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A novel bis(pinacolato)diboron-mediated N–O bond deoxygenative route to C6 benzotriazolyl purine nucleoside derivatives[†]

Vikram Basava^a, Lijia Yang^a, Padmanava Pradhan^a, and Mahesh K. Lakshman^{a,b}

Mahesh K. Lakshman: mlakshman@ccny.cuny.edu

^aDepartment of Chemistry, The City College of New York, 160 Convent Avenue, New York, New York, 10031, USA

^bThe Ph.D. Program in Chemistry, The Graduate Center of the City University of New York, New York, New York 10016, USA

Abstract

Reaction of amide bonds in *t*-butyldimethylsilyl-protected inosine, 2'-deoxyinosine, guanosine, 2'-deoxyguanosine, and 2-phenylinosine with commercially available peptide-coupling agents (benzotriazol-1*H*-yloxy)tris(dimethylaminophosphonium) hexafluorophosphate (BOP), (6-chloro-benzotriazol-1*H*-yloxy)trispyrrolidinophosphonium hexafluorophosphate (PyClocK), and (7-azabenzotriazol-1*H*-yloxy)trispyrrolidinophosphonium hexafluorophosphate (PyAOP) gave the corresponding *O*⁶-(benzotriazol-1-yl) nucleoside analogues containing a C–O–N bond. Upon exposure to bis(pinacolato)diboron and base, the *O*⁶-(benzotriazol-1-yl) and *O*⁶-(6-chlorobenzotriazol-1-yl) purine nucleoside derivatives obtained from BOP and PyClocK, respectively, underwent N–O bond reduction and C–N bond formation, leading to the corresponding C6 benzotriazolyl purine nucleoside analogues. In contrast, the 7-azabenzotriazolyl purine nucleoside derivatives did not undergo efficient deoxygenation, but gave unsymmetrical nucleoside dimers instead. This is consistent with a prior report on the slow reduction of 1-hydroxy-1*H*-4-aza and 1-hydroxy-1*H*-7-azabenzotriazoles. Because of the limited number of commercial benzotriazole-based peptide coupling agents, and to show applicability of the method when such coupling agents are unavailable, 1-hydroxy-1*H*-5,6-dichlorobenzotriazole was synthesized. Using this compound, silyl-protected inosine and 2'-deoxyinosine were converted to the *O*⁶-(5,6-dichlorobenzotriazol-1-yl) derivatives via *in situ* amide activation with PyBroP. The *O*⁶-(5,6-dichlorobenzotriazol-1-yl) purine nucleosides so obtained also underwent smooth reduction to afford the corresponding C6 5,6-dichlorobenzotriazolyl purine nucleoside derivatives. A total of 13 examples were studied with successful reactions occurring in 11 cases (the azabenzotriazole derivatives, mentioned above, being the only unreactive entities). To understand whether these reactions are intra or intermolecular processes, a crossover experiment was conducted. The results of this experiment as well as those from reactions conducted in the absence of bis(pinacolato)diboron and in the presence of water indicate that detachment of the

[†]Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, and copies of ¹H and ¹³C NMR spectra.

Correspondence to: Mahesh K. Lakshman, mlakshman@ccny.cuny.edu.

benzotriazoloxy group from the nucleoside likely occurs, followed by reduction, and reattachment of the ensuing benzotriazole, leading to products.

Graphical Abstract

Introduction

Nucleosides are central to life processes and, therefore, it is not altogether unexpected that modified nucleosides continue to play a major role in biochemistry, biology, as probes of biological processes, and as pharmaceuticals.^{1–10} In the context of developing novel approaches to modified nucleosides, we and others have been involved with the development of $\text{S}_{\text{N}}\text{Ar}$ reactions of nucleosides *not* involving conventional leaving groups such as halides and sulfonates.^{11–19} Specifically, our efforts have been directed towards the use of benzotriazole-based peptide-coupling agents for activation of the amide groups in purine nucleosides. Briefly, reactions of the purinyl amides with (benzotriazol-1-yl)oxytris(dimethylaminophosphonium) hexafluorophosphate (BOP) lead to the O^6 -(benzotriazol-1-yl)purine nucleosides. These compounds can either be isolated for subsequent $\text{S}_{\text{N}}\text{Ar}$ reaction with nucleophiles,^{11–13,15,16,19} or amide activation can be done *in situ* followed by reaction with nucleophiles (Scheme 1).¹⁷

In the course of these investigations we had attempted to use 3',5'-*O*-disilyl protected O^6 -(benzotriazol-1-yl)-2'-deoxyinosine for Pd-catalyzed C–C bond formation.¹² In this reaction only deoxygenation was observed, leading to the C6 benzotriazol-1-yl nucleoside analogue. This had prompted us to consider use of the oxophilic bis(pinacolato)diboron $[(\text{pinB})_2]$ for the deoxygenation, and with this reagent the O^6 -(benzotriazol-1-yl) nucleoside was smoothly converted to the benzotriazol-1-yl derivative.¹² This has now prompted us to query whether such a deoxygenation can be generally accomplished to access C6 benzotriazolyl nucleosides in a *metal-free* process. Notably, other than our previous results on the deoxygenation chemistry and two Pd-mediated reactions reported therein for structure elucidation purposes,¹² *only a solitary example exists* on the synthesis of 6-(benzotriazol-1-yl)ribofuranosylpurine.²⁰ In the latter work, 6-chloropurine riboside was reacted with 30 mol % excess of 1,2,3-benzotriazole, as a melt at 150°C .²⁰ Whereas this procedure was applicable to the synthesis of the ribonucleosides, its applicability to the synthesis of the more sensitive 2'-deoxyribonucleosides remains unknown. Further, high-temperature reactions of benzotriazoles can potentially be hazardous due to the possibility for their exothermic decomposition.²¹

Results and Discussion

At the outset we wanted to compare our proposed method for the synthesis of 6-benzotriazolyl purine nucleosides, which can also be considered *N*-aryl benzotriazoles, to other approaches. The relevant ones for this comparison are: (*a*) the single known example of a neat reaction between 6-chloropurine riboside and benzotriazole at 150 °C,²⁰ (*b*) aryne-azide cycloaddition,²² and (*c*) metal-catalyzed C–N bond formation between benzotriazoles and an aryl halide.^{12,23} Between these, (*a*) and (*b*) are comparable to the proposed approach (*d*) because they are both *metal-free* transformations (Scheme 2).

Because we have previously developed the synthesis of 6-azidopurine nucleosides from *O*⁶-(benzotriazol-1-yl) nucleoside derivatives,²⁴ we decided to evaluate the aryne-azide cycloaddition first. 6-Azido-9-(2-deoxy-3,5-di-*O*-acetyl- β -D-ribofuranosyl)purine was synthesized as described,²⁴ and this compound was exposed to benzyne generated from *o*-(trimethylsilylphenyl) trifluoromethanesulfonate and CsF in MeCN. In contrast to the facile reaction of various organic azides with benzyne, this nucleoside azide did not yield any product either in the presence or absence of 18-Cr-6. One plausible reason could be that nucleoside azides can exist in the alternate tetrazolyl forms.²⁴

The failure of the aryne-azide cycloaddition only left the diboron-mediated deoxygenation of *O*⁶-(benzotriazol-1-yl) nucleosides to be investigated as the alternate metal-free approach. In our previous report, under unoptimized conditions, compound **4** was observed to undergo conversion to product **5** with (pinB)₂/Cs₂CO₃ in PhMe at 100 °C.¹² This formed the basis for our present investigations and optimizations (Table 1). Precursors **1** and **4** are readily available via our published procedures.¹¹

The results in Table 1 point to several important facts. First, base is essential for the reaction (entries 1–3), in the absence of which no reaction occurred (entry 4). Cs₂CO₃ is best, giving only the *M1* isomer (entry 1), and although K₃PO₄ gave a good overall yield, formation of the *N2* isomer was observed (entry 2). It is easy to ascertain structures of the *M1* and *N2* isomers on the basis of the symmetry or lack thereof in the benzotriazolyl unit. Use of MeCN as solvent for the Cs₂CO₃/(pinB)₂ combination proved to be inferior (entry 5). In contrast to this, with both K₃PO₄ and K₂CO₃, reactions in MeCN gave good yields, but the *N2* isomer was formed in both (entries 6 and 7). The Cs₂CO₃/(pinB)₂ combination in PhMe at 100 °C again provided an excellent yield of the *M1* isomer **5** from precursor **4** (entry 8). But the K₃PO₄/(pinB)₂ combination in MeCN, which was quite good in the case of the ribose substrate **1**, proved to be inferior (entry 9). Use of B₂(OH)₂ in place of (pinB)₂, under otherwise identical conditions, gave an incomplete reaction and multiple products. Thus, this avenue was not pursued.

For further exploration, several precursors (Figure 1) were prepared by reactions of commercially available nucleosides, protected as TBDMS ethers, with BOP, PyAOP, and PyClock. Syntheses of compounds **1**, **4**, **7**, and **8** have been published previously,^{11,15} and compounds **9–14** were synthesized via analogous procedures.

In addition to these ten precursors, one more unnatural nucleoside-based ribosyl precursor was synthesized as shown in Scheme 3. Conversion of *O*⁶-(benzotriazol-1-yl)guanosine

derivative **7** to the O^6 -allyl compound **15** was accomplished as described.¹⁵ Diazotization-bromination then gave the 2-bromo- O^6 -allyl guanosine derivative **16**.²⁵ Notably, when this reaction was conducted in CH_2Cl_2 a minor byproduct (**17**) was observed that was consistent with the allyl group dibromination, on the basis of ^1H NMR and HRMS analysis. In CH_2Br_2 , not only was the yield of bromide **16** lower (36%) but the amount of the tribromo byproduct **17** also increased (13%). The C2 chlorination product formed in CH_2Cl_2 would not be a problem as this would be reactive in the subsequent step. Via a minor modification of our previous results,²⁶ C–C cross coupling and deprotection of the O^6 -allyl group was performed in a single step to yield 2-phenylinosine derivative **18**. Finally, reaction of the amide group with BOP, using DBU as base, in MeCN gave the desired precursor **19**.

With substrates **1**, **4**, **7–14**, and **19** the next step was an evaluation of the ability of $(\text{pinB})_2/\text{Cs}_2\text{CO}_3$ to deoxygenate these in PhMe at 100 °C. We were aware that with substrates **9–14**, we had to pay particular attention to the benzotriazolyl substitution in the product, i.e., we had to query whether the locations of the pyridyl N atom and the Cl atom were identical to those in the precursors or whether some rearrangement had occurred. With all these considerations, each substrate was subjected to the deoxygenation conditions and the results from these experiments are shown in Table 2.

As can be seen from Table 2, successful product formation was observed in nine of the eleven cases (see Figure 2 for product structures). Reactions of precursors **1** and **4** proceeded uneventfully on the larger scales yielding products **2** and **5**, respectively. No *N2* products were observed. Comparably, reactions of the O^6 -(benzotriazol-1-yl)guanine nucleosides **7** and **8** also proceeded well to give the C6 benzotriazolyl products **20** and **22**. In these cases, trace amounts of what could be *N2* isomers **21** and **23** were observed by TLC. Also, the appearance of symmetrical benzotriazolyl resonances in one chromatographically obtained fraction from the reaction of precursor **7** supports this.

In contrast to these, in reactions of the 7-azabenzotriazolyl substrates **9** and **10**, only a small amount of deoxygenated product **24** was isolated from the deoxyribose precursor **10**. In both cases, the major products isolated were dimers **25** and **26** (see Figure 2). We have previously independently prepared **26**¹¹ and identified its formation in a failed C–C cross-coupling reaction.¹² Here, comparable product **25** was identified from substrate **9**. The exact structure of product **24** arising from compound **10** has not been unequivocally assigned, but the *N1* structure is proposed because *N1* products predominate in all other cases. We also cannot unequivocally comment on the location of the pyridyl N atom, i.e., whether A = N and B = CH or whether A = CH and B = N. In a second reaction of compound **10**, use of 2 equiv. of $(\text{pinB})_2$ only led to an increased amount of dimer **26** (32%). We have previously shown that deoxygenations of 1-hydroxy-1*H*-4-aza and 1-hydroxy-1*H*-7-azabenzotriazoles with $\text{B}_2(\text{OH})_4$ occur slowly.²⁷ Therefore, dimer formation, rather than slow deoxygenation may be a competing reaction.

Monochloro precursors **11–14** can potentially yield three products, two different *N1* isomers and one *N2* isomer. Deoxygenation of **11** gave two products in 1:1.6 ratio and the reaction of **12** also gave two products in 1:1.4 ratio. Small amounts of products from precursor **12** were separated for characterization and, first, their NOESY spectra were analyzed. The

chromatographically *early*-eluting product showed a weak but definite correlation between a benzotriazolyl doublet ($\delta = 8.72$ ppm, $J = 8.8$ Hz) and a purinyl singlet ($\delta 8.99$ ppm). Hence, we propose that this compound is the 5-chloro isomer **28a**. No NOESY correlation was observed in the case of the *slower*-eluting product, which we assign as **28b**. That **28b** is also likely a *M1* isomer comes from its hydrogenation with 10% Pd-C and Et₃N, in EtOH, at room temperature. From this reduction, a 51% yield of compound **5** was obtained, indicating that **28b** is a *M1* benzotriazolyl compound (a purple byproduct, which was sensitive to CDCl₃, was also obtained in the reduction and it could not be characterized). Comparable reduction of **28a** also gave compound **5** in 66% yield, and along with the NOESY data above, this supports the assigned structure. Reduction of product **27b** gave a 54% yield of compound **2**, again indicating that this was an *M1* isomeric product (formation of a purple byproduct occurred and due to its sensitivity to CDCl₃ it could not be characterized). Structures of regioisomeric ribose derivatives **27a** and **27b** were assigned by comparison of the benzotriazolyl and purinyl proton resonances to those of the deoxy analogues **28a** and **28b** (see Table 3).

Deoxygenation of precursors **13** and **14** each gave two products, in a 1:4 and 1:1 ratio, respectively. The two products obtained from **14** were inseparable and were characterized as a mixture. However, the products arising from **13** were separable and NOESY spectra of the individual products were analyzed. Similar to data obtained with **28a** and **28b**, the chromatographically *early*-eluting product showed a weak but definite correlation between a benzotriazolyl doublet ($\delta = 8.54$ ppm, $J = 9.3$ Hz) and the NH₂ resonance ($\delta 5.20$ ppm). Hence, this product was assigned the 5-chloro structure **29a**. By analogy, we surmise **29b** to be the 6-chloro isomer. Structures of the inseparable deoxy derivatives **30a** and **30b** were made by comparison of chemical shifts of the benzotriazolyl and purinyl proton resonances to those of **29a** and **29b**. Table 3 shows the chemical shifts of the benzotriazolyl and purinyl proton resonances in compounds **27–30**. Finally, the deoxygenation of *O*⁶-(benzotriazol-1-yl)-2-phenylinosine **19** derivative proceeded efficiently to yield product **31** in excellent yield.

All preceding reactions were conducted with substrates prepared from commercially available peptide-coupling agents. A legitimate question, therefore, would be the applicability of this chemistry to access products where peptide-coupling agents are not available. To investigate this there are three potential approaches, all requiring access to aryl-ring substituted 1-hydroxy-1*H*-benzotriazoles. (a) The peptide-coupling reagent is independently synthesized from the hydroxybenzotriazole and then reacted with the nucleoside, (b) the nucleoside is converted to a phosphonium salt, which is then reacted with the hydroxybenzotriazole, and (c) a peptide-coupling agent is prepared *in situ* from the hydroxybenzotriazole and then reacted with the nucleoside. Although synthesis of BOP and PyAOP are well known and can be applied to the synthesis of similar compounds,^{28,29} we excluded option (a) as being more labor intensive. We have previously investigated approach (b) and initially attempted this.^{12,13}

Synthesis of 1-hydroxy-1*H*-benzotriazoles are well documented in the literature (*Caution*,^{21,30}),^{27,31} On this basis, we chose to prepare 5,6-dichloro-1-hydroxy-1*H*-benzotriazole (**34** in Scheme 4) and test this for additional reactions. Although this hydroxybenzotriazole is listed as commercially available, it is not readily obtained. Thus, it

was prepared from the relatively cheap and commercially available 1,2,4-trichlorobenzene (**32**) via nitration (96%)³² and reaction with hydrazine³³ (56%, Scheme 4). In addition to the routine spectroscopic analyses, compound **34** was also assessed by its reduction to 5,6-dichloro-1*H*-benzotriazole (**35**) under conditions we have recently reported.²⁷

Next, a series of attempts were directed towards conversion of TBDMS-protected inosine (I) and 2'-deoxyinosine (dI) to the *O*⁶-(5,6-dichloro-1*H*-benzotriazol-1-yl)inosine derivatives *via* the nucleoside phosphonium salt (Scheme 5). (a) Reaction of hydroxy benzotriazole **34** with HMPT, I₂, di-*O*-silyl dI, DIPEA in CH₂Cl₂ at 50 °C resulted in the phosphordiamidite **36** (Scheme 5) in 42% yield (see the ESI for data). (b) The same reaction was then conducted stepwise. HMPT was first reacted with I₂, followed by the sequential addition of DIPEA and di-*O*-silyl dI, followed by stirring at room temperature for 15 minutes. Finally, hydroxybenzotriazole **34** was added, and the reaction conducted at 50 °C for 20 h. In this event, among several products that formed, two that could be characterized were dichlorobenzotriazole **35** and silylated *N*⁶,*N*⁶-dimethyl-2'-deoxyadenosine **37**. Formation of compound **37** is not entirely unanticipated, as we have previously observed its formation in reactions of HMPT and I₂.³⁴ (c) In variations of the procedure described in (b), PPh₃ was used in place of HMPT, and reactions were conducted at room temperature and at 45 °C. In both reactions dichlorobenzotriazole **35** was formed and significant amounts of the nucleoside precursor were left unreacted.

Because of these unsuccessful attempts, we next focused on the use of commercially available bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP) for activating the purinyl amide and to form the peptide-coupling agent *in situ*. Both reactions can lead to the desired *O*⁶-(5,6-dichlorobenzotriazol-1-yl)inosine derivatives as shown in Scheme 6.

Initial attempts were the conversion of TBDMS-protected dI to the desired product **40** with 3.8 equiv. of PyBroP and 4.5 equiv. of hydroxybenzotriazole **34**. In these reactions, expected product **40** predominated. However, in addition, various other products were also observed, such as the C6 pyrrolidino nucleoside **38**, the C6 benzotriazolyl derivative **39**, and the reduced benzotriazole **35** (all shown in Scheme 5). The best yield of the desired **40** was 48%. Similarly, reaction of TBDMS-protected I gave a 49% yield of product **41**. Further experiments revealed that by lowering the amount of PyBroP to 1.9 equiv., and with 4.5 equiv. of hydroxybenzotriazole **34**, substantial yield improvements and cleaner reactions could be attained (70% each of **40** and **41**). Reactions of **40** and **41** with (pinB)₂ and Cs₂CO₃ under the optimized conditions proceeded smoothly to provide products **42** and **43** in 61 and 56% yield, respectively (Scheme 7).

At this point we had shown the generality of this deoxygenative approach to C6 benzotriazolyl purine nucleoside derivatives with substrates obtained from commercially available benzotriazole-based peptide-coupling agents, analyzed the isomeric products formed in some cases, and demonstrated the applicability of the approach when peptide-coupling agents are unavailable. The next focus was to gain some understanding of a plausible mechanistic pathway and there are two plausible mechanisms. One is an intramolecular process where the benzotriazolyl unit does not become completely detached from the nucleoside but transfers the oxygen atom to the diboron. In a second

pathway, the benzotriazolyloxy moiety can become detached from the purine, undergo deoxygenation as hydroxybenzotriazoles do,²⁷ and then become reattached to the purine.

We reasoned that a crossover experiment involving two precursors with differently substituted benzotriazoles could shed light on the underlying mechanism. If an intramolecular process were operational, then each substrate would yield the corresponding deoxygenation product, and only two products would be obtained. However, should the mechanism involve detachment of the benzotriazolyloxy group from the purine, then four products could be expected. After TLC analysis of prospective starting materials and potential products, we found that *O*⁶-(benzotriazol-1-yl)-2'-deoxyinosine derivative **4** and *O*⁶-(5,6-dichlorobenzotriazol-1-yl)inosine derivative **41** would be optimal. An equimolar mixture of compounds **4** and **41** was subjected to the deoxygenation conditions. Four separable products **2**, **5**, **42**, and **43** were obtained (Scheme 8) and the mole fractions of these were 0.30:0.38:0.17:0.14, respectively. This outcome indicated that the benzotriazolyloxy and 5,6-dichlorobenzotriazolyloxy units likely become detached from the purine and then undergo deoxygenation. Subsequently, the ensuing reduced benzotriazolyl and 5,6-dichlorobenzotriazolyl anions can function as nucleophiles, reacting via the S_NAr mechanism with either substrate, again producing the two benzotriazolyloxy anions. The N–O reduction/S_NAr process can then continue until each substrate is consumed. Such a mechanism would readily account for the observed crossover results. The product distribution shows, as would be expected, that the dichlorobenzotriazole species is less reactive than the unhalogenated analogue. The ribose appears less reactive than the 2'-deoxy derivative, plausibly for electronic and steric reasons.

Two final tests were conducted (Scheme 9). In the first, a reaction of substrate **1** was conducted in the absence of (pinB)₂. A 29% yield of the dimer **25** was obtained, indicating that there is the possibility of a background reaction leading to the release of the benzotriazolyloxy group. This can then potentially be a mechanism that initiates the N–O reduction/S_NAr cycle. For this background reaction we then considered the role of trace amounts of moisture that could hydrolyze the *O*⁶-(benzotriazol-1-yl) substrates, releasing the benzotriazolyloxy group. Such hydrolysis could also readily account for the dimer formation. Thus, a final experiment was conducted wherein substrate **1** was exposed to (pinB)₂ (1.1 equiv.) and Cs₂CO₃ (2 equiv.) in 9:1 PhMe–H₂O at 100 °C. In a 4-hour reaction time, product **2** was isolated in 81% yield, a result that is slightly lower than the 90% yield obtained in the absence of water (entry 1 in Table 2). Contrary to expectation though, no significant hydrolysis of the substrate to silyl-protected **I** was observed. Therefore, at the present time we are not entirely certain of the mechanism by which the benzotriazolyloxy group becomes detached from the purine (perhaps a very minor hydrolysis reaction), but the crossover experiment does indicate that such a process could be occurring.

In attempting to elucidate underlying mechanisms, two plausible pathways can be postulated (*a* and *b* in Scheme 10). It is currently not possible to comment on pathway *a* involving a one-step deoxygenation with or without intermediacy of a benzotriazolyl *N*-oxide intermediate that can be formed via rearrangement (shown in the box in Scheme 10).

On the other hand, even if a low concentration of 1*H*-benzotriazol-1-olate (BtO^-) is initially accessible (pathway **b**), this can undergo reduction with $(\text{pinB})_2$. The resulting benzotriazolyl anion (Bt^-) can then yield additional BtO^- by $\text{S}_{\text{N}}\text{Ar}$ displacement, and the reaction can continue along the sequential reduction/ $\text{S}_{\text{N}}\text{Ar}$ reactions. The N3 atom of the benzotriazolyl unit in one substrate can function as a nucleophile in displacing BtO^- from another, and this can be one way for the formation of BtO^- . Notably, if a *N*-oxide intermediate (shown in the box in Scheme 10) is formed in any pathway, this will also undergo reduction by $(\text{pinB})_2$. Pathway **b** would be consistent with the crossover results and, in support of this, we have previously shown that benzotriazole is capable of displacing BtO^- from compound **4**.¹² The role of Cs_2CO_3 in these reactions is not clear at this time.

Conclusions

Herein we have demonstrated a new approach to the preparation of C6 benzotriazolyl purine nucleoside derivatives. The chemistry hinges on an unusual conversion of a C–O–N linkage to a C–N via the use of $(\text{pinB})_2$ and Cs_2CO_3 . Thus, this is effectively a *metal-free* C–N bond-forming reaction. The requisite precursors were readily prepared by reactions of amide linkages in purine nucleosides with commercially available, benzotriazole-based peptide coupling agents, or with *in situ*-formed reagents when peptide-coupling agents are not available commercially. Although isomeric *N1* benzotriazolyl products are formed from unsymmetrical benzotriazolyl peptide-coupling agents, and traces of *N2* products are seen in rare cases, regioisomeric product formation also occurs in metal-catalyzed C–N bond-forming reactions of benzotriazoles and in aryne-azide cycloadditions leading to *N*-substituted benzotriazoles.^{22,23} The use of diboron reagents for deoxygenating N–O bonds can be traced back to the reductions of 4-methylmorpholine, pyridine, and 4-phenylpyridine *N*-oxides, by $(\text{pinB})_2$ and bis(catecholato)diboron $[(\text{catB})_2]$.³⁵ In these cases, the free amines remained complexed to the electrophilic boron center in the B–O–B product. Silica gel chromatography was adequate to release the uncomplexed pyridines, but the 4-methylmorpholine adduct of $(\text{pinB})_2\text{O}$ was isolated in good yield.³⁵ In 2011, we comprehensively demonstrated broadly-applicable synthetic use of $(\text{pinB})_2$ and $(\text{catB})_2$ for the reduction of alkyl amino, pyridyl, and anilino *N*-oxides.³⁶ The use of $\text{B}_2(\text{OH})_4$ for reduction of pyridyl *N*-oxides was demonstrated in 2013,³⁷ and in 2015 we successfully demonstrated a general synthesis of 1*H*-benzotriazoles from 1-hydroxy-1*H*-benzotriazoles with this reagent.²⁷ In the present work, $\text{B}_2(\text{OH})_4$ was ineffective in comparison to $(\text{pinB})_2$. From a mechanism standpoint, a crossover experiment indicated that the benzotriazolyl group likely becomes detached from the purine, undergoes reduction with $(\text{pinB})_2$, and the formed benzotriazole can then function as a nucleophile for $\text{S}_{\text{N}}\text{Ar}$ displacement. The observation of two isomeric *N1*-aryl benzotriazoles from unsymmetrically substituted precursors, and the formation of *N2* products in some cases is consistent with this mechanistic manifold.

The results described here contribute to an emerging area on the synthetic applicability of diboron reagents in reductive processes. Importantly, as shown here and as we clearly demonstrated previously,³⁶ the reductions are generally facile and insensitive to water. This feature, when combined with the benign nature of the boron-based byproducts, makes such reactions broadly applicable in a variety of contexts. For instance, $(\text{pinB})_2$ has been used for

the reduction of convergine to hippodamine, both ladybeetle alkaloids, allowing for an otherwise difficult quantification of these alkaloids due to the thermal lability of convergine.³⁸ Also, (pinB)₂, and plausibly B₂(OH)₄ formed from the hydrolysis of (pinB)₂, have shown biocompatibility in aqueous reactions.³⁹ It should be noted that despite the recently claimed novelty of amine *N*-oxide reduction by diboron-based reagents,³⁹ that report is really an application of prior discoveries by others and by us.^{12,35–37} The present results further amplify the utility of diboron reducing agents for effecting a range of N–O deoxygenations under a variety of conditions. This type of diboron-reagent-mediated deoxygenation appears to be quite broadly applicable, and additional results of this chemistry are forthcoming from our laboratories.

Experimental Section

General information

Thin layer chromatography was performed on 200 µm aluminum-foil-backed silica gel plates, and column chromatography was performed using 230–400 mesh silica gel. PhMe was distilled from sodium, MeCN and DME were distilled from CaH₂. Et₃N and DIPEA were distilled from CaH₂ and stored over KOH. 6-Azido-9-(2-deoxy-3,5-di-*O*-acetyl-β-*D*-ribofuranosyl)purine was synthesized as described.²⁴ *O*⁶-(Benzotriazol-1-yl) derivatives of inosine, 2'-deoxyinosine, guanosine, and 2'-deoxyguanosine (**1**, **4**, **7**, and **8**) were synthesized by reported procedures.^{11,15} The remaining analogues shown in Figure 1 were synthesized by application of these known routes (see the ESI). *O*⁶-Allyl-2',3',5'-tri-*O*-(*t*-butyldimethylsilyl)guanosine (**15**) was prepared from guanosine¹⁵ and converted to the *O*⁶-allyl-2-bromo nucleoside (**16**) on the basis of our previously published route.²⁶ All other reagents were used as received from commercial suppliers. ¹H NMR spectra were obtained at 500 MHz in CDCl₃ and are referenced to the residual protonated solvent resonance. ¹³C NMR spectra were obtained at 125 MHz in CDCl₃ and are referenced to the solvent resonance. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are in hertz (Hz). Standard abbreviations are used to designate resonance multiplicities.

***O*⁶-Allyl-2',3',5'-tri-*O*-(*t*-butyldimethylsilyl)-2-bromoinosine (**16**)**—A stirred mixture of nucleoside derivative **15** (300.0 mg, 0.45 mmol) and SbBr₃ (227.7 mg, 0.63 mmol) in dry CH₂Cl₂ (5 mL) was cooled to –10 °C. To the cooled mixture *t*-BuONO (374.0 µL, 3.15 mmol) was added dropwise and the stirring was continued at –10 °C for 3 h. The mixture was then poured into cold saturated aq. NaHCO₃, filtered, and the residual solid was washed with CH₂Cl₂. The filtrate was washed with water and brine. The aqueous layer was back extracted with CH₂Cl₂. The organic layer was dried with anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. Purification of the crude material by flash chromatography (SiO₂, eluted with 5% EtOAc in hexanes) gave 123.0 mg (55% yield) of product **16** (and the C2 chloro analogue) as a white, fluffy solid. In this reaction compound **17** (26.8 mg, 7% yield) was formed as a minor separable product. *R*_f (20% EtOAc in hexanes) = 0.64. ¹H NMR of pure **16** (500 MHz, CDCl₃): δ 8.27 (s, 1H, Ar-H), 6.17–6.12 (m, 1H, =CH), 5.98 (d, *J* = 4.9 Hz, 1H, H-1'), 5.48 (d, *J* = 17.1 Hz, 1H, =CH_{trans}), 5.32 (dd, *J* = 0.9, 10.0 Hz, 1H, =CH_{cis}), 5.10 (d, *J* = 5.8 Hz, 2H, OCH₂), 4.61 (t, *J* = 4.4 Hz, 1H,

H-2'), 4.31 (t, $J = 3.9$ Hz, 1H, H-3'), 4.16–4.13 (m, 1H, H-4'), 4.05 (dd, $J = 4.4$, 11.3 Hz, 1H, H-5'), 3.80 (dd, $J = 2.0$, 11.3 Hz, 1H, H-5'), 0.95, 0.93, and 0.83 (3s, 27H, *t*-Bu), 0.15, 0.14, 0.10, 0.09, –0.01, and –0.17 (6s, 18H, SiCH₃). ¹³C NMR (125 MHz, CDCl₃): δ 160.6, 152.8, 143.2, 141.7, 131.8, 121.4, 119.4, 89.0, 85.4, 75.8, 71.6, 68.6, 62.3, 26.1, 25.8, 25.7, 18.5, 18.1, 17.9, –4.3, –4.7, –4.8, –5.0, –5.4. HRMS (ESI/TOF) calcd for C₃₁H₅₇BrN₄O₅Si₃Na [M + Na]⁺ 751.2712, found 751.2714.

2',3',5'-Tri-O-(*t*-butyldimethylsilyl)-2-phenylinosine (18).²⁶—In a clean, dry screw-cap vial containing a stirring bar were placed the bromo nucleoside **16** (140.0 mg, 0.192 mmol), PhB(OH)₂ (70.1 mg, 0.575 mmol), and anhydrous K₃PO₄ (122.0 mg, 0.575 mmol). Anhydrous 1,4-dioxane (4 mL) was added, the vial was flushed with nitrogen gas for 5 min followed by the addition of (dcpf)PdCl₂ (43.5 mg, 0.0575 mmol). The vial was capped and the mixture was stirred at 100 °C for 7 h. Then the mixture was cooled to room temperature, filtered through Celite, and the filtrate was evaporated to dryness. Purification of the crude material by flash chromatography (SiO₂, eluted with 3% CH₃OH in CH₂Cl₂) gave 124.5 mg (95% yield) of product **18** as a pale-brown, fluffy solid. R_f (5% CH₃OH in CH₂Cl₂) = 0.37. ¹H NMR (500 MHz, C₆D₆): δ 10.30 (br s, 1H, NH), 8.23 (s, 1H, Ar-H), 8.06–8.02 (m, 2H, Ar-H), 7.59–7.55 (m, 3H, Ar-H), 6.10 (d, $J = 4.4$ Hz, 1H, H-1'), 4.54 (t, $J = 4.1$ Hz, 1H, H-2'), 4.36–4.34 (m, 1H, H-3'), 4.16–4.13 (m, 1H, H-4'), 4.00 (dd, $J = 3.6$, 11.3 Hz, 1H, H-5'), 3.82 (dd, $J = 1.9$, 11.0 Hz, 1H, H-5'), 0.96, 0.94, and 0.82 (3s, 27H, *t*-Bu), 0.14, 0.13, 0.12, 0.10, –0.05, –0.14 (6s, 18H, SiCH₃). ¹³C NMR (125 MHz, CDCl₃): δ 158.0, 153.1, 149.2, 139.3, 134.0, 131.8, 129.2, 127.2, 88.3, 85.2, 76.4, 71.7, 62.4, 26.1, 25.8, 25.7, 20.2, 18.5, 18.1, 17.9, –4.3, –4.6, –4.9, –5.3.

O⁶-(Benzotriazol-1-yl)-2',3',5'-tri-O-(*t*-butyldimethylsilyl)-2-phenylinosine (19)—In a clean, dry, screw-cap vial a mixture of 2-phenylinosine derivative **18** (120.0 mg, 0.175 mmol), BOP (154.5 mg, 0.349 mmol), and DBU (52.0 μ L, 0.349 mmol) was stirred in anhydrous MeCN (1.5 mL) for 24 h, under a nitrogen atmosphere. The mixture was diluted with EtOAc and washed with water containing a small amount of NaCl. The aqueous layer was back extracted with EtOAc, the combined organic layer was dried with anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. Purification of the crude material by flash chromatography (SiO₂, eluted with 10% EtOAc in hexanes) gave 49.0 mg (40% yield) of pure product **19** as a white, fluffy solid. (An equal amount of product containing trace amounts of impurities was also obtained. The more polar starting material was isolated by elution with 90% EtOAc in acetone.) R_f (10% EtOAc in hexanes) = 0.27. ¹H NMR (500 MHz, C₆D₆): δ 8.52 (s, 1H, Ar-H), 8.15 (dd, $J = 1.5$, 8.0 Hz, 2H, Ar-H), 7.92–7.90 (m, 1H, Ar-H), 7.05–7.01 (m, 3H, Ar-H), 6.94 (dd, $J = 2.6$, 6.5 Hz, 1H, Ar-H), 6.89–6.86 (m, 2H, Ar-H), 6.22 (d, $J = 3.6$ Hz, 1H, H-1'), 4.74 (t, $J = 3.9$ Hz, 1H, H-2'), 4.55 (t, $J = 4.8$ Hz, 1H, H-3'), 4.25–4.28 (m, 1H, H-4'), 3.99 (dd, $J = 4.0$, 11.3 Hz, 1H, H-5'), 3.74 (dd, $J = 2.2$, 11.4 Hz, 1H, H-5'), 0.98 and 0.91 (2s, 27H, *t*-Bu), 0.11, 0.10, 0.08, 0.01, –0.016, –0.023 (6s, 18H, SiCH₃). ¹³C NMR (125 MHz, C₆D₆): δ 159.2, 158.5, 154.9, 143.9, 136.6, 130.6, 128.4, 128.3, 128.0, 127.7, 127.6, 124.1, 120.5, 119.2, 110.0, 108.6, 89.2, 84.5, 76.2, 71.2, 61.9, 26.0, 25.8, 25.6, 18.4, 18.0, 17.9, –4.4, –4.7, –4.8, –4.9, –5.5, –5.6. HRMS (ESI/TOF) calcd for C₄₀H₆₁N₇O₅Si₃Na [M + Na]⁺ 826.3934, found 826.3925.

Representative procedure: deoxygenation of O⁶-(benzotriazol-1-yl)inosine derivative (1)

In a clean, dry, screw-cap vial a mixture of compound **1** (121.9 mg, 0.167 mmol), (pinB)₂ (46.1 mg, 0.182 mmol), and Cs₂CO₃ (109.0 mg, 0.335 mmol) was stirred in anhydrous PhMe (1.5 mL) at 100 °C over 4 h, under a nitrogen atmosphere. The mixture was cooled, diluted with EtOAc, filtered through Celite, and evaporated under reduced pressure. The crude material was purified by flash chromatography (SiO₂, eluted with 15% EtOAc in hexanes) to give 107.4 mg (90% yield) of product **2**¹² as a white, fluffy solid. *R*_f (20% EtOAc in hexanes) = 0.46. ¹H NMR (500 MHz, CDCl₃): δ 8.99 (s, 1H, Ar-H), 8.77 (d, *J* = 8.3 Hz, 1H, Ar-H), 8.61 (s, 1H, Ar-H), 8.23 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.68 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.52 (t, *J* = 7.8 Hz, 1H, Ar-H), 6.26 (d, *J* = 5.4 Hz, 1H, H-1'), 4.71 (t, *J* = 4.6 Hz, 1H, H-2'), 4.35 (br s, 1H, H-3'), 4.19 (br s, 1H, H-4'), 4.03 (dd, *J* = 3.0, 11.2 Hz, 1H, H-5'), 3.83 (dd, *J* = 2.0, 11.2 Hz, 1H, H-5'), 0.97, 0.95, and 0.79 (3s, 27H, *t*-Bu), 0.16, 0.15, 0.12, -0.02, and -0.25 (5s, 18H, SiCH₃). ¹³C NMR (125 MHz, CDCl₃): δ 154.3, 151.9, 147.8, 146.4, 144.7, 132.3, 129.5, 125.7, 123.9, 120.5, 115.3, 88.3, 86.2, 76.3, 72.4, 62.8, 26.3, 26.0, 25.8, 18.7, 18.2, 18.0, -4.3, -4.4, -4.5, -4.8, -5.1, -5.2.

Deoxygenation of O⁶-(benzotriazol-1-yl)-2'-deoxyinosine derivative (4)

As described for the deoxygenation of compound **1**, this reaction was carried out with compound **4** (110.0 mg, 0.167 mmol), (pinB)₂ (46.1 mg, 0.182 mmol), and Cs₂CO₃ (109.0 mg, 0.335 mmol) in PhMe (1.5 mL) at 100 °C over 4 h. Purification by flash chromatography (SiO₂, eluted with 20% and 25% EtOAc in hexanes) gave 84.4 mg (87% yield) of product **5**¹² as a white, fluffy solid. *R*_f (20% EtOAc in hexanes) = 0.16. ¹H NMR (500 MHz, CDCl₃): δ 9.00 (s, 1H, Ar-H), 8.76 (d, *J* = 8.3 Hz, 1H, Ar-H), 8.57 (s, 1H, Ar-H), 8.23 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.68 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.53 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.64 (app t, *J* = 6.3 Hz, 1H, H-1'), 4.68–4.65 (m, 1H, H-3'), 4.10–4.08 (m, 1H, H-4'), 3.90 (dd, *J* = 3.9, 11.2 Hz, 1H, H-5'), 3.82 (dd, *J* = 2.9, 11.2 Hz, 1H, H-5'), 2.70 (app quint, *J*_{app} ~ 6.4 Hz, 1H, H-2'), 2.54 (ddd, *J* = 3.3, 6.1, 13.1 Hz, 1H, H-2'), 0.94 and 0.92 (2s, 18H, *t*-Bu), 0.13, 0.10, and 0.09 (3s, 12H, SiCH₃). ¹³C NMR (125 MHz, CDCl₃): δ 153.9, 151.8, 147.7, 146.4, 144.3, 132.2, 129.5, 125.7, 124.1, 120.5, 115.2, 88.4, 84.8, 72.3, 63.0, 41.6, 26.1, 25.9, 18.6, 18.2, -4.5, -4.6, -5.2, -5.3.

Deoxygenation of O⁶-(benzotriazol-1-yl)guanosine derivative (7)

As described for the deoxygenation of compound **1**, this reaction was carried out with compound **7** (124.4 mg, 0.167 mmol), (pinB)₂ (46.1 mg, 0.182 mmol), and Cs₂CO₃ (109.0 mg, 0.335 mmol) in PhMe (1.5 mL) at 100 °C over 4 h. Purification by flash chromatography (SiO₂, eluted with 20% EtOAc in hexanes) gave 100.0 mg (82% yield) of product **20** as a pale-brown, fluffy solid. A trace amount of *N*2 isomer **21** was observed in this reaction. *R*_f (30% EtOAc in hexanes) = 0.40. ¹H NMR (500 MHz, CDCl₃): δ 8.59 (d, *J* = 8.3 Hz, 1H, Ar-H), 8.30 (s, 1H, Ar-H), 8.20 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.63 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.49 (t, *J* = 7.4 Hz, 1H, Ar-H), 6.08 (d, *J* = 5.4 Hz, 1H, H-1'), 5.28 (br s, 2H, NH₂), 4.59 (t, *J* = 4.9 Hz, 1H, H-2'), 4.31 (t, *J* = 4 Hz, 1H, H-3'), 4.15–4.13 (m, 1H, H-4'), 3.98 (dd, *J* = 3.4, 11.3 Hz, 1H, H-5'), 3.81 (dd, *J* = 2.7, 11.5 Hz, 1H, H-5'), 0.95, 0.94, and 0.82 (3s, 27H, *t*-Bu), 0.15, 0.14, 0.12, 0.00, -0.03, and -0.16 (6s, 18H, SiCH₃). ¹³C NMR (125 MHz, CDCl₃): δ 158.9, 156.2, 148.1, 146.2, 141.4, 132.0, 128.9, 125.3, 120.3, 118.1, 115.0, 87.5, 85.6, 76.2, 72.2, 62.8,

26.1, 25.9, 25.7, 18.6, 18.1, 17.9, -4.3, -4.5, -4.6, -4.9, -5.2, -5.3. HRMS (ESI/TOF) calcd for $C_{34}H_{58}N_8O_4Si_3Na$ $[M + Na]^+$ 749.3787, found 749.3781.

Deoxygenation of O^6 -(benzotriazol-1-yl)-2'-deoxyguanosine derivative (8)—As

described for the deoxygenation of compound **7**, this reaction was carried out with compound **8** (102.6 mg, 0.167 mmol), (pinB)₂ (46.1 mg, 0.182 mmol), and Cs₂CO₃ (109.0 mg, 0.335 mmol) in PhMe (1.5 mL) at 100 °C over 4 h. Purification by flash chromatography (SiO₂, eluted with 30% EtOAc in hexanes) gave 90.9 mg (91% yield) of product **22** as an off-white, fluffy solid. A trace amount of *N2* isomer **23** was observed in this reaction. R_f (40% EtOAc in hexanes) = 0.37. ¹H NMR (500 MHz, CDCl₃): δ 8.58 (d, J = 8.3 Hz, 1H, Ar-H), 8.28 (s, 1H, Ar-H), 8.21 (d, J = 8.3 Hz, 1H, Ar-H), 7.64 (t, J = 7.6 Hz, 1H, Ar-H), 7.50 (t, J = 7.7 Hz, 1H, Ar-H), 6.47 (t, J = 6.6 Hz, 1H, H-1'), 5.24 (br s, 2H, NH₂), 4.63–4.60 (m, 1H, H-3'), 4.06–4.04 (m, 1H, H-4'), 3.86–3.78 (m, 2H, 2H-5'), 2.60 (app quint, J_{app} ~ 6.7 Hz, 1H, H-2'), 2.46 (ddd, J = 3.4, 5.8, 13.2 Hz, 1H, H-2'), 0.94 and 0.92 (2s, 18H, *t*-Bu), 0.13, 0.12, 0.10, and 0.09 (4s, 12H, SiCH₃). ¹³C NMR (125 MHz, CDCl₃): δ 158.9, 155.9, 146.2, 141.2, 132.0, 129.0, 125.3, 120.2, 118.1, 114.9, 88.0, 83.8, 113.8, 72.2, 62.9, 41.0, 26.0, 25.8, 24.9, 18.4, 18.0, -4.6, -4.7, -5.3, -5.4. HRMS (ESI/TOF) calcd for $C_{28}H_{44}N_8O_3Si_2Na$ $[M + Na]^+$ 619.2973, found 619.2979.

Attempted deoxygenation of O^6 -(7-azabenzotriazol-1-yl)inosine derivative (9)

—As described for the deoxygenation of compound **1**, this reaction was attempted with compound **9** (58.8 mg, 81.0 μmol), (pinB)₂ (22.24 mg, 87.6 μmol), and Cs₂CO₃ (52.6 mg, 0.161 mmol) in PhMe (0.75 mL) at 100 °C over 4 h. Evaporation of the reaction mixture and purification by flash chromatography (SiO₂, eluted with 40% EtOAc in hexanes) gave 24.6 mg (25% yield) of compound **25** as an oily product. R_f (40% EtOAc in hexanes) = 0.84. ¹H NMR (500 MHz, CDCl₃): δ 8.99 (s, 1H, Ar-H), 8.60 (s, 1H, Ar-H), 8.26 (s, 1H, Ar-H), 8.25 (s, 1H, Ar-H), 6.17 (d, J = 3.4 Hz, 1H, H-1'), 6.02 (d, J = 3.9 Hz, 1H, H-1'), 4.57 (t, J = 3.6 Hz, 1H, H-2'), 4.50 (t, J = 4.2 Hz, 1H, H-2'), 4.37 (t, J = 4.4 Hz, 1H, H-3'), 4.33 (t, J = 4.4 Hz, 1H, H-3'), 4.18–4.14 (m, 2H, H-4'), 4.06–4.01 (m, 2H, H-5'), 3.83–3.79 (m, 2H, H-5'), 0.96, 0.93, 0.86, and 0.85 (4s, 54H, *t*-Bu), 0.15, 0.14, 0.12, 0.11, 0.10, 0.03, -0.04, -0.07 (8s, 36H, SiCH₃). ¹³C NMR (125 MHz, CDCl₃): δ 155.1, 153.5, 152.2, 147.8, 147.1, 145.9, 144.9, 138.9, 129.9, 124.9, 89.0, 88.7, 85.0, 84.9, 83.5, 76.4, 71.2, 71.0, 62.1, 62.0, 26.1, 25.9, 25.74, 25.7, 25.0, 18.6, 18.1, 17.9, -4.2, -4.3, -4.6, -4.8, -5.28, -5.33. HRMS (ESI/TOF) calcd for $C_{56}H_{106}N_8O_9Si_6Na$ $[M + Na]^+$ 1225.6596, found 1225.6604.

Attempted deoxygenation of O^6 -(7-azabenzotriazol-1-yl)-2'-deoxyinosine derivative (10)—As described for the deoxygenation of compound **1**, this reaction was

attempted with compound **10** (48.3 mg, 80.7 μmol), (pinB)₂ (22.2 mg, 87.6 μmol), and Cs₂CO₃ (52.6 mg, 0.161 mmol) in PhMe (0.75 mL) at 100 °C over 4 h. Evaporation of the reaction mixture and purification by preparative TLC (1 mm, 20 × 20 cm SiO₂ plate eluted with 60% EtOAc in hexanes) gave 22.0 mg (29% yield) of compound **26** as an oily product, and 5.0 mg (10% yield) of compound **24** as an off-white, fluffy solid. R_f of **26** (50% EtOAc in hexanes) = 0.17. ¹H NMR of **26** (500 MHz, CDCl₃): δ 8.98 (s, 1H, Ar-H), 8.50 (s, 1H, Ar-H), 8.25 (s, 1H, Ar-H), 8.14 (s, 1H, Ar-H), 6.56 (t, J = 6.4 Hz, 1H, H-1'), 6.42 (t, J = 6.4 Hz, 1H, H-1'), 4.64–4.59 (m, 2H, H-3'), 4.06–4.02 (m, 2H, H-4'), 3.89–3.84 (m, 2H, H-5'),

3.80–3.77 (dd, $J = 2.6, 11.4$ Hz, 2H, H-5'), 2.67 (app quint, $J_{\text{app}} \sim 6.5$ Hz, 1H, H-2'), 2.56 (app quint, $J_{\text{app}} \sim 6.4$ Hz, 1H, H-2'), 2.50 (ddd, $J = 3.9, 6.4, 13.0$ Hz, 1H, H-2'), 2.45 (ddd, $J = 3.9, 6.2, 13.0$ Hz, 1H, H-2'), 0.92, 0.917, 0.914, and 0.89 (4s, 36H, *t*-Bu), 0.12, 0.11, 0.10, 0.09, 0.08, and 0.07 (6s, 36H, SiCH₃). HRMS of **26** (ESI/TOF) calcd for C₄₄H₇₈N₈O₇Si₄Na [M + Na]⁺ 965.4968, found 965.4963. Compound **26** is known in the literature.¹¹ R_f of **24** (50% EtOAc in hexanes) = 0.07. ¹H NMR of **24** (500 MHz, CDCl₃): δ 9.09 (d, $J = 8.3$ Hz, 1H, Ar-H), 8.99 (s, 1H, Ar-H), 8.88 (d, $J = 4.4$ Hz, 1H, Ar-H), 8.62 (s, 1H, Ar-H), 7.62 (dd, $J = 4.4, 8.3$ Hz, 1H, Ar-H), 6.64 (t, $J = 6.6$ Hz, 1H, H-1'), 4.67–4.65 (m, 1H, H-3'), 4.11–4.08 (m, 1H, H-4'), 3.90 (dd, $J = 3.9, 11.2$ Hz, 1H, H-5'), 3.81 (dd, $J = 2.5, 11.2$ Hz, 1H, H-5'), 2.68 (app quint, $J_{\text{app}} \sim 6.5$ Hz, 1H, H-2'), 2.54 (ddd, $J = 3.4, 5.9, 13.2$ Hz, 1H, H-2'), 0.94 and 0.91 (2s, 18H, *t*-Bu), 0.13 and 0.10 (2s, 12H, SiCH₃). HRMS of **24** (ESI/TOF) calcd for C₂₇H₄₂N₈O₃Si₂Na [M + Na]⁺ 605.2816, found 605.2814. A ¹³C NMR spectrum could not be obtained because of low quantity of the material isolated.

Deoxygenation of O⁶-(6-chlorobenzotriazol-1-yl)inosine derivative (**11**)—As

described for the deoxygenation of compound **1**, this reaction was carried out with compound **11** (127.6 mg, 0.167 mmol), (pinB)₂ (46.1 mg, 0.182 mmol), and Cs₂CO₃ (109.0 mg, 0.335 mmol) in PhMe (1.5 mL) at 100 °C for 4 h. Purification by flash chromatography (SiO₂, eluted with 15% EtOAc in hexanes) gave isomer **27a** (31.1 mg) and **27b** (48.3 mg), each as an off-white, fluffy solid, for an overall yield of 64%. R_f of **27a** (20% EtOAc in hexanes) = 0.55. ¹H NMR of **27a** (500 MHz, CDCl₃): δ 8.99 (s, 1H, Ar-H), 8.74 (d, $J = 9.3$ Hz, 1H, Ar-H), 8.63 (s, 1H, Ar-H), 8.21 (s, 1H, Ar-H), 7.64 (d, $J = 8.7$ Hz, 1H, Ar-H), 6.27 (d, $J = 5.5$ Hz, 1H, H-1'), 4.70 (app t, $J = 4.9$ Hz, 1H, H-2'), 4.34 (t, $J = 3.2$ Hz, 1H, H-3'), 4.20–4.18 (m, 1H, H-4'), 4.03 (dd, $J = 3.5, 11.2$ Hz, 1H, H-5'), 3.83 (d, $J = 11.5$ Hz, 1H, H-5'), 0.97, 0.96, and 0.79 (3s, 27H, *t*-Bu), 0.17, 0.16, 0.13, –0.02, and –0.25 (5s, 18H, SiCH₃). ¹³C NMR of **27a** (125 MHz, CDCl₃): δ 154.4, 151.8, 147.3, 147.0, 144.9, 131.4, 130.9, 130.2, 123.8, 119.9, 116.2, 88.3, 86.2, 76.4, 72.3, 62.8, 26.3, 25.9, 25.7, 18.7, 17.9, –4.3, –4.4, –4.5, –4.9, –5.1, –5.2. HRMS of **27a** (ESI/TOF) calcd for C₃₄H₅₆O₄ClN₇Si₃Na [M + Na]⁺ 768.3282, found 768.3282. R_f of **27b** (20% EtOAc in hexanes) = 0.42. ¹H NMR of **27b** (500 MHz, CDCl₃): δ 9.01 (s, 1H, Ar-H), 8.85 (s, 1H, Ar-H), 8.63 (s, 1H, Ar-H), 8.15 (d, $J = 8.8$ Hz, 1H, Ar-H), 7.50 (d, $J = 7.2$ Hz, 1H, Ar-H), 6.27 (d, $J = 5.5$ Hz, 1H, H-1'), 4.71 (t, $J = 4.9$ Hz, 1H, H-2'), 4.35 (t, $J = 3.4$ Hz, 1H, H-3'), 4.20–4.18 (m, 1H, H-4'), 4.04 (dd, $J = 3.3, 11.0$ Hz, 1H, H-5'), 3.82 (d, $J = 11.5$ Hz, 1H, H-5'), 0.97, 0.96, and 0.79 (3s, 27H, *t*-Bu), 0.17, 0.16, 0.13, –0.02, and –0.25 (5s, 18H, SiCH₃). ¹³C NMR of **27b** (125 MHz, CDCl₃): δ 154.2, 151.6, 147.1, 144.7, 144.6, 135.8, 132.5, 126.6, 123.6, 121.0, 115.1, 88.1, 86.0, 76.1, 72.2, 62.6, 26.1, 25.8, 25.5, 18.5, 18.0, 17.7, –4.5, –4.6, –4.7, –5.1, –5.3, –5.4. HRMS of **27b** (ESI/TOF) calcd for C₃₄H₅₆O₄ClN₇Si₃Na [M + Na]⁺ 768.3282, found 768.3282.

Deoxygenation of O⁶-(6-chlorobenzotriazol-1-yl)-2'-deoxyinosine derivative (**12**)—As

described for the deoxygenation of compound **1**, this reaction was carried out with compound **12** (105.8 mg, 0.167 mmol), (pinB)₂ (46.1 mg, 0.182 mmol), and Cs₂CO₃ (109.0 mg, 0.335 mmol) in PhME (1.5 mL) at 100 °C for 4 h. Purification by flash chromatography (SiO₂, eluted with 20% EtOAc in hexanes) gave isomers **28a** (27.2 mg), **28b** (14 mg), and a mixture of **28a** + **28b** (45.6 mg), each as an off-white, amorphous solid, for an overall yield

of 64%. R_f of **28a** (50% EtOAc in hexanes) = 0.79. ^1H NMR of **28a** (500 MHz, CDCl_3): δ 8.99 (s, 1H, Ar-H), 8.72 (d, J = 8.8 Hz, 1H, Ar-H), 8.59 (s, 1H, Ar-H), 8.21 (s, 1H, Ar-H), 7.64 (dd, J = 2.0, 8.8 Hz, 1H, Ar-H), 6.64 (t, J = 6.4 Hz, 1H, H-1'), 4.66–4.64 (m, 1H, H-3'), 4.09–4.07 (m, 1H, H-4'), 3.89 (dd, J = 3.9, 11.3 Hz, 1H, H-5'), 3.81 (dd, J = 3.0, 11.2 Hz, 1H, H-5'), 2.68 (app quint, J_{app} ~ 6.5 Hz, 1H, H-2'), 2.54 (ddd, J = 3.5, 5.8, 12.9 Hz, 1H, H-2'), 0.94 and 0.91 (2s, 18H, *t*-Bu), 0.13, 0.10, and 0.09 (3s, 12H, SiCH_3). ^{13}C NMR of **28a** (125 MHz, CDCl_3): δ 153.8, 151.7, 147.1, 146.8, 144.4, 131.3, 130.8, 130.1, 123.8, 119.7, 116.1, 88.3, 84.8, 72.1, 62.8, 41.5, 26.0, 25.8, 18.4, 18.0, -4.6, -4.7, -5.3, -5.4. HRMS of **28a** (ESI/TOF) calcd for $\text{C}_{28}\text{H}_{43}\text{O}_3\text{ClN}_7\text{Si}_2$ $[\text{M} + \text{H}]^+$ 616.2654, found 616.2643. R_f of **28b** (50% EtOAc in hexanes) = 0.69. ^1H NMR of **28b** (500 MHz, CDCl_3): δ 8.99 (s, 1H, Ar-H), 8.81 (d, J = 1.0 Hz, 1H, Ar-H), 8.58 (s, 1H, Ar-H), 8.12 (d, J = 8.8 Hz, 1H, Ar-H), 7.48 (dd, J = 1.4, 8.8 Hz, 1H, Ar-H), 6.63 (t, J = 6.6 Hz, 1H, H-1'), 4.66–4.64 (m, 1H, H-3'), 4.09–4.07 (m, 1H, H-4'), 3.89 (dd, J = 4.2, 11.0 Hz, 1H, H-5'), 3.80 (dd, J = 2.9, 11.2 Hz, 1H, H-5'), 2.69 (app quint, J_{app} ~ 6.4 Hz, 1H, H-2'), 2.53 (ddd, J = 3.4, 5.9, 13.1 Hz, 1H, H-2'), 0.93 and 0.90 (2s, 18H, *t*-Bu), 0.12, 0.09, and 0.08 (3s, 12H, SiCH_3). ^{13}C NMR of **28b** (125 MHz, CDCl_3): δ 153.7, 151.6, 147.1, 144.7, 144.3, 135.8, 132.5, 126.6, 123.6, 121.0, 115.1, 88.2, 84.7, 72.1, 62.8, 41.4, 25.9, 25.7, 18.4, 17.9, -4.7, -4.8, -5.4, -5.5. HRMS of **28b** (ESI/TOF) calcd for $\text{C}_{28}\text{H}_{42}\text{O}_3\text{ClN}_7\text{Si}_2\text{Na}$ $[\text{M} + \text{Na}]^+$ 638.2468, found 638.2467.

Deoxygenation of O⁶-(6-chlorobenzotriazol-1-yl)guanosine derivative (13)—As described for the deoxygenation of compound **1**, this reaction was carried out with compound **13** (130.2 mg, 0.167 mmol), $(\text{pinB})_2$ (46.1 mg, 0.182 mmol), and Cs_2CO_3 (109.0 mg, 0.335 mmol) in PhMe (1.5 mL) at 100 °C for 4 h. Purification by flash chromatography (SiO_2 , eluted with 15% EtOAc in hexanes) gave isomers **29a** (19.1 mg), **29b** (46.4 mg) and a mixture of **29a** + **29b** (46.4 mg), each as an off-white to white fluffy solid, for an overall yield of 84%. R_f of **29a** (20% EtOAc in hexanes) = 0.42. ^1H NMR of **29a** (500 MHz, CDCl_3): δ 8.54 (d, J = 9.3 Hz, 1H, Ar-H), 8.28 (s, 1H, Ar-H), 8.17 (d, J = 1.7 Hz, 1H, Ar-H), 7.57 (dd, J = 1.6, 8.8 Hz, 1H, Ar-H), 6.07 (d, J = 5.4 Hz, 1H, H-1'), 5.20 (s, 2H, NH_2), 4.56 (t, J = 4.7 Hz, 1H, H-2'), 4.30 (t, J = 3.8 Hz, 1H, H-3'), 4.13–4.15 (m, 1H, H-4'), 3.98 (dd, J = 3.3, 11.5 Hz, 1H, H-5'), 3.81 (dd, J = 2.2, 11.5 Hz, 1H, H-5'), 0.96, 0.95, and 0.82 (3s, 27H, *t*-Bu), 0.15, 0.14, 0.12, 0.00, and -0.16 (5s, 18H, SiCH_3). ^{13}C NMR of **29a** (125 MHz, CDCl_3): δ 158.9, 156.4, 147.6, 146.8, 141.6, 131.0, 130.7, 129.6, 119.6, 117.9, 115.9, 87.4, 85.8, 76.3, 72.3, 62.8, 26.1, 25.9, 25.7, 18.6, 18.1, 17.9, -4.3, -4.5, -4.6, -4.9, -5.2, -5.3. HRMS of **29a** (ESI/TOF) calcd for $\text{C}_{34}\text{H}_{58}\text{O}_4\text{ClN}_8\text{Si}_3$ $[\text{M} + \text{H}]^+$ 761.3572, found 761.3567. R_f of **29b** (20% EtOAc in hexanes) = 0.30. ^1H NMR of **29b** (500 MHz, CDCl_3): δ 8.64 (d, J = 1.7 Hz, 1H, Ar-H), 8.29 (s, 1H, Ar-H), 8.11 (d, J = 8.2 Hz, 1H, Ar-H), 7.46 (dd, J = 1.6, 8.8 Hz, 1H, Ar-H), 6.07 (d, J = 5.4 Hz, 1H, H-1'), 5.22 (s, 2H, NH_2), 4.57 (t, J = 4.4 Hz, 1H, H-2'), 4.31–4.30 (m, 1H, H-3'), 4.15–4.13 (m, 1H, H-4'), 3.98 (dd, J = 3.3, 11.5 Hz, 1H, H-5'), 3.81 (dd, J = 2.2, 11.5 Hz, 1H, H-5'), 0.96, 0.95, and 0.83 (3s, 27H, *t*-Bu), 0.16, 0.15, 0.12, 0.00, and -0.16 (5s, 18H, SiCH_3). ^{13}C NMR of **29b** (125 MHz, CDCl_3): δ 158.8, 156.4, 147.7, 144.7, 141.7, 135.4, 132.5, 126.4, 121.0, 118.0, 115.0, 87.5, 85.7, 76.2, 72.2, 62.7, 26.1, 25.9, 25.7, 18.6, 18.1, 17.9, -4.3, -4.5, -4.6, -4.9, -5.2, -5.3. HRMS of **29b** (ESI/TOF) calcd for $\text{C}_{34}\text{H}_{58}\text{O}_4\text{ClN}_8\text{Si}_3$ $[\text{M} + \text{H}]^+$ 761.3572, found 761.3577.

Deoxygenation of O⁶-(6-chlorobenzotriazol-1-yl)-2'-deoxyguanosine derivative

(14)—As described for the deoxygenation of compound **1**, this reaction was carried out with compound **14** (108.4 mg, 0.167 mmol), (pinB)₂ (46.1 mg, 0.182 mmol), and Cs₂CO₃ (109.0 mg, 0.335 mmol) in PhMe (1.5 mL) at 100 °C for 4 h. Purification by flash chromatography (SiO₂, eluted with 25% EtOAc in hexanes) gave 83 mg (79% yield) a 1:1 mixture of **30a** + **30b** as an off-white, fluffy solid. *R_f*(30% EtOAc in hexanes) = 0.37, 0.30. ¹H NMR (500 MHz, CDCl₃): δ 8.59 (d, *J* = 1.1 Hz, 1H, Ar-H), 8.48 (d, *J* = 8.7 Hz, 1H, Ar-H), 8.23 (s, 1H, Ar-H), 8.22 (s, 1H, Ar-H), 8.14 (s, 1H, Ar-H), 8.08 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.52 (dd, *J* = 1.1, 8.8 Hz, 1H, Ar-H), 7.42 (dd, *J* = 1.6, 8.8 Hz, 1H, Ar-H), 6.43 (t, *J* = 6.0 Hz, 2H, H-1'), 5.32 and 5.27 (2s, 4H, NH₂), 4.62–4.60 (m, 2H, H-3'), 4.04–4.02 (m, 2H, H-4'), 3.84–3.73 (m, 4H, H-5'), 2.60 (app quint, *J*_{app} ~ 4.4 Hz, 2H, H-2'), 2.45–2.40 (m, 2H, H-2'), 0.92 and 0.90 (2s, 36H, *t*-Bu), 0.12, 0.08, and 0.07 (3s, 24H, SiCH₃). ¹³C NMR (125 MHz, CDCl₃): δ 158.9, 158.8, 156.0, 147.6, 147.5, 146.7, 144.7, 141.5, 141.4, 135.5, 132.5, 131.0, 130.6, 129.7, 126.4, 121.0, 119.6, 118.0, 117.9, 115.8, 114.9, 88.0, 83.8, 62.9, 41.1, 26.0, 25.8, 18.4, 18.0, -4.6, -4.7, -5.3, -5.5. HRMS (ESI/TOF) calcd for C₂₈H₄₄O₃ClN₈Si₂ [M + H]⁺ 631.2758, found 631.2745.

Deoxygenation of O⁶-(benzotriazol-1-yl)-2',3',5'-tri-O-(*t*-butyldimethylsilyl)-2-phenylinosine (19)

—As described for the deoxygenation of compound **1**, this reaction was carried out with compound **19** (40.0 mg, 0.05 mmol), (pinB)₂ (13.7 mg, 0.054 mmol), and Cs₂CO₃ (32.4 mg, 0.1 mmol) in PhMe (1 mL) at 100 °C for 4 h. Purification by flash chromatography (SiO₂, eluted with 20% and 25% EtOAc in hexanes) gave 35.1 mg (89% yield) of product **31** as a pale pink, fluffy solid. *R_f*(20% EtOAc in hexanes) = 0.47. ¹H NMR (500 MHz, C₆D₆): δ 8.78 (d, *J* = 7.4 Hz, 2H, Ar-H), 8.71 (d, *J* = 8.3 Hz, 1H, Ar-H), 8.63 (s, 1H, Ar-H), 7.97 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.42 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.30 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.23 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.01 (t, *J* = 7.6 Hz, 1H, Ar-H), 6.42 (d, *J* = 4.4 Hz, 1H, H-1'), 4.91 (t, *J* = 4.2 Hz, 1H, H-2'), 4.60 (t, *J* = 4.2 Hz, 1H, H-3'), 4.33–4.31 (m, 1H, H-4'), 4.03 (dd, *J* = 3.5, 11.2 Hz, 1H, H-5'), 3.78 (dd, *J* = 1.5, 11.3 Hz, 1H, H-5'), 1.02, 0.98, and 0.93 (3s, 27H, *t*-Bu), 0.16, 0.15, 0.11, 0.05, 0.00, and -0.01 (6s, 12H, SiCH₃). ¹³C NMR (125 MHz, C₆D₆): δ 158.5, 155.0, 147.9, 146.6, 144.4, 137.9, 132.2, 130.4, 128.5, 128.4, 128.0, 127.8, 127.6, 124.8, 123.6, 120.1, 114.5, 88.7, 84.9, 76.2, 71.7, 62.2, 25.9, 25.7, 25.6, 18.3, 18.0, 17.8, 1.0, -4.4, -4.8, -4.9, -5.6, -5.62. HRMS (ESI/TOF) calcd for C₄₀H₆₂O₄N₇Si₃ [M + H]⁺ 788.4166, found 788.4151.

Synthesis of 5,6-dichloro-1-hydroxy-1*H*-benzotriazole (34)

Step 1: preparation of 1,2,4-trichloro-5-nitrobenzene (33).³² In a clean, dry, round-bottomed flask a mixture of KNO₃ (8.34 g, 82.5 mmol) in conc. H₂SO₄ (110 mL) was cooled at 0 °C with stirring. To this stirring mixture was added 1,2,4-trichlorobenzene (6.9 mL, 55.5 mmol) dropwise. The mixture was then warmed to 50 °C for 3 h. The mixture was cooled to 0 °C and neutralized with 2M aq. NaOH. The crystals formed were filtered, washed with water, and crystallized from petroleum ether to yield compound **33** as fine, pale-yellow crystals. To remove impurity traces, further purification was done by flash chromatography (SiO₂, eluted with hexanes) to give 12.0 g (96% yield) of compound **33**. *R_f* (20% EtOAc/hexanes) = 0.71. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.49 (s, 1H, Ar-H), 8.25 (s, 1H, Ar-H). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 146.4, 136.5, 132.8, 131.2, 127.1, 124.9.

Step 2: conversion of 33 to 34: In a clean, dry, round-bottomed flask equipped with a stirring bar were placed compound **33** (3.3 g, 14.6 mmol), EtOH (33 mL), PhMe (16.5 mL), Na₂CO₃ (2.01 g, 18.9 mmol), and water (1.8 mL) in that order. To the gently stirring mixture was added hydrazine (4.57 g, 145.7 mmol) and the mixture was heated to reflux at 100 °C for 20 h. The mixture was cooled to room temperature and the flask was transferred to an ice-cold water bath. Upon acidification to pH 2 with 1M HCl a precipitate formed, which was filtered, and washed with cold water. The crude material was recrystallized from 1:1 H₂O/EtOH to give 1.678 g (56% yield) of product **34** as a pale-brown powder. *R_f*(10% CH₃OH in CH₂Cl₂) = 0.60. ¹H NMR (500 MHz, DMSO-*d*₆): δ 14.05 (br s, 1H, OH), 8.40 (s, 1H, Ar-H), 8.09 (s, 1H, Ar-H). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 141.8, 130.8, 127.7, 127.02, 120.7, 111.3, 124.9. HRMS (ESI/TOF) calcd for C₆H₃OCl₂N₃Na [M + Na]⁺ 225.9545, found 225.9546.

Reduction of 5,6-dichloro-1-hydroxy-1*H*-benzotriazole (34) to 5,6-dichloro-1*H*-benzotriazole (35)—To a mixture of 5,6-dichloro-1-hydroxy-1*H*-benzotriazole (**34**, 50.0 mg, 0.245 mmol) in CH₃CN (1 mL) was added Et₃N (41.0 μL, 0.294 mmol), and the mixture was stirred at room temperature for 30 min. To this mixture was added B₂(OH)₄ (26.3 mg, 0.294 mmol) and the mixture was stirred at 50 °C for 30 min. The mixture was cooled and evaporated under reduced pressure. Purification of the crude material by flash chromatography (SiO₂, eluted with 40% EtOAc in hexanes) to gave 33.3 mg (72% yield) of 5,6-chloro-1-hydroxy-1*H*-benzotriazole (**35**) as a pale-yellowish-brown powder. *R_f*(10% CH₃OH in CH₂Cl₂) = 0.63. ¹H NMR (500 MHz, DMSO-*d*₆): δ 16.05 (s, 1H, NH), 8.34 (s, 2H, Ar-H). HRMS (ESI/TOF) calcd for C₆H₄Cl₂N₃ [M + H]⁺ 187.9777, found 187.9779.

O⁶-(5,6-Dichlorobenzotriazol-1yl)-3',5'-di-O-(*t*-butyldimethylsilyl)-2'-deoxyinosine (40)—To a stirred solution of 5,6-dichloro-1-hydroxy-1*H*-benzotriazole (**34**, 286.0 mg, 1.404 mmol) in anhydrous DME (3 mL) were added Et₃N (195.8 μL, 1.404 mmol) and MeCN (1.5 mL), and the mixture was stirred at room temperature for 15 min. PyBroP (276.3 mg, 0.59 mmol) was added and the stirring was continued at room temperature for 15 min. 3',5'-Di-*O*-TBDMS-protected 2'-deoxyinosine (150.0 mg, 0.312 mmol) was added, followed by the dropwise addition of DIPEA (198.0 μL, 1.135 mmol). The mixture was stirred at room temperature for 20 h and then evaporated under reduced pressure. Purification by flash chromatography (SiO₂, eluted with 15% EtOAc in hexanes) gave 146.0 mg (70% yield) of product **40** as a yellow, fluffy solid. *R_f*(20% EtOAc in hexanes) = 0.43. ¹H NMR (500 MHz, CDCl₃): δ 8.55 (s, 1H, Ar-H), 8.41 (s, 1H, Ar-H), 8.26 (s, 1H, Ar-H), 7.64 (s, 1H, Ar-H), 6.55 (t, *J* = 6.3 Hz, 1H, H-1'), 4.65–4.63 (m, 1H, H-3'), 4.07–4.05 (m, 1H, H-4'), 3.92 (dd, *J* = 3.9, 11.0 Hz, 1H, H-5'), 3.80 (dd, *J* = 3.1, 11.3 Hz, 1H, H-5'), 2.64 (app quint, *J_{app}* ~ 6.3 Hz, 1H, H-2'), 2.52 (ddd, *J* = 4.4, 6.0, 13.2 Hz, 1H, H-2'), 0.92 (1s, 18H, *tert*-Bu), 0.11 and 0.109 (2s, 12H, SiCH₃). ¹³C NMR (125 MHz, CDCl₃): δ 158.6, 153.7, 151.2, 143.9, 142.2, 134.2, 130.0, 128.1, 121.5, 119.8, 110.1, 88.2, 85.1, 71.6, 62.6, 41.7, 26.0, 25.7, 18.4, 18.0, -4.6, -4.8, -5.4, -5.5. HRMS (ESI/TOF) calcd for C₂₈H₄₁Cl₂N₇O₄Si₂Na [M + Na] 688.2028, found 688.2029.

O⁶-(5,6-Dichlorobenzotriazol-1yl)-2',3',5'-tri-O-(*t*-butyldimethylsilyl)inosine (41)—As described for the preparation of compound **40**, this synthesis was performed with

5,6-dichloro-1-hydroxy-1*H*-benzotriazole (**34**, 286.4 mg, 1.404 mmol), anhydrous DME (3 mL), Et₃N (195.0 μ L, 1.404 mmol), CH₃CN (1.5 mL), PyBroP (276.3 mg, 0.59 mmol), 2', 3', 5'-tri-*O*-TBDMS-protected inosine (190.6 mg, 0.312 mmol), and DIPEA (198.0 μ L, 1.815 mmol). After addition of the last reagent the mixture was stirred at room temperature for 7 h and evaporated under reduced pressure. Purification by flash chromatography (SiO₂, eluted with 5% and 10% EtOAc in hexanes) gave 174.0 mg (70% yield) of product **41** as an off-white, fluffy solid. (Trace amounts of **38** and **39** were observed and removed chromatographically). *R_f*(15% EtOAc in hexanes) = 0.64. ¹H NMR (500 MHz, CDCl₃): δ 8.64 (s, 1H, Ar-H), 8.41 (s, 1H, Ar-H), 8.26 (s, 1H, Ar-H), 7.63 (s, 1H, Ar-H), 6.15 (d, *J* = 3.9 Hz, 1H, H-1'), 4.57 (t, *J* = 3.9 Hz, 1H, H-2'), 4.34 (t, *J* = 4.4 Hz, 1H, H-3'), 4.19–4.17 (m, 1H, H-4'), 4.05 (dd, *J* = 3.4, 11.7 Hz, 1H, H-5'), 3.82 (d, *J* = 11.7 Hz, 1H, H-5'), 0.97, 0.93, and 0.82, (3s, 27H, *t*-Bu), 0.17, 0.16, 0.11, 0.10, 0.004, and –0.15 (6s, 18H, SiCH₃). ¹³C NMR (125 MHz, CDCl₃): δ 158.7, 154.1, 151.5, 144.3, 142.4, 134.4, 130.1, 128.2, 121.6, 110.2, 89.1, 85.6, 76.7, 71.6, 62.3, 26.3, 26.0, 25.8, 18.7, 18.2, 18.0, –4.2, –4.5, –4.6, –4.8, –5.2, –5.3, –11.7. HRMS (ESI/TOF) calcd for C₃₄H₅₅Cl₂N₇O₅Si₃Na [M + Na]⁺ 818.2842, found 818.2862.

Deoxygenation of O⁶-(5,6-dichlorobenzotriazol-1yl)-3',5'-di-O-(*t*-butyldimethylsilyl)-2'-deoxyinosine (40**)**—As described for the deoxygenation of compound **1**, this reaction was carried out with compound **40** (100.0 mg, 0.15 mmol), (pinB)₂ (41.3 mg, 0.163 mmol), and Cs₂CO₃ (97.7 mg, 0.29 mmol) in PhMe (1.5 mL) at 100 °C for 4 h. Purification by flash chromatography (SiO₂, eluted with 20% and 30% EtOAc in hexanes) gave 60.0 mg (61% yield) of product **42** as a yellow, fluffy solid. *R_f* (20% EtOAc in hexanes) = 0.25. ¹H NMR (500 MHz, CDCl₃): δ 9.01 (s, 1H, Ar-H), 8.94 (s, 1H, Ar-H), 8.60 (s, 1H, Ar-H), 8.33 (s, 1H, Ar-H), 6.64 (t, *J* = 6.6 Hz, 1H, H-1'), 4.67–4.65 (m, 1H, H-3'), 4.10–4.08 (m, 1H, H-4'), 3.90 (dd, *J* = 3.6, 11.2 Hz, 1H, H-5'), 3.82 (d, *J* = 11 Hz, 1H, H-5'), 2.68 (app quint, *J_{app}* ~ 3.3 Hz, 1H, H-2'), 2.54 (ddd, *J* = 3.4, 6.7, 12.9 Hz, 1H, H-2'), 0.94 and 0.91 (2s, 18H, *t*-Bu), 0.13, 0.10, and 0.10 (3s, 12H, SiCH₃). HRMS (ESI/TOF) calcd for C₂₈H₄₂Cl₂N₇O₃Si₂ [M + H]⁺ 650.2259, found 650.2260.

Deoxygenation of O⁶-(5,6-dichlorobenzotriazol-1yl)-2',3',5'-tri-O-(*t*-butyldimethylsilyl)inosine (41**)**—As described for the deoxygenation of compound **1**, this reaction was carried out with compound **41** (119.5 mg, 0.15 mmol), (pinB)₂ (41.3 mg, 0.163 mmol), and Cs₂CO₃ (97.7 mg, 0.29 mmol) in PhMe (1.5 mL) at 100 °C for 4 h. Purification by flash chromatography (SiO₂, eluted with 10% EtOAc in hexanes) gave 61.1 mg (56% yield) of product **43** as a pale-yellow powder. *R_f*(15% EtOAc in hexanes) = 0.46. ¹H NMR (500 MHz, CDCl₃): δ 9.00 (s, 1H, Ar-H), 8.99 (s, 1H, Ar-H), 8.64 (s, 1H, Ar-H), 8.32 (s, 1H, Ar-H), 6.26 (d, *J* = 5.4 Hz, 1H, H-1'), 4.69 (t, *J* = 4.6 Hz, 1H, H-2'), 4.34–4.33 (m, 1H, H-3'), 4.20–4.18 (m, 1H, H-4'), 4.03 (dd, *J* = 3.6, 11.4 Hz, 1H, H-5'), 3.83 (d, *J* = 11.7 Hz, 1H, H-5'), 0.97, 0.95, and 0.78 (3s, 27H, *t*-Bu), 0.17, 0.16, 0.12, –0.03, and –0.26 (5s, 18H, SiCH₃). HRMS (ESI/TOF) calcd for C₃₄H₅₆Cl₂N₇O₄Si₃ [M + H]⁺ 780.3073, found 780.3073.

Crossover experiment involving compounds **4 and **41****—As described for the deoxygenation of compound **1**, a mixture of compounds **4** (50.0 mg, 83.7 μ mol), **41** (66.7

mg, 83.7 μ mol), (pinB)₂ (46.1 mg, 0.182 mmol), and Cs₂CO₃ (109 mg, 0.335 mmol) in PhMe (1.5 mL) was stirred at 100 °C for 4 h. The mixture was cooled and evaporated under reduced pressure. Chromatographic separation by preparatory TLC (1 mm, 20 × 20 cm SiO₂ plate eluted with 30% EtOAc in hexanes) gave compounds **43** (15.4 mg), **2** (28.8 mg), **42** (15.1 mg), and **5** (30.2 mg). *R_f* values (30% EtOAc in hexanes) of **43**: 0.82, **2**: 0.70, **42**: 0.53, and **5**: 0.34.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Herdewijn, P., editor. *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*. Wiley-VCH; Weinheim: 2008.
2. Blackburn, GM.; Gait, MJ.; Loakes, D.; Williams, DM., editors. *Nucleic Acids in Chemistry and Biology*. 3. RSC Publishing; Cambridge, UK: 2006.
3. Simons, C. *Nucleoside Mimetics: Their Chemistry and Biological Properties*. Gordon and Breach; Amsterdam: 2001.
4. Kisakürek, MV.; Rosemeyer, H., editors. *Perspectives in Nucleoside and Nucleic Acid Chemistry*. Verlag Helvetica Chimica Acta, Zurich and Wiley-VCH; Weinheim: 2000.
5. Suhadolnik, RJ. *Nucleosides as Biological Probes*. Wiley; New York: 1979.
6. Chu, CK., editor. *Antiviral Nucleosides: Chiral Synthesis and Chemotherapy*. Elsevier; Amsterdam: 2003.
7. Venkatesan N, Seo YJ, Bang EK, Park SM, Lee YS, Kim BH. *Bull Korean Chem Soc*. 2006; 27:613–630.
8. Wiebe LI. *Braz Arch Biol Technol*. 2007; 50:445–459.
9. Bergstrom DE. *Curr Protoc Nucleic Acids Chem*. 2009; 37:1.4:1.4.1–1.4.32.
10. Srivatsan SG, Sawant AA. *Pure Appl Chem*. 2011; 83:213–232.
11. Bae S, Lakshman MK. *J Am Chem Soc*. 2007; 129:782–789. [PubMed: 17243813]
12. Bae S, Lakshman MK. *J Org Chem*. 2008; 73:1311–1319. [PubMed: 18205381]
13. Bae S, Lakshman MK. *J Org Chem*. 2008; 73:3707–3713. [PubMed: 18429630]
14. Bae S, Lakshman MK. *Org Lett*. 2008; 10:2203–2206. [PubMed: 18476663]
15. Lakshman MK, Frank J. *Org Biomol Chem*. 2009; 7:2933–2940. [PubMed: 19582304]
16. Satishkumar S, Vuram PK, Relangi SS, Gurram V, Zhou H, Kreitman RJ, Martínez Montemayor MM, Yang L, Kaliyaperumal M, Sharma S, Pottabathini N, Lakshman MK. *Molecules*. 2015; 20:18437–18463.
17. Wan ZK, Binnun E, Wilson DP, Lee J. *Org Lett*. 2005; 7:5877–5880. [PubMed: 16354089]
18. Wan ZK, Wacharasindhu S, Levins CG, Lin M, Tabei K, Mansour TS. *J Org Chem*. 2007; 72:10194–10210. [PubMed: 18044930]
19. Ashton TD, Scammells PJ. *Aust J Chem*. 2008; 61:49–58.
20. Qu GR, Zhang HL, Niu HY, Xue ZK, Lv XX, Guo HM. *Green Chem*. 2012; 14:1877–1879.
21. Malow M, Wehrstedt KD, Neuenfeld S. *Tetrahedron Lett*. 2007; 48:1233–1235.

22. See for leading examples: Shi F, Waldo JP, Chen Y, Larock RC. *Org Lett*. 2008; 10:2409–2412. [PubMed: 18476707] Campbell-Verduyn L, Elsinga PH, Mirfeizi L, Dierckx RA, Feringa BL. *Org Biomol Chem*. 2008; 6:3461–3463. [PubMed: 19082144]
23. (a) Antilla JC, Baskin JM, Barder TE, Buchwald SL. *J Org Chem*. 2004; 69:5578–5587. [PubMed: 15307726] (b) Ueda S, Su M, Buchwald SL. *Angew Chem Int Ed*. 2011; 50:8944–8947.
24. Lakshman MK, Singh MK, Parrish D, Balachandran R, Day BW. *J Org Chem*. 2010; 75:2461–2473. [PubMed: 20297785]
25. (a) Harwood EA, Sigurdsson ST, Edfeldt NBF, Reid BR, Hopkins PB. *J Am Chem Soc*. 1999; 121:5081–5082. (b) Qian M, Glaser R. *J Am Chem Soc*. 2005; 127:880–887. [PubMed: 15656626]
26. Gurram V, Pottbathini N, Garlapati R, Chaudhary AB, Patro B, Lakshman MK. *Chem Asian J*. 2012; 7:1853–1861. [PubMed: 22570232]
27. Gurram V, Akula HK, Garlapati R, Pottabathini N, Lakshman MK. *Adv Synth Catal*. 2015; 357:451–462. [PubMed: 25729343]
28. (a) Dormoy J-R, Castro B. *Tetrahedron Lett*. 1979; 20:3321–3322. (b) Coste J, Le-Nguyen D, Castro B. *Tetrahedron Lett*. 1990; 31:205–208.
29. Rivero IA, Somanathan R, Hellberg LH. *Synth Commun*. 1995; 25:2185–2188.
30. Wehrstedt KD, Wandrey PA, Heitkamp D. *J Hazard Mater*. 2005; 126:1–7. [PubMed: 16084016]
31. Leonard NJ, Golankiewicz K. *J Org Chem*. 1969; 34:359–365.
32. Legrand YM, Gray M, Cooke G, Rotello VM. *J Am Chem Soc*. 2003; 125:15789–15795. [PubMed: 14677969]
33. (a) Augustynowicz-Kopec E, Zwolska Z, Orzeszko A. *Acta Pol Pharm Drug Res*. 2008; 65:435–439. (b) Dabhade PS. *Asian J Biomed Pharm Sci*. 2013; 3:29–34.
34. Lakshman MK, Choudhury A, Bae S, Rochttis E, Pradhan P, Kumar A. *Eur J Org Chem*. 2009:152–159.
35. Carter, CAG.; John, KD.; Mann, G.; Martin, RL.; Cameron, TM.; Baker, RT.; Bishop, KL.; Broene, RD.; Westcott, SA. Bifunctional Lewis acid reactivity of diol-derived diboron reagents. In: Shapiro, PJ.; Atwood, DA., editors. *Group 13 Chemistry/From Fundamentals to Applications*. American Chemical Society; Washington, DC: 2002. p. 70-87. ACS Symposium Series 822
36. Kokatla HP, Thomson PF, Bae S, Lakshman MK. *J Org Chem*. 2011; 76:7842–7848. [PubMed: 21812467]
37. Londregan AT, Piotrowski DW, Xiao J. *Synlett*. 2013; 24:2695–2700.
38. Wheeler CA, Millar JG, Cardé RT. *Chemoecology*. 2015; 25:123–133.
39. Kim J, Bertozzi CR. *Angew Chem Int Ed*. 2016; 54:15777–15781.

Fig. 1.
Structures of commercially available peptide coupling agents and precursors prepared with them. PG = TBDMS.

Fig. 2.

Structures of products formed from the deoxygenation reactions. PG = TBDMS.

Scheme 1.

Formation of *O*⁶-(benzotriazol-1-yl)purine nucleoside derivatives and their conversion to other modified purine nucleosides.

Scheme 2.

Four possible approaches to 6-(benzotriazol-1-yl)purine nucleosides.

Scheme 3.

Synthesis of an O^6 -(benzotriazol-1-yl)-2-phenylinosine derivative. PG = TBDMS.

Scheme 4.
Synthesis of 5,6-dichloro-1-hydroxy-1*H*-benzotriazole.

Scheme 5.

Products formed in the various attempted conversions of TBDMS-protected I and dI to the *O*⁶-(5,6-dichlorobenzotriazol-1-yl)inosine derivatives.

Scheme 6.

Use of PyBroP for conversion of TBDMS-protected dI and I to the corresponding *O*⁶-(5,6-dichlorobenzotriazol-1-yl) derivatives.

Scheme 7. Deoxygenation of *O*⁶-(5,6-dichloro-1*H*-benzotriazol-1-yl)inosine

Scheme 8.

The crossover experiment and the products obtained.

Scheme 9.

Two additional experiments, in the absence of $(\text{pinB})_2$, and in the presence of water.

Scheme 10.

Plausible reactions pathways that can result in the deoxygenation.

Table 1

Evaluation of conditions for the deoxygenation of *O*⁶-(benzotriazol-1-yl)inosine and 2'-deoxyinosine derivatives^a

Entry	Substrate	Conditions	Result	Total yield
1	1	Cs ₂ CO ₃ , (pinB) ₂ , PhMe, 100 °C	2 : 98%, 3 : 0%	98%
2	1	K ₃ PO ₄ , (pinB) ₂ , PhMe, 100 °C	2 : 82%, 3 : 8%	90% ^{b,c}
3	1	K ₂ CO ₃ , (pinB) ₂ , PhMe, 100 °C	2 : 74%, 3 : 0%	74% ^d
4	1	<i>no base</i> , (pinB) ₂ , PhMe, 100 °C	2 : 0%, 3 : 0%	0% ^e
5	1	Cs ₂ CO ₃ , (pinB) ₂ , MeCN, 75 °C	2 : 38%, 3 : 0%	38%
6	1	K ₃ PO ₄ , (pinB) ₂ , MeCN, 75 °C	2 : 94%, 3 : 4%	98%
7	1	K ₂ CO ₃ , (pinB) ₂ , MeCN, 75 °C	2 : 81%, 3 : 11%	92% ^c
8	4	Cs ₂ CO ₃ , (pinB) ₂ , PhMe, 100 °C	5 : 90%, 6 : 0%	90%
9	4	K ₃ PO ₄ , (pinB) ₂ , MeCN, 75 °C	5 : 63%, 6 : 6%	69% ^{b,c}

^aReactions were conducted on 76.5 μmol of the nucleoside at 0.1 M concentration in the reaction solvent, with 2 equiv. of base, and 1.1 equiv. of (pinB)₂. Yields reported are after chromatographic isolation of products or product mixtures.

^bReaction did not reach completion.

^cThe *N*1 and *N*2 isomers were collected as a combined fraction and the ratio was assessed by the integration of their purinyl resonances.

^dThe reaction was incomplete, and the starting material and the *N*1 isomer were collected as a single fraction. The % of the *N*1 isomer was estimated from the integration of the H-1' resonances.

^eNo reaction was observed and compound **1** was still present.

Table 2

Deoxygenation of various *O*⁶-(benzotriazol-1-yl)purine nucleoside derivatives to 6-(benzotriazolyl)purine nucleosides^a

Entry	Substrate	N1 isomer	N2 isomer	Other
1 ^b	1 : A = B = CH, Z = H, R = H (ribo)	2 : 90%	—	—
2 ^b	4 : A = B = CH, Z = H, R = H (deoxyribo)	5 : 87%	—	—
3 ^b	7 : A = B = CH, Z = NH ₂ , R = H (ribo)	20 : 82%	21 : Trace	—
4 ^b	8 : A = B = CH, Z = NH ₂ , R = H (deoxyribo)	22 : 91%	23 : Trace	—
5 ^b	9 : A = N, B = CH, Z = H, R = H (ribo)	—	—	25 : 25% ^c
6 ^b	10 : A = N, B = CH, Z = H, R = H (deoxyribo)	24 : 11%	—	26 : 29% ^c
7 ^b	11 : A = B = CH, Z = H, R = 6-Cl (ribo)	27a+b : 64%	—	—
8 ^b	12 : A = B = CH, Z = H, R = 6-Cl (deoxyribo)	28a+b : 84% ^{d,e}	—	—
9 ^b	13 : A = B = CH, Z = NH ₂ , R = 6-Cl (ribo)	29a+b : 84% ^{d,e}	—	—
10 ^b	14 : A = B = CH, Z = NH ₂ , R = 6-Cl (deoxyribo)	30a+b : 79%	—	—
11 ^f	19 : A = B = CH, Z = Ph, R = H (ribo)	31 : 89%	—	—

^aYields of the N1 and N2 products are of isolated, purified products.

^bReactions were conducted at 0.1 M nucleoside (0.167 mmol) in PhMe, with 2 equiv. of Cs₂CO₃, and 1.1 equiv. of (pinB)₂.

^cFormation of dimers (**25** and **26**) was observed in these cases (see text).

^dTwo N1 isomers were observed (see text).

^eSmall amounts of each isomer were separated for characterization.

^fReaction was conducted with 0.05 mmol of compound **19** at a 0.1 M concentration in PhMe.

Table 3Chemical shifts of the benzotriazolyl and purinyl proton resonances in chloro benzotriazolyl products **27–30**^a

Compound	Benzotriazolyl proton resonances	Purinyl proton resonances
27a	$\delta = 8.74, 8.21, 7.64$ ppm	$\delta = 8.99, 8.63$ ppm
28a	$\delta = 8.72, 8.21, 7.64$ ppm	$\delta = 8.99, 8.59$ ppm
29a	$\delta = 8.54, 8.17, 7.57$ ppm	$\delta = 8.28$ ppm
30a	$\delta = 8.48, 8.14, 7.52$ ppm	$\delta = 8.23$ ppm
27b	$\delta = 8.85, 8.15, 7.50$ ppm	$\delta = 9.01, 8.63$ ppm
28b	$\delta = 8.81, 8.12, 7.48$ ppm	$\delta = 8.99, 8.58$ ppm
29b	$\delta = 8.64, 8.11, 7.46$ ppm	$\delta = 8.29$ ppm
30b	$\delta = 8.59, 8.08, 7.42$ ppm	$\delta = 8.22$ ppm

^aProton NMR spectra were obtained in CDCl₃.