h	None		
	(b) then **3** (2.4 mol eq), 100 °C, 7 h[d]	**6** **3**		
D	pinB-Bpin (2 mol eq), **3** (1 mol eq), KOAc (2 mol eq), 100 °C, 21 h	**3**		

6.40 6.20 ppm | 1.26 1.18 1.10 ppm | 33 29 25 ppm

[a] The reactions were performed at similar concentrations of pinB-Bpin (**A**: 0.075 M; **B**: 0.085 M; **C**: 0.084 M; **D**: 0.089 M). [b] In toluene-d_8 ^{1}H resonance of pinB-Bpin appeared at δ 1.02 ppm and that of pinB-O-Bpin at δ 1.05 ppm. [c] In toluene-d_8 ^{11}B signal of pinB-Bpin appeared at δ 31.36 ppm and that of pinB-O-Bpin at δ 22.91 ppm. [d] Slight downfield shifts of the H-1′ resonances during the reaction course are an artifact (see Figure 2).

SCHEME 4. Possible Mechanisms for the Deoxygenation Reaction



is observed (panel **A**(a) in Table 4 compared with panel **C**(b) in Table 3). Addition of **3** (1 mol equiv) and continued heating at 100 °C for 27 h led to complete consumption of **3** and the formation of **6** that was isolated in 73% yield. A noteworthy point is that **6** is formed and is stable in the presence of excess HOBt and Cs_2CO_3, indicating that S_NAr displacement of benzotriazolide does not occur. Some other interesting features were also observed and are described below.

Although pinB-Bpin was stable to elevated temperature (panel **A**, Table 3) in toluene, exposure to HOBt (2 mol equiv) in the *absence* of Cs_2CO_3 led to ^{11}B resonances different from that observed in the presence of Cs_2CO_3 (panel **A**(a) compared to panel **B** in Table 4). This indicates that interactions of pinB-Bpin with HOBt may be different depending upon the presence or absence of Cs_2CO_3. Replacement of Cs_2CO_3 with K_2CO_3 or KOAc again led to different ^{11}B NMR patterns (panel **C**(a) and panel **D**(a) in Table 4). However, in each of these cases, addition of **3** and continued heating led to some formation of product **6** (panel **C**(b) and panel **D**(b) in Table 4), but these reactions were incomplete and were not as clean as with Cs_2CO_3 (~6% **6** with K_2CO_3 and ~63% **6** with KOAc). A major difference emerges in these cases where HOBt was allowed to react initially with pinB-Bpin in the presence of a base prior to addition of **3**. As can be seen from panels **B** and **D** of Table 3, when **3** was present at the beginning of reactions involving K_2CO_3 or KOAc, formation of **6** was not observed. Finally, an experiment was conducted to determine whether benzotriazole could produce displacement of BtO^-. Reaction of **3** with benzotriazole in the presence of Cs_2CO_3 in toluene at 100 °C led to a 67% yield of **6** within 4 h. Thus, from a mechanistic consideration, it is conceivable that a formation of BtO^- and its reduction to benzotriazolide could result in product formation. However, the deoxygenation may be a complex process, with more than one contributing pathway.

Synthesis of 1,N^6-Ethano- and 1,N^6-Propano-2′-deoxyadenosine Analogues. Alkylating nitrosoureas as a class are used in the chemotherapy of solid tumors and leukemias.[16] Among these, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU, carmustine) is a potent analogue for the treatment of brain tumors.[17] The DNA cross-linking properties of 2-chloroethyl-1-nitrosoureas are associated with their anti-tumor activities.[18] However, the reaction of BCNU with DNA results in a variety of other alkylation products, one of which is 1,N^6-ethano-2′-deoxyadenosine.[19] This compound is related to the 1,N^6-ethenoadenine derivatives that are formed from the reaction of the carcinogen vinyl chloride with 9-methyladenine[20] or adenosine.[21] Since the hydrogen-bonding sites of 2′-deoxyadenosine are directly involved in the ring formation, synthetic access to 1,N^6-ethano-2′-deoxyadenosine has been of interest in order to understand the biological consequences to its formation in DNA. 1,N^6-

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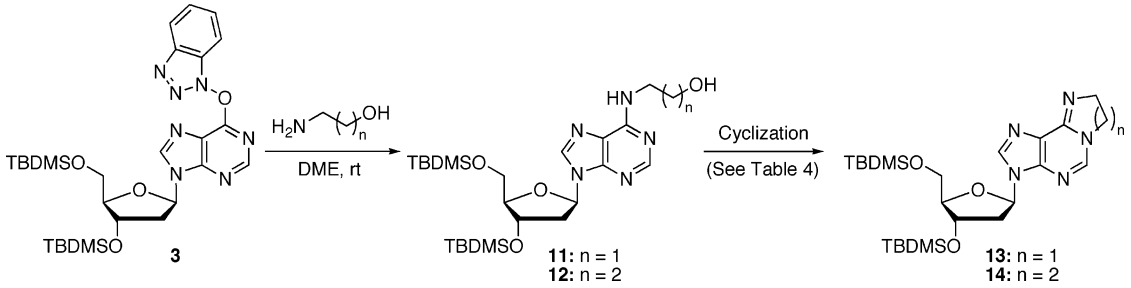
TABLE 4. Monitoring the Conversion of 3→6 and pinB-Bpin→pinB-O-Bpin by ^{1}H and ^{11}B{^{1}H} NMR in Toluene-d_8 in the Presence of Added HOBt[a]

entry	conditions	H-1' of Nucleoside	pinB-Bpin and/or pinB-O-Bpin ^{1}H NMR (CH_3)[b]	pinB-Bpin and/or pinB-O-Bpin ^{11}B{^{1}H} NMR[c]
A	(a) pinB-Bpin (1 mol eq), HOBt (2 mol eq), Cs_2CO_3 (2 mol eq), 100 °C, 18 h	None		
	(b) then **3** (1 mol eq), 100 °C, 24 h[d]	**6** **3**		
B	pinB-Bpin (1 mol eq), HOBt (2mol eq), 100 °C, 44 h	None		
C	(a) pinB-Bpin (1 mol eq), HOBt (2 mol eq), K_2CO_3 (2 mol eq), 100 °C, 18 h	None		
	(b) **3** (1 mol eq), 100 °C, 24 h[e]	**6** **3**		
D	(a) pinB-Bpin (1 mol eq), HOBt (2 mol eq), KOAc (2 mol eq), 100 °C, 18 h	None		
	(b) **3** (1 mol eq), 100 °C, 24 h[f]	**6** **3**		
		6.60 6.40 6.20 ppm	1.26 1.18 1.10 ppm	38 32 26 ppm

[a] The reactions were performed at similar concentrations of pinB-Bpin (**A**: 0.072 M; **B**: 0.068 M; **C**: 0.070 M; **D**: 0.069 M). [b] In toluene-d_8 ^{1}H resonance of pinB-Bpin appeared at δ 1.02 ppm and that of pinB-O-Bpin at δ 1.05 ppm. [c] In toluene-d_8 ^{11}B signal of pinB-Bpin appeared at δ 31.36 ppm and that of pinB-O-Bpin at δ 22.91 ppm. [d] Compound **6** was isolated (73% yield). [e] The ratio of **3**:**6** ~94:6 by ^{1}H NMR (in $CDCl_3$) of the crude mixture. [f] The ratio of **3**:**6**:unknown ~32:63:5 by ^{1}H NMR (in $CDCl_3$) of the crude mixture.

SCHEME 5. Synthesis of 1,N^6-Ethano- (13) and 1,N^6-propano-2′-deoxyadenosine (14)



Ethano-2′-deoxyadenosine has previously been synthesized from 6-chloro-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine, a compound that is not easily synthesized.[22,23]

We reasoned that **3** would not only be a suitable precursor to 1,N^6-ethano-2′-deoxyadenosine, but the synthetic methodology would be adequately flexible to accommodate chain length variation. This led us to consider the synthesis of 1,N^6-propano-2′-deoxyadenosine as well. Our approach to the synthesis of these two compounds is shown in Scheme 5.

In our previous report on O^6-(benzotriazol-1-yl)inosine nucleosides we had described that **3** could undergo reactions with both alcohols and amines; however, the former required Cs_2CO_3.[3] Using this difference in reactivity, in the present case **3** was allowed to react with either 2-aminoethanol or 3-amino-1-propanol in 1,2-dimethoxyethane (DME) at room temperature. The amination products **11** and **12** were obtained in excellent 95% and 96% yields, respectively. Conversion of the terminal hydroxyl group in **11** and **12** to an iodide should result in spontaneous cyclization to **13** and **14**. For this cyclization two methods were evaluated: $(PhO)_3P^+MeI^-/Et_3N$ in DMF[22,24] and PPh_3/I_2/DIPEA/CH_2Cl_2. The results from these experiments are shown in Table 5. Both sets of reagents produced the desired cyclization in reasonably comparable yields. Interestingly, DIPEA proved to be suitable in the reaction involving PPh_3/I_2 and its replacement with imidazole proved unsatisfactory.

In summary, in this continued investigation on the reactions of the new class of O^6-(benzotriazol-1-yl)inosine nucleosides, we have discovered an unusual deoxygenation reaction that results in the formation of C-6 benzotriazol-1-yl purine nucleosides. This reaction has been probed in detail, and proceeds in the presence of pinB-Bpin and Cs_2CO_3 but without need for any metal catalyst. Although this deoxygenative C−O−N →

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TABLE 5. Conditions Tested for the Cyclization of 11 and 12

entry	substrate	cyclization conditions	product, yield[a]
1	**11**, $n = 1$	$(PhO)_3P^+MeI^-$, Et_3N, DMF, rt, 3 h	**13**, 51% (67%)[b]
2	**11**, $n = 1$	PPh_3, I_2, DIPEA, CH_2Cl_2, rt, 8 h	**13**, 61%
3	**12**, $n = 2$	$(PhO)_3P^+MeI^-$, Et_3N, DMF, rt, 3 h	**14**, 78%
4	**12**, $n = 2$	PPh_3, I_2, DIPEA, CH_2Cl_2, rt, 8 h	**14**, 62%

[a] Yield of isolated and purified product. [b] Yield reported in ref 22.

C−N transformation does not appear to have prior precedent, whether such deoxygenation can be applied to other classes of compounds is an interesting question. The structures of the C-6 benzotriazol-1-yl purine nucleosides, produced by the deoxygenation, were unambiguously ascertained via a Pd-catalyzed amination methodology. Finally, we have demonstrated that silyl protected O^6-(benzotriazol-1-yl)-2′-deoxyinosine (**3**) can be used for the synthesis of nontrivial nucleoside derivatives such as that arising from the reaction of BCNU with 2′-deoxyadenosine residues in DNA, circumventing the use of the 6-chloropurine nucleoside as precursor. All these results contribute to a greater understanding of the chemistry and applications of these new compounds.

Experimental Section

***O*^{6}-(Benzotriazol-1-yl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (3).**[3] In a 50 mL round-bottomed flask equipped with a stirring bar were placed PPh_3 (823 mg, 3.14 mmol) and I_2 (800 mg, 3.15 mmol) in dry CH_2Cl_2 (11.0 mL), and the mixture was allowed to stir at room temperature for 20 min. DIPEA (1.5 mL, 8.62 mmol) and 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (**1**) (500 mg, 1.04 mmol) were added, and the mixture was allowed to stir at room temperature for 26 h. To this mixture was added HOBt (0.211 g, 1.561 mmol) and the stirring was continued for 22 h at which point the reaction was complete. The mixture was evaporated to dryness and chromatographic purification of the crude product mixture (SiO_2, elution with 20% EtOAc in hexanes) gave 578 mg (93% yield) of compound **3** as a beige foam.

***O*^{6}-(Benzotriazol-1-yl)-2′,3′,5′-tris-*O*-(*tert*-butyldimethylsilyl)-inosine (4).**[3] As described for the synthesis of O^6-(benzotriazol-1-yl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (**3**), this ribose derivative was prepared by reaction of PPh_3 (645 mg, 2.46 mmol), I_2 (632 mg, 2.49 mmol), DIPEA (1.2 mL, 6.89 mmol), 2′,3′,5′-tris-*O*-(*tert*-butyldimethylsilyl)inosine (**2**) (500 mg, 0.818 mmol), and HOBt (166 mg, 1.23 mmol) in dry CH_2Cl_2 (9.0 mL). Evaporation of the reaction mixture and chromatographic purification (SiO_2, elution with 20% EtOAc in hexanes) gave 537 mg (90% yield) of compound **4** as a yellowish-white foam.

6-(Benzotriazol-1-yl)-9-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-*β*-D-ribofuranosyl]purine (6). Method A. In a clean, dry vial equipped with a stirring bar were placed O^6-(benzotriazol-1-yl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (**3**) (90.7 mg, 0.152 mmol), pinB-Bpin (41.4 mg, 0.163 mmol), and Cs_2CO_3 (98.0 mg, 0.301 mmol). Dry toluene (1.5 mL) was added, the reaction vial was flushed with nitrogen gas, and the mixture was allowed to stir at 100 °C for 4 h. The reaction mixture was diluted with EtOAc then filtered through Celite and the residue was washed with EtOAc. The filtrate was evaporated to dryness and the resulting solid residue was triturated with *n*-pentane to give 56.4 mg (64% yield) of **6** as a beige powder. The material obtained by evaporation of the mother liquor from the trituration was purified by flash chromatography (SiO_2, elution with 20% EtOAc in hexanes) to give an additional 14.8 mg (17%) of compound **6** for a total yield of 81%. R_f (SiO_2, 20% EtOAc in hexanes) 0.07. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.99 (s, 1H, Ar−H), 8.75 (d, 1H, Ar−H, $J = 8.2$ Hz), 8.58 (s, 1H, Ar−H), 8.23 (d, 1H, Ar−H, $J = 8.2$ Hz), 7.68 (t, 1H, Ar−H, $J = 7.6$ Hz), 7.52 (t, 1H, Ar−H, $J = 7.5$ Hz), 6.64 (t, 1H, H−1′, $J = 6.7$ Hz), 4.66 (app quint, 1H, H−3′, $J \approx 2.9$ Hz), 4.09 (q, 1H, H−4′, $J = 3.4$ Hz), 3.89 (dd, 1H, H−5′, $J = 11.3$, 4.1 Hz), 3.81 (dd, 1H, H−5′, $J = 11.3$, 3.1 Hz), 2.69 (m, 1H, H−2′), 2.53 (ddd, 1H, H−2′, $J = 13.1$, 6.1, 3.4 Hz), 0.94, 0.91 (2s, 18H, *t*-Bu), 0.13, 0.10, 0.09 (3s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.7, 151.6, 147.5, 146.2, 144.1, 132.0, 129.3, 125.4, 123.8, 120.2, 115.0, 88.2 (C−4′), 84.6 (C−1′), 72.1 (C−3′), 62.8 (C−5′), 41.4 (C−2′), 25.9, 25.7, 18.4, 17.9, −4.7, −4.8, −5.4, −5.5. ESI HRMS calcd for $C_{28}H_{43}N_7O_3Si_2Na$ ($M^+ + Na$) 604.285812, found 604.2852534.

Method B. In a clean, dry vial equipped with a stirring bar were placed 6-bromo-9-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-*β*-D-ribofuranosyl]purine (**9**)[14] (65.7 mg, 0.121 mmol), $Pd(OAc)_2$ (3.0 mg, 13.4 μmol), Xantphos (10.5 mg, 18.1 μmol), 1*H*-benzotriazole (28.6 mg, 0.240 mmol), and Cs_2CO_3 (59.1 mg, 0.123 mmol) in 1,4-dioxane (1.0 mL). The reaction vial was flushed with nitrogen gas and the mixture was allowed to stir at 100 °C for 4 h. The reaction mixture was diluted with EtOAc then filtered through Celite, and the residue was washed with EtOAc. The filtrate was evaporated to dryness and chromatographic purification of the crude material (SiO_2, elution with 20% EtOAc in hexanes followed by 5% MeOH in CH_2Cl_2) afforded 54.8 mg (78% yield) of compound **6** as a beige solid.

6-(Benzotriazol-1-yl)-9-[2,3,5-tris-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (8). Method A. As described for the synthesis of benzotriazolyl derivative **6**, compound **8** was prepared by reaction of O^6-(benzotriazol-1-yl)-2′,3′,5′-tris-*O*-(*tert*-butyldimethylsilyl)inosine (**4**) (111.4 mg, 0.153 mmol), pinB-Bpin (42.2 mg, 0.166 mmol), and Cs_2CO_3 (100.5 mg, 0.308 mmol) in dry toluene (1.5 mL) at 100 °C over 4 h. Workup as described under Method A for **6** followed by chromatographic purification (SiO_2, 10% EtOAc in hexanes) afforded 86.1 mg (79% yield) of compound **8** as a white foam. R_f (20% EtOAc in hexanes) 0.34. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.99 (s, 1H, Ar−H), 8.77 (d, 1H, Ar−H, $J = 8.2$ Hz), 8.61 (s, 1H, Ar−H), 8.23 (d, 1H, Ar−H, $J = 8.5$ Hz), 7.68 (t, 1H, Ar−H, $J = 7.3$ Hz), 7.52 (t, 1H, Ar−H, $J = 7.5$ Hz), 6.26 (d, 1H, H−1′, $J = 5.8$ Hz), 4.71 (app t, 1H, H−2′, $J \approx 4.9$ Hz), 4.35 (t, 1H, H−3′, $J = 3.8$ Hz), 4.19 (br q, 1H, H−4′, $J = 3.1$ Hz), 4.03 (dd, 1H, H−5′, $J = 11.5$, 3.7 Hz), 3.83 (dd, 1H, H−5′, $J = 11.3$, 2.7 Hz), 0.97, 0.962, 0.96, 0.79 (4s, 27H, *t*-Bu), 0.17, 0.16, 0.12, −0.03, −0.25 (5s, 18H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 151.7 (purinyl C), 147.7, 146.3, 144.5 (purinyl C), 132.1, 129.4 (benzotriazolyl C), 125.5 (benzotriazolyl C), 123.9, 120.3 (benzotriazolyl C), 115.1 (benzotriazolyl C), 88.2 (C−1′), 86.0 (C−4′), 76.2 (C−2′), 72.2 (C−3′), 62.7 (C−5′), 26.1, 25.8, 25.6, 18.6, 18.1, 17.8, −4.4, −4.6, −4.7, −5.0, −5.3, −5.34. ESI HRMS calcd for $C_{34}H_{57}N_7O_4Si_3Na$ ($M^+ + Na$) 734.367204, found 734.365678.

Method B. As described for the synthesis of benzotriazolyl derivative **6**, compound **8** was prepared by a reaction of 6-bromo-9-[2,3,5-tris-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (**10**)[14] (67.8 mg, 0.101 mmol), $Pd(OAc)_2$ (2.8 mg, 12.5 μmol), Xantphos (8.7 mg, 15.0 μmol), 1*H*-benzotriazole (24.4 mg, 0.205 mmol), and Cs_2CO_3 (46.3 mg, 0.142 mmol) in 1,4-dioxane (1.0 mL). The reaction vial was flushed with nitrogen gas and the mixture was stirred at 100 °C for 24 h. Workup as described under Method B for compound **6** followed by chromatographic purification (SiO_2, elution with 10% EtOAc in hexanes followed by 20% EtOAc in hexanes) afforded 64.2 mg (90% yield) of the compound **8** as a white, foamy solid.

***N*^{6}-(2-Hydroxyethyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (11).**[22] In a clean flask equipped with a stirring bar and balloon filled with nitrogen gas were placed O^6-(benzotriazol-1-yl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (**3**) (317 mg, 0.530 mmol) and 2-aminoethanol (0.13 mL, 2.2 mmol) in dry DME (5.0 mL). The mixture was allowed to stir for 4 h at room temperature and then concentrated under reduced pressure. Chromatographic purification (SiO_2, elution with 5% MeOH in CH_2-

Cl_2) afforded 265 mg (95% yield) of compound **11** as a clear gum. R_f (5% MeOH in CH_2Cl_2) 0.18. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (s, 1H, Ar−H), 8.11 (s, 1H, Ar−H), 6.44 (t, 1H, H-1′, J = 6.4 Hz), 6.28 (br s, 1H, NH, D_2O exchangeable), 4.65 (br, 1H, OH, D_2O exchangeable), 4.60 (dt, 1H, H−3′, J = 5.8, 3.7 Hz), 4.01 (app q, 1H, H−4′, $J \approx$ 3.7 Hz), 3.90 (br, 2H, CH_2), 3.87 (dd, 1H, H−5′, J = 11.3, 4.3 Hz), 3.81 (br, 2H, CH_2), 3.77 (dd, 1H, H−5′, J = 11.3, 3.1 Hz), 2.62 (app quint, 1H, H−2′, $J \approx$ 6.3 Hz), 2.43 (ddd, 1H, H−2′, J = 13.1, 6.3, 4.1 Hz), 0.92, 0.91 (2s, 18H, *t*-Bu), 0.10, 0.09 (2s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.9, 152.9, 148.4, 138.0, 119.8, 87.7, 84.3, 71.5, 62.6, 61.9, 43.7, 41.4, 25.9, 25.7, 18.4, 17.9, −4.7, −4.9, −5.5, −5.54. ESI HRMS calcd for $C_{24}H_{45}N_5O_4Si_2Na$ (M^+ + Na) 546.290229, found 546.2899493.

N^6-(3-Hydroxypropyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (12). As described for the synthesis of **11**, compound **12** was prepared by reaction of O^6-(benzotriazol-1-yl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (**3**) (363 mg, 0.608 mmol) and 3-amino-1-propanol (0.20 mL, 2.6 mmol) in dry DME (6.0 mL) at room temperature over 14 h. Evaporation of the reaction mixture and chromatographic purification of the crude material (SiO_2, elution with 5% MeOH in CH_2Cl_2) afforded 313 mg (96% yield) of compound **12** as a brownish gum. R_f (5% MeOH in CH_2Cl_2) 0.15. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (s, 1H, Ar−H), 8.10 (s, 1H, Ar−H), 6.44 (t, 1H, H−1′, J = 6.4 Hz), 5.89 (br, 1H, NH, D_2O exchangeable), 4.72 (br, 1H, OH, D_2O exchangeable), 4.61 (app dt, 1H, H−3′, $J \approx$ 6.0, 3.6 Hz), 4.01 (app q, 1H, H−4′, $J \approx$ 3.6 Hz), 3.87 (dd, 1H, H−5′, J = 11.3, 4.3 Hz), 3.81 (br, 2H, CH_2), 3.77 (dd, 1H, H−5′, J = 11.3, 3.4 Hz), 3.62 (br, 2H, CH_2), 2.63 (app quint, 1H, H−2′, $J \approx$ 6.4 Hz), 2.43 (ddd, 1H, H−2′, J = 13.1, 6.1, 4.0 Hz), 1.82 (br app quint, 2H, CH_2, $J \approx$ 5.6 Hz), 0.92, 0.91 (2s, 18H, *t*-Bu), 0.10, 0.09, 0.087 (3s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 152.8, 148.4, 138.4, 119.8, 87.8, 84.3, 71.8, 62.7, 58.1, 41.2, 36.8, 33.2, 25.9, 25.7, 18.4, 18.0, −4.7, −4.8, −5.4, −5.5. ESI HRMS calcd for $C_{25}H_{47}N_5O_4Si_2Na$ (M^+ + Na) 560.305879, found 560.304681.

1,N^6-Ethano-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl-2′-deoxyadenosine (13).[22] **Method A.** In a clean flask equipped with a stirring bar and balloon filled with nitrogen gas was placed N^6-(2-hydroxyethyl)-3′,5′-*O*-bis-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (**11**) (117.0 mg, 0.223 mmol). Dry DMF (3.0 mL) and Et_3N (0.20 mL, 1.4 mmol) were added and the mixture was cooled in an ice bath. $(PhO)_3P^+MeI^-$ (397 mg, 0.878 mmol) was then added and the reaction mixture was brought to room temperature and allowed to stir for 3 h, then concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 and washed with 5% aqueous $NaHCO_3$ followed by brine. The organic layer was separated, dried over Na_2SO_4, and evaporated to dryness. Chromatographic purification (SiO_2, elution with 0.5/5/90 Et_3N/MeOH/CH_2Cl_2) afforded 57.0 mg (51% yield) of ethano nucleoside **13** as a yellow, gummy foam. R_f (0.5/5/90 Et_3N/MeOH/CH_2Cl_2) 0.16. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (s, 1H, Ar−H), 7.94 (s, 1H, Ar−H), 6.29 (t, H−1′, J = 6.4 Hz), 4.56 (m, 1H, H−3′), 4.34−4.30 (m, 2H, CH_2), 4.20 (app t, 3H, CH_2, $J \approx$ 9.2 Hz), 3.98 (br q, 1H, H−3′, J = 3.6 Hz), 3.78 (dd, 1H, H−5′, J = 11.3, 4.4 Hz), 3.74 (dd, 1H, H−5′, J = 11.3, 3.4 Hz), 2.49 (app quint, 1H, H−2′, $J \approx$ 6.4 Hz), 2.37 (ddd, 1H, J = 13.1, 6.1, 3.7 Hz), 0.90, 0.89 (2s, 18H, *t*-Bu), 0.09, 0.07, 0.06 (3s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.0, 145.2, 143.3, 137.8, 119.9, 87.9 (C−4′), 84.2 (C−1′), 71.8 (C−3′), 62.7 (C−5′), 52.0 (NCH_2), 47.0 (NCH_2), 41.3 (C−2′), 25.9, 25.7, 18.3, 17.9, −4.7, −4.9, −5.4, −5.5. ESI HRMS calcd for $C_{24}H_{44}N_5O_3Si_2$ (M^+ + H) 506.297720, found 506.296320.

Method B. In a clean, dry vial equipped with a stirring bar were placed PPh_3 (131 mg, 0.501 mmol) and I_2 (124 mg, 0.488 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction vial was flushed with nitrogen gas and the mixture was stirred at room temperature for 20 min. DIPEA (0.25 mL, 1.4 mmol) and a solution of nucleoside **11** (86.0 mg, 0.164 mmol) in CH_2Cl_2 (3.0 mL) were added, the reaction vial was again flushed with nitrogen gas, and the mixture was allowed to stir at room temperature for 8 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 5% aqueous $NaHCO_3$ followed by brine. The organic layer was separated, dried over Na_2SO_4, and evaporated to dryness. Chromatographic purification (SiO_2, elution with 0.5/5/90 Et_3N/MeOH/CH_2Cl_2) afforded 51.0 mg (61% yield) of compound **13** as a brown foam.

1,N^6-Propano-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (14). Method A. In a clean flask equipped with a stirring bar and balloon filled with nitrogen gas was placed nucleoside **12** (89.3 mg, 0.166 mmol). Dry DMF (2.0 mL) and Et_3N (0.12 mL, 0.86 mmol) were added and the mixture was cooled in an ice bath. $(PhO)_3P^+MeI^-$ (188 mg, 0.415 mmol) was added and the reaction mixture was brought to room temperature and allowed to stir for 2 h. At this time the reaction was 50% complete based upon TLC analysis and therefore additional $(PhO)_3P^+MeI^-$ (180 mg, 0.398 mmol) was added to the mixture at room temperature. The reaction was allowed to proceed for an additional 1 h at which time it was complete. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 and then washed with 5% aqueous $NaHCO_3$ followed by brine. The organic layer was separated, dried over Na_2SO_4, and evaporated to dryness. Chromatographic purification (SiO_2, elution with 1/5/95 Et_3N/MeOH/CH_2Cl_2 then 1/10/95 Et_3N/MeOH/CH_2Cl_2) afforded 67.0 mg (78% yield) of compound **14** as a white, foamy solid. R_f (0.5/5/90 Et_3N/MeOH/CH_2Cl_2) 0.07. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (s, 1H, Ar−H), 7.34 (s, 1H, Ar−H), 6.25 (t, 1H, H−1′, J = 6.4 Hz), 4.56 (br m, 1H, H−3′), 3.96 (m, 1H, H−4′), 3.93 (br t, 2H, CH_2, J = 5.8 Hz), 3.78 (dd, 1H, H−5′, J = 11.0, 4.4 Hz), 3.74 (dd, 1H, H−5′, J = 11.0, 3.4 Hz), 3.65 (t, 2H, CH_2, J = 5.5 Hz), 2.49 (app quint, 1H, H−2′, $J \approx$ 6.4 Hz), 2.34 (ddd, 1H, H−2′, J = 13.0, 6.0, 4.0 Hz), 2.03 (br quint, 2H, CH_2, $J \approx$ 5.6 Hz), 0.90, 0.897 (2s, 18H, *t*-Bu), 0.08, 0.06 (2s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.3, 142.8, 141.1, 136.1, 124.4, 87.6 (C−4′), 83.7 (C−1′), 71.6 (C−3′), 62.6 (C−5′), 47.0 (NCH_2), 43.5 (NCH_2), 41.1 (C−2′), 25.8, 25.6, 20.7 (−CH_2−), 18.3, 17.8, −4.8, −4.9, −5.5, −5.6. ESI HRMS calcd for $C_{25}H_{46}N_5O_3Si_2$ (M^+ + H) 520.313370, found 520.312607

Method B. As described under Method B for the synthesis of 1,N^6-ethano-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (**13**), compound **14** was prepared by a reaction between N^6-(3-hydroxypropyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (**12**) (94.3 mg, 0.175 mmol), PPh_3 (138 mg, 0.527 mmol), I_2 (134 mg, 0.528 mmol), and DIPEA (0.25 mL, 1.4 mmol) in dry CH_2Cl_2 (6 mL). The reaction was complete within 8 h. Workup as described under Method B for compound **13** followed by chromatographic purification (SiO_2, elution with 0.5/5/90 Et_3N/MeOH/CH_2Cl_2 followed by 0.5/10/90 Et_3N/MeOH/CH_2Cl_2) afforded 56.0 mg (62% yield) of compound **14** as a beige foam.

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Supporting Information Available: ^{11}B{^{1}H} NMR spectra of pinB-Bpin and pinB-O-Bpin, ^{1}H and ^{13}C NMR spectra of **6**, **8**, **11**, **12**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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