

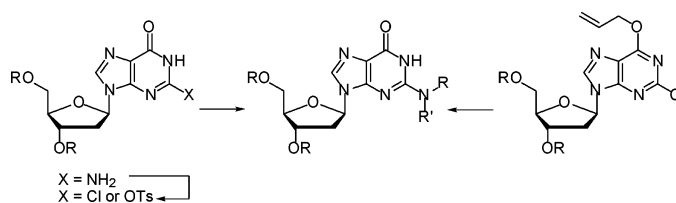
Synthesis and Reactions of 2-Chloro- and 2-Tosyloxy-2'-deoxyinosine Derivatives

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Received April 26, 2005



Convenient syntheses of 2-chloro- and 2-tosyloxy-2'-deoxyinosine as their *tert*-butyldimethylsilyl ethers are described. Both compounds can be synthesized via a common route and rely on commercially available 2'-deoxyguanosine. The present method leading to the chloro nucleoside is operationally simpler compared to previously reported glycosylation techniques where isomeric products were obtained. Both electrophilic nucleosides can be used for the preparation of N-substituted 2'-deoxyguanosine analogues via displacement of the leaving groups, and a comparison of their reactivities shows the chloro analogue to be superior. Interestingly, a Pd catalyst-mediated, two-step, one-pot conversion of an allyl-protected chloro nucleoside intermediate to the final modified 2'-deoxyguanosine derivatives is also feasible. On the basis of these observations, initial assessments of Pd-catalyzed aryl amination as well as a C–C cross-coupling have also been performed with the chloro and tosyloxy nucleoside substrates. Results indicate a potentially high synthetic utility of 2-chloro-2'-deoxyinosine and in many instances this derivative can supplant the bromo and fluoro analogues that are more cumbersome to prepare or are not readily available.

Introduction

The introduction of leaving groups into positions 2 and 6 of purine nucleosides produces reactive, electrophilic nucleosides that can be further manipulated via nucleophilic displacement mechanisms. An abundance of these types of transformations is available in the literature, and N-modified adenine and guanine nucleosides can also be prepared via these methods.¹ Due to their lability, synthesis of halo purine deoxynucleosides can be problematic. Among the electrophilic C-2-functionalized 2'-deoxyinosine nucleoside analogues, the fluoro, chloro, and bromo derivatives have been reported in the literature. On the other hand, a 2-iodo-2'-deoxyinosine derivative has been stated to be unstable.²

There are two approaches to the syntheses of 2-halo-2'-deoxyinosines. One is fusion chemistry, which has been utilized to prepare 2-fluoro-2'-deoxyinosine (as the O6-

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benzyl derivative) from 2-fluoro-6-benzylpurine and 1,3,5-tri-*O*-acetyl-2-deoxy- β -D-erythro-pentofuranose.³ Similarly, 2-bromo-2'-deoxyinosine has been synthesized by a condensation between 2-bromohypoxanthine and 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl- α -D-erythro-pentofuranose.⁴ In many cases, the glycosylation reaction can produce isomeric products that need separation. A second approach is nonaqueous diazotization–halogenation that alleviates many problems due to its reliance on the commercially available β -anomers of nucleosides. Generally, such procedures not only are operationally simple but also provide a more facile access to halo nucleosides compared to glycosylation techniques.⁵ Such nonaqueous diazotization has therefore provided routes to 2-fluoro-2'-deoxyinosine derivatives (O6-protected⁶ and unprotected⁷) as well as those of 2-bromo-2'-deoxyinosine (O6-protected⁸).

Synthesis of 2-chloro-2'-deoxyinosine as well as a limited study on its use in displacement reactions with amines have been reported in the literature.^{9–12} In these reports, the synthesis of the chloro nucleoside relied upon the glycosylation technique. Briefly, the sodium salt of 2,6-dichloropurine was allowed to react with 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl- α -D-erythro-pentofuranose to yield 2,6-dichloro-9-(2-deoxy-3,5-di-*O*-*p*-toluoyl- β -D-erythro-pentofuranosyl)purine.¹³ Although this reaction proceeded in good yield (72%), the desired N-9 nucleoside (59%) required chromatographic separation from the N-7 isomer (13%).¹³ In this context, it is noteworthy that synthesis of the relatively labile chloro sugar required for the glycosylation from 2-deoxy-D-ribose is a nontrivial, multistep procedure.¹⁴ Once the required N-9 2,6-dichloropurine nucleoside isomer was obtained, the C-6 chloride was selectively replaced with an allyloxy group. This step also produced deprotection of the sugar hydroxyls that were reprotected after deallylation to afford the necessary 2-chloro-2'-deoxyinosine derivative.^{9–11}

Among nonhalo, electrophilic 2'-deoxyinosine analogues, the C-2 triflate is known, albeit only as its O6-protected derivatives, which have been used in displacement reactions with amines.^{15,16} As described later, O6-protection may be detrimental to displacement reactions at the C-2 position. Due to our interest in studying metal-

catalyzed reactions¹⁷ at the C-2 position of purine nucleosides and because of the lack of a convenient route to 2-chloro- and 2-tosyloxy-2'-deoxyinosine derivatives, we decided to develop their syntheses. We also reasoned that both compounds could be prepared from common intermediates. Therefore, this paper describes a simple route to 2-chloro-2'-deoxyinosine and the first synthesis of the corresponding C-2 tosyloxy analogue. Since neither compound has been studied in detail, the relative reactivities of the two electrophilic nucleosides have been evaluated in direct displacement reactions with amines, and an initial assessment of their utilities for Pd-mediated transformations has also been made. As elaborated later, there are distinct advantages to the described syntheses and compounds.

Results and Discussion

Our synthesis commenced with the silylation of 2'-deoxyguanosine (**1**). Conversion of **2** to **3a** was accomplished via the Mitsunobu reaction.⁷ Although we have reported a two-step conversion of **2** to **3a** that circumvents the Mitsunobu reaction,¹⁸ the presence of excess benzyl alcohol in this procedure renders product purification somewhat difficult on a large scale. For the diazotization–chlorination, we initially chose conditions analogous to those reported for the bromination.⁸ Halogenation of **3a** with $\text{SbCl}_5/\text{tert-BuONO}$ in CH_2Cl_2 at -10°C was low yielding ($\sim 15\%$). More recently, the use of TMSCl and CH_3COCl has been reported for the halogenation of several nucleosides.²⁰ This procedure is operationally simple and was attempted in the present case. Diazotization–chlorination of **3a** with $\text{TMSCl}/\text{tert-BuONO}$ in CH_2Cl_2 at -10°C was again disappointing ($\sim 20\%$ yield of **4a**).²¹ In trying to understand the difficulty faced in the present case, we realized that TMSI had been utilized for the cleavage of nucleoside methyl ethers.²² On this basis we surmised that one potential problem in reactions of **3a** could reside with the O6-benzyl group, which could be susceptible to cleavage by TMSCl . Therefore, we chose further experimentation with the O6-allyl derivative **3b**. Due to the lower boiling point of allyl alcohol compared to benzyl alcohol, it was generally more convenient to prepare **3b** via a two-step method we have previously

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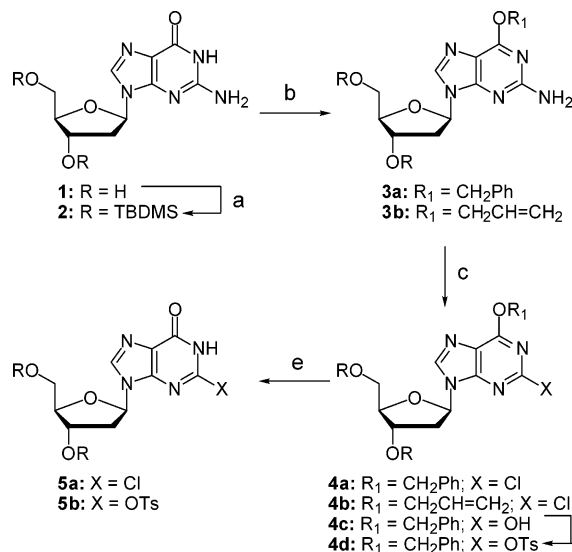
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(21) ¹H NMR for **4a** (500 MHz, CDCl_3): δ 8.25 (s, 1H, H-8), 7.54 (d, 2H, $J = 7.0$), 7.38–7.31 (m, 3H, Ar-H), 6.43 (app t, 1H, H-1', $J_{\text{app}} \sim 6.3$), 5.64 (AB_{quart}, 2H, $-\text{OCH}_2$, $J = 12.0$), 4.62 (m, 1H, H-3'), 4.00 (app q, 1H, H-4', $J_{\text{app}} \sim 3.5$), 3.89 (dd, 1H, H-5', $J = 11.3$; 4.0), 3.76 (dd, 1H, H-5', $J = 11.5$; 3.0), 2.59 (app quint, 1H, H-2', $J = 13.0$; 6.4), 2.43 (ddd, 1H, H-2', $J = 13.0$; 6.4; 4.0), 0.91 and 0.90 (2s, 18H, $\text{C}(\text{CH}_3)_3$), 0.099, 0.086 (2s, 12H, SiCH_3). FAB HRMS calcd for $\text{C}_{29}\text{H}_{46}\text{ClN}_4\text{O}_4\text{Si}_2$ ($\text{M}^+ + \text{H}$): 605.2746, found 605.2774.

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SCHEME 1. Synthesis of 3',5'-Bis-*O*-*tert*-butyldimethylsilyl 2-Chloro- and 2-Tosyloxy-2'-deoxyinosine^a



^a Key: (a) TBDMSCl, imidazole, DMF; (b) **3a**: PhCH₂OH, PPh₃, DEAD, 1,4-dioxane; **3b**: ref 18; (c) **4a,b**: *tert*-BuONO, TMSCl, CH₂Cl₂, -10 °C (see text for details); **4c**: NaNO₂, AcOH, H₂O-acetone; (d) *p*-TsCl, Et₃N, CH₂Cl₂; (e) **5a**: see text for details; **5b**: H₂, 10% Pd/C, 1:1 THF-MeOH.

reported.¹⁸ Through this procedure, **3b** was routinely synthesized on multigram scales with good overall yields (55–60%). At least in our hands, purification of products obtained by this route was simpler compared to the Mitsunobu reaction.

Diazotization–chlorination of **3b** with TMSCl/*tert*-BuONO in CH₂Cl₂ at -10 °C was much more successful, and **4b** could be routinely obtained in 50–55% yield. Since allyl group cleavage can be effected under either Pd or Ni catalysis,²³ we needed to determine whether metal insertion into the C–Cl bond would compete with allyl deprotection. This is in connection with our previous studies on C-6 halopurine nucleosides, where a chloro nucleoside has been shown to be remarkably effective in Pd-catalyzed cross-coupling reactions.²⁴ For this reason, we chose to evaluate the debenzoylation of **4a** under catalytic hydrogenation conditions. Loss of the halogen under these conditions could indicate reactivity at this position. When subjected to hydrogenation with 1 atm hydrogen pressure and 5% Pd–C, **4a** underwent debenzoylation cleanly with no loss of chlorine, as evidenced by the presence of a singlet at δ 8.12 ppm in the aromatic region (89% yield of **5a**). These results led us to the conclusion that metal insertion would not complicate the deallylation reaction.

Several methods were analyzed for deprotection of the O6-allyl group in **4b**.²⁵ An attempt using Pd(PPh₃)₄ and dimedone in THF proved to be impractical, although product formation was observed. Pd₂(dba)₃/(±)-BINAP/

TABLE 1. Reactions of 5a and 5b with Various Amines^a

entry	amine	yield with 5a	yield with 5b
1		6a : 84% ^b	6a : 43% ^b
2		6b : 98% ^b	6b : 43% ^b
3		6c : 73% ^b	6c : 39% ^b
4		6d : 56% ^b	6d : 39% ^b
5		6e : 73% ^c	6e : 43% ^b
6		6f : 73% ^d	6f : 53% ^b
7		6g : 69% ^e	ND ^f

^a Reactions were conducted in *tert*-BuOH at 85 °C. ^b Performed with 5 molar equiv of amine. ^c Performed with 2.5 molar equiv of amine. ^d Performed with 7.5 molar equiv of amine. ^e Performed with 30 molar equiv of amine. ^f Reaction was not performed.

morpholine in THF was promising on a small scale; however, competing reaction of **5a** with morpholine was observed on larger scales even at room temperature. Similarly, the combination of Pd(PPh₃)₄ and morpholine resulted in the morpholino product. Pd₂(dba)₃/(±)-BINAP/Et₂NH₂⁺HCO₃⁻ in CH₂Cl₂ was quite successful, although variability in both reaction times and yields were observed (60–90%).²⁶ Best results, however, were obtained with 10% Pd–C, EtOH, Et₃N, and 1 atm H₂.⁹ Under these conditions, deprotection was complete within 30 min, and **5a** was obtained in 96% yield after chromatography.

Next, attention was directed toward the synthesis of the 2-tosyloxy derivative of 2'-deoxyinosine **5b**. Conversion of **3a** to the hypoxanthine derivative **4c** was performed as reported in the literature (67% yield).²⁷ Reaction of **4c** with *p*-TsCl and Et₃N in CH₂Cl₂ afforded **4d** in 97% yield. Finally, catalytic debenzoylation of **4d** with 10% Pd–C and 1 atm H₂ in 1:1 THF–MeOH gave **5b** (47% yield).

Although **5a** has been used for displacement reactions with amines, such use has been relatively limited (two primary^{10,12} and one secondary¹¹), and **5b** has not been

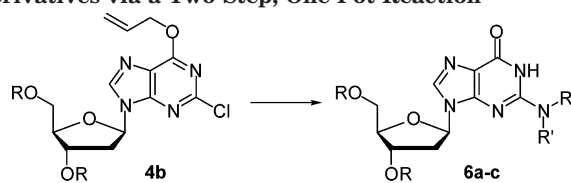
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TABLE 2. Synthesis of N²-Modified 2'-Deoxyguanosine Derivatives via a Two-Step, One-Pot Reaction^a

entry	amine	product, yield
1		6a : 84%
2		6b : 94%
3		6c : 85%

^a Reactions were conducted with 1 mol % Pd₂(dba)₃/2 mol % (±)-BINAP and 5 molar equiv of amine in *tert*-BuOH at 85 °C.

studied. Therefore, at this stage the effectiveness of **5a** and **5b** was tested in displacement reactions with a diverse set of amines. Previous reactions were conducted in 2-methoxyethanol solvent at 90 °C, but we chose *tert*-BuOH. Results from the reactions of **5a** and **5b** with various amines are shown in Table 1.

From Table 1, it is evident that both nucleoside derivatives do undergo reaction with a variety of amines. The chloro nucleoside **5a** is substantially more effective under the conditions tested, resulting in good to high product yields compared to the tosyloxy analogue **5b**. It is plausible, however, that **5b** may find other applications under conditions different from those utilized in this study. Of note are entries 4 and 5 that involve a sensitive ketal (perhaps accounting for the lowered yield) and a substituted piperazine, respectively.

One other aspect of interest that emerged was based upon the analysis of the deallylation reaction described earlier. We had observed that use of Pd₂(dba)₃/(±)-BINAP/morpholine in THF led to not only **5a**, but, in some cases, also competitive formation of **6a**. Thus, we reasoned that cleavage of the allyl group in **4b** and replacement of the chloride could be accomplished as a two-step, one-pot reaction through the use of Pd₂(dba)₃/(±)-BINAP/amine in *tert*-BuOH at 85 °C. Three amines were tested, and the results of these experiments are shown in Table 2.

As seen in Table 2, even at low Pd concentration, the overall yields from this two-step procedure compare very favorably with the yields from the displacement reaction (Table 1). Therefore, it is possible that in many instances this approach will provide a one-step reduction in the synthesis of such N-substituted nucleosides. An observation that emerged from this analysis was that the two-step reactions appeared to be generally faster than the direct displacement. What is presently unclear is whether deallylation occurs prior to halide displacement or whether Pd catalyzes the reactions of **4b** and/or **5a** in these cases. However, as described below, we present preliminary

evidence that a chloride at the C-2 position of a purine nucleoside can be effectively activated for Pd-catalyzed amination under suitable conditions (Scheme 2). To prevent undesired deallylation and to maximize catalytic activity for amination, an aryl amination reaction was performed on the O⁶-benzyl-2-chloro nucleoside **4a**.

Under conditions we have utilized in a previous report on C–N bond formation,²⁴ a reaction of **4a** with *p*-toluidine was complete within 2 h at 85 °C in 1,2-DME. The isolated yield of the known compound **7** after chromatographic purification was 63%.²⁴ Similarly, a C–C bond-forming reaction was attempted with **4a** and PhB(OH)₂ under conditions reported previously.²⁴ This reaction was complete within 3 h and afforded a 62% yield of the known C-2 phenyl compound **8**.²⁴ Both unoptimized results clearly demonstrate that a C–Cl bond at the 2 position of purine nucleosides can be activated for Pd-catalyzed C–N and C–C bond formation. Further work in our laboratories is currently focused on understanding the details of these metal-catalyzed reactions. A C–C cross-coupling reaction of tosylate **4d** with PhB(OH)₂ was also attempted. With catalytic systems derived from various ligands (Xantphos, XPhos, 2-(dicyclohexylphosphino)-2'-(*N,N*-dimethylamino)-1,1'-biphenyl, BINAP, DPPF, and 2-(di-*tert*-butylphosphino)biphenyl) less than 5% product formation was observed over 96 h. This result also warrants comment based upon our successful Pd-catalyzed amination²⁸ and C–C cross-coupling²⁹ reactions of O⁶-arylsulfonyl 2'-deoxyguanosine derivatives. It currently appears that the reactivity of a C-6 sulfonate is quite different from that of the C-2 sulfonate in **4d**. The reasons behind this difference are not immediately obvious and will be evaluated in the course of our future studies on metal catalysis.

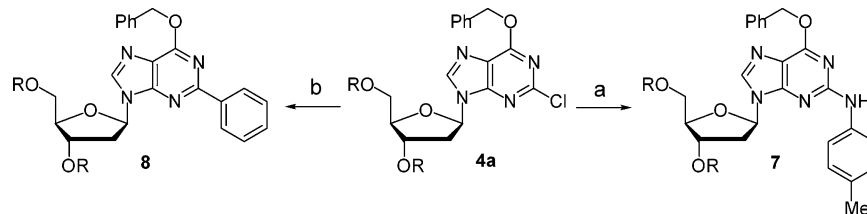
Conclusion

In summary, we have demonstrated that 2-chloro-2'-deoxyinosine and the corresponding 2-tosyloxy derivative can be readily synthesized. Among the two, not only is the chloro derivative useful for direct displacement reactions but metal-mediated chemistry also appears to be feasible with this compound. On the basis of the overall simplicity of the chlorination described, 2-chloro-2'-deoxyinosine may prove to be a useful substitute for the bromo and fluoro derivatives, with certain noteworthy points in this comparison. Synthesis of the bromo analogue, O⁶-benzyl-2-bromo-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyinosine, via diazotization–halogenation requires the use of hazardous SbBr₃. Further, only this O⁶-protected form is currently available via the methodology⁸ since removal of the O⁶ protection by catalytic debenzoylation could be accompanied by halide cleavage. It has been reported that attempted direct displacement of bromide from this protected derivative by *n*-butylamine resulted in decomposition of the nucleoside.³⁰ This result as well as our present work indicate that effective direct displacement of a leaving group from the C-2 position of

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SCHEME 2. Pd-Catalyzed C–N and C–C Bond Formation with 3',5'-Bis-*O*-*tert*-butyldimethylsilyl 2-Chloro-2'-deoxyinosine^a


^a Key: (a) Pd₂(dba)₃, 2-(dicyclohexylphosphino)-2'-(*N,N*-dimethylamino)-1,1'-biphenyl, K₃PO₄, *p*-toluidine, 1,2-DME, 85 °C. (b) Pd(OAc)₂, 2-(dicyclohexylphosphino)biphenyl, K₃PO₄, PhB(OH)₂, 1,4-dioxane, 90 °C.

inosine nucleosides may require that the O6 position be unprotected. O6-Unprotected 2-bromo-2'-deoxyinosine can be obtained but via glycosylation chemistry where formation of isomeric product mixtures is a limitation.⁴ When considering addition–elimination-type reactions, leaving group ability may also be a factor (in simple aryl systems F > Cl > Br), and 2-chloro-2'-deoxyinosine may offer advantages over the bromo analogue. Although the highly reactive 2-fluoro-2'-deoxyinosine can be prepared in the O6-unprotected form, HF-pyridine is needed for its synthesis, which precludes the use of a silylated precursor and therefore requiring protecting group interconversions and a longer synthesis.⁷ For these reasons, it is our expectation that the easily synthesized 2-chloro-2'-deoxyinosine derivative (**5a**) will find substantial synthetic utility. Although in this study the tosyloxy compound **5b** was less reactive compared to **5a**, this stable xanthine derivative may find suitable applications elsewhere, particularly because the corresponding C-2 triflate is available only in its O6-protected form. Finally, the synthesis described here may also derive applications in other fields of research. For instance, 2-chloroinosine has been utilized to probe the mechanism of inosine monophosphate dehydrogenase.³¹ 2-Chloroinosine is also formed in low yield upon diazotization of guanosine in the presence of NaCl, leading to the hypothesis that 2-chloroinosine could be produced in the human stomach and may have a unique role in gastric cancer.³² More recently, 2-chloro-2'-deoxyinosine has been identified as a metabolite of the clinically used cladribine.³³ Thus, 2-chlorohypoxanthine nucleosides needed for various studies can now be accessed via routes described herein. Furthermore, the operationally simple direct displacement as well as the two-step, one-pot procedure may also be applicable to the synthesis of other N-modified guanine nucleosides.

Experimental Section

Thin-layer chromatography was performed on 250 μm silica plates, and column chromatographic purifications were performed on 200–300 mesh silica gel. All other reagents were obtained from commercial sources and used without further purification. ¹H NMR spectra were recorded at 500 or 600 MHz, and ¹³C NMR spectra were recorded at 125 or 151 MHz in deacidified CDCl₃ (pre-

pared by percolating the solvent through a bed of solid NaHCO₃ and basic alumina). All spectra were referenced to residual CHCl₃ in CDCl₃. Chemical shifts are reported in δ parts per million, and coupling constants are in hertz. The sugar protons are numbered 1'–5' beginning at the anomeric carbon and proceeding via the carbon chain to the primary carbinol carbon. Proton assignments were made on the basis of ¹H–¹H COSY and analogy to known nucleoside derivatives.

O⁶-Allyl-2-chloro-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyguanosine (4b**).** A solution of *tert*-butylnitrite (0.24 mL, 2.1 mmol) in CH₂Cl₂ (16.4 mL) was cooled to –10 °C while being stirred. Chlorotrimethylsilane (0.27 mL, 2.1 mmol) was added dropwise to this stirred solution followed by dropwise addition of a solution of compound **3b** (0.43 g, 0.80 mmol) in CH₂Cl₂ (7.8 mL). The reaction mixture was stirred for 2 h at –10 °C, diluted with CH₂Cl₂, and extracted twice with water followed by saturated aqueous NaHCO₃. The organic layer was separated, dried over Na₂SO₄, and evaporated under reduced pressure. The resulting yellow oil was applied to a silica gel column packed in CH₂Cl₂. Sequential elution with CH₂Cl₂, 1% EtOAc in CH₂Cl₂, and 2% EtOAc in CH₂Cl₂ gave 0.23 g (52% yield) of **4b** as a clear yellow oil. *R*_f (5% EtOAc in CH₂Cl₂) = 0.5. ¹H NMR (500 MHz, CDCl₃): δ 8.26 (s, 1H, H-8), 6.43 (t, 1H, H-1', *J* = 6.5), 6.18–6.10 (m, 1H, –CH=), 5.48 (ddd, 1H, =CH_{trans}, *J* = 17.2; 1.7; 1.2), 5.32 (ddd, 1H, =CH_{cis}, *J* = 10.2; 1.6; 1.2), 5.10 (d, 2H, –OCH₂, *J* = 5.8), 4.70–4.55 (m, 1H, H-3'), 4.00 (app q, 1H, H-4', *J*_{app} ~ 3.5), 3.89 (dd, 1H, H-5', *J* = 11.3; 3.9), 3.77 (dd, 1H, H-5', *J* = 11.3; 3.0), 2.59 (app quint, 1H, H-2', *J* = 12.8; 6.5), 2.44 (ddd, 1H, H-2', *J* = 12.8; 6.5; 4.3), 0.91 (s, 18H, C(CH₃)₃), 0.10, 0.09 (2s, 12H, SiCH₃). ¹³C NMR (125 MHz, CDCl₃): δ 160.6, 152.8, 152.6, 141.4, 131.8, 120.9, 119.3, 88.1, 84.6, 71.7, 68.5, 62.7, 41.4, 25.9, 25.8, 18.4, 18.0, –4.7, –4.8, –5.4, –5.5. FAB HRMS calcd for C₂₅H₄₄ClN₄O₄Si₂ (M⁺ + H) 555.2590, found 555.2608.

O⁶-Benzyl-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyxanthosine (4c**).** To a solution of compound **3a** (2.11 g, 3.61 mmol) in acetone (20 mL) were added water (13 mL), acetic acid (12 mL), and NaNO₂ (4.98 g, 72.2 mmol). This reaction mixture was stirred for 4 h at room temperature and then quenched with saturated aqueous NaHCO₃ (400 mL). The mixture was extracted with ethyl acetate (2 × 200 mL), and the organic layer was dried with MgSO₄ and evaporated. The resulting yellow oil was applied to a silica gel column packed in 20% EtOAc in *n*-hexane. Sequential elution with 20% EtOAc in *n*-hexane and 50% EtOAc in *n*-hexane gave 1.41 g (67%

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yield) of **4c** as a white, foamy solid. R_f (50% EtOAc in *n*-hexane) = 0.5. ^1H NMR (500 MHz, CDCl_3): δ 11.8 (br, 1H, NH), 7.92 (s, 1H, H-8), 7.51 (d, 2H, $J = 7.0$), 7.37–7.30 (m, 3H, Ar–H), 6.35 (app t, 1H, H-1', $J_{\text{app}} \sim 5.7$), 5.68 (AB_{quart}, 2H, $-\text{OCH}_2$, $J = 12.0$), 4.56 (app q, 1H, H-3', $J_{\text{app}} \sim 4.8$), 3.99 (m, 1H, H-4'), 3.94 (dd, 1H, H-5', $J = 11.5$; 2.0), 3.81 (dd, 1H, H-5', $J = 11.5$; 2.0), 2.50 (app quint, 1H, H-2', $J_{\text{app}} \sim 5.9$), 2.33 (app q, 1H, H-2', $J_{\text{app}} \sim 6.1$), 0.93 and 0.90 (2s, 18H, $\text{C}(\text{CH}_3)_3$), 0.13, 0.12 and 0.09 (3s, 12H, SiCH_3). ^{13}C NMR (125 MHz, CDCl_3): δ 162.5, 158.4, 147.5, 136.9, 135.6, 128.6, 128.4, 128.3, 115.0, 87.8, 85.0, 71.0, 69.5, 62.3, 42.1, 26.1, 25.7, 18.5, 18.0, 4.6, -4.9 , -5.3 , -5.4 . FAB HRMS calcd for $\text{C}_{29}\text{H}_{47}\text{N}_4\text{O}_5\text{Si}_2$ ($\text{M}^+ + \text{H}$) 587.3085, found 587.3104.

O⁶-Benzyl-3',5'-bis-O-(tert-butyldimethylsilyl)-O²-(4-methylphenylsulfonyl)-2'-deoxyxanthosine (4d). To a solution of compound **4c** (1.37 g, 2.39 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (0.33 mL, 2.39 mmol). To this mixture was added *p*-TsCl (0.47 g, 2.39 mmol), and the mixture was allowed to stir for 12 h at room temperature. Water (15 mL) was added, and the mixture was stirred for 5 min after which the organic layer was separated, dried over MgSO_4 , and evaporated under reduced pressure to give an oily residue. This product was purified by flash chromatography on a silica gel column eluted with 20% EtOAc in *n*-hexane to give 1.67 g (97% yield) of **4d** as a clear, gummy foam. R_f (20% EtOAc in *n*-hexane) = 0.2. ^1H NMR (600 MHz, CDCl_3): δ 8.20 (s, 1H, H-8), 7.92 (d, 2H, Ar–H, $J = 8.4$), 7.43 (d, 2H, Ar–H, $J = 7.2$), 7.35–7.29 (m, 5H, Ar–H), 6.33 (t, 1H, H-1', $J = 6.3$), 5.45 (AB_{quart}, 2H, $-\text{OCH}_2$, $J = 12.0$), 4.58 (m, 1H, H-3'), 3.99 (app q, 1H, H-4', $J_{\text{app}} \sim 3.6$), 3.85 (dd, 1H, H-5', $J = 11.4$; 4.2), 3.76 (dd, 1H, H-5', $J = 11.4$; 3.6), 2.53 (app quint, 1H, H-2', $J_{\text{app}} \sim 6.6$), 2.42 (s, 3H, CH_3), 2.39 (ddd, 1H, H-2', $J = 13.2$; 6.0; 4.2), 0.93 and 0.90 (2s, 18H, $\text{C}(\text{CH}_3)_3$), 0.112, 0.110 and 0.076 (3s, 12H, SiCH_3). ^{13}C NMR (151 MHz, CDCl_3): δ 161.5, 154.0, 152.7, 145.3, 141.5, 135.6, 134.9, 129.7, 128.9, 128.7, 128.6, 128.5, 120.6, 88.4, 85.0, 72.1, 69.5, 63.0, 41.7, 26.1, 26.0, 21.8, 18.6, 18.2, -4.5 , -4.6 , -5.2 , -5.3 . FAB HRMS calcd for $\text{C}_{36}\text{H}_{53}\text{N}_4\text{O}_7\text{SSi}_2$ ($\text{M}^+ + \text{H}$) 741.3174, found 741.3189.

2-Chloro-3',5'-bis-O-(tert-butyldimethylsilyl)-2'-deoxyinosine (5a): Method A. In an oven-dried 50 mL flask equipped in with a stirring bar were placed **4b** (0.70 g, 1.3 mmol) and $\text{Et}_2\text{NH}_2^+\text{HCO}_3^-$ (0.95 g, 7.8 mmol). Dry CH_2Cl_2 (20 mL) was added slowly via a syringe to this mixture at room temperature. In a vial a solution of (\pm)-BINAP (0.014 g, 0.023 mmol) and $\text{Pd}_2(\text{dba})_3$ (0.01 g, 0.011 mmol) in anhydrous CH_2Cl_2 (4.5 mL) was prepared. This catalyst solution was added dropwise via a syringe to the reaction mixture. The reaction mixture was allowed to stir at room temperature for 4 h at which time TLC indicated the reaction to be incomplete. Therefore, another aliquot of (\pm)-BINAP (0.014 g, 0.023 mmol) and $\text{Pd}_2(\text{dba})_3$ (0.01 g, 0.011 mmol) in CH_2Cl_2 (2 mL) was prepared and added to the mixture. The reaction was allowed to continue and was complete in 18 h. The reaction mixture was evaporated under reduced pressure, and the resulting orange-yellow foam was applied to a silica gel column packed in CH_2Cl_2 . Sequential elution with CH_2Cl_2 , 1% MeOH in CH_2Cl_2 , and 2% MeOH in CH_2Cl_2 gave 0.57 g (87% yield) of **5a** as pale yellow, foam. R_f (5% MeOH in CH_2Cl_2) = 0.15. ^1H NMR (500 MHz,

CDCl_3): δ 8.12 (s, 1H, H-8), 6.34 (t, 1H, H-1', $J = 6.4$), 4.59 (m, 1H, H-3'), 4.05 (app q, 1H, H-4', $J_{\text{app}} \sim 3.5$), 3.86 (dd, 1H, H-5', $J = 11.4$; 3.8), 3.77 (dd, 1H, H-5', $J = 11.4$; 3.3), 2.54 (app quint, 1H, H-2', $J = 13.1$; 6.4), 2.43 (ddd, 1H, H-2', $J = 13.1$; 6.4; 4.1), 0.91, 0.90 (2s, 18H, $\text{C}(\text{CH}_3)_3$), 0.12, 0.09, 0.087, 0.05 (4s, 12H, SiCH_3). ^{13}C NMR (125 MHz, CDCl_3): δ 158.8, 148.1, 143.8, 138.9, 123.4, 88.1, 84.6, 71.7, 62.6, 41.6, 25.9, 25.7, 18.4, 17.9, -4.7 , -4.8 , -5.4 , -5.5 . FAB HRMS calcd for $\text{C}_{22}\text{H}_{40}\text{ClN}_4\text{O}_4\text{Si}_2$ ($\text{M}^+ + \text{H}$) 515.2277, found 515.2278. **Method B.** To a solution of compound **4b** (60 mg, 0.11 mmol) in EtOH (2 mL) was added Et_3N (0.017 mL, 0.12 mmol). To this mixture was added 10% Pd–C (10 mg), and the mixture was allowed to stir at 1 atm H_2 pressure (balloon) for 30 min at room temperature. The reaction mixture was filtered and washed with MeOH (5 mL), and the filtrate was evaporated to dryness. This product was applied to a silica gel column packed in CH_2Cl_2 . Sequential elution with CH_2Cl_2 , 1% MeOH in CH_2Cl_2 , and 2% MeOH in CH_2Cl_2 gave 0.054 g (96% yield) of **5a** as pale yellow, foamy solid.

3',5'-Bis-O-(tert-butyldimethylsilyl)-O²-(4-methylbenzenesulfonyl)-2'-deoxyxanthosine (5b). To a solution of **4d** (0.65 g, 0.88 mmol) in 1:1 THF–MeOH (20 mL) was added 10% Pd–C (50 mg). The flask was evacuated and flushed with hydrogen, and this procedure was repeated three times. The reaction mixture was then stirred for 3 h under a hydrogen balloon. Upon completion of the reaction, the mixture was filtered through a plug of Celite, and the filtrate was evaporated to dryness. Purification of the crude material by flash chromatography on a silica gel column eluted with 20% EtOAc in MeOH gave 0.27 g (47% yield) of **5b** as a white, foam. R_f (20% EtOAc in MeOH) = 0.5. ^1H NMR (600 MHz, $\text{DMSO}-d_6$): δ 7.94 (s, 1H, H-8), 7.89 (d, 2H, Ar–H, $J = 8.4$), 7.42 (d, 2H, Ar–H, $J = 8.4$), 6.02 (t, 1H, H-1', $J = 6.9$), 4.45 (m, 1H, H-3'), 3.78 (m, 1H, H-4'), 3.65 (dd, 1H, H-5', $J = 11.1$; 6.3), 3.56 (dd, 1H, H-5', $J = 11.1$; 4.5), 2.68 (m, 1H, H-2'), 2.39 (s, 3H, CH_3), 2.12 (ddd, 1H, H-2', $J = 13.2$; 6.3; 3.0), 0.89 and 0.83 (2s, 18H, $\text{C}(\text{CH}_3)_3$), 0.10 and 0.08 (2s, 12H, SiCH_3). ^{13}C NMR (151 MHz, $\text{DMSO}-d_6$): δ 155.4, 149.1, 146.7, 138.9, 134.2, 130.4, 129.3, 123.9, 117.1, 87.9, 84.2, 72.9, 63.4, 39.0, 26.4, 21.9, 21.8, 18.6, 18.4, -4.1 , -4.2 , -4.3 , -4.8 . FAB HRMS calcd for $\text{C}_{29}\text{H}_{46}\text{N}_4\text{NaO}_7\text{SSi}_2$ ($\text{M}^+ + \text{Na}$) 673.2523, found 673.2544.

3',5'-Bis-O-(tert-butyldimethylsilyl)-2-morpholinyl-2'-deoxyinosine (6a). In a clean, dry vial were placed a stirring bar and **5a** (0.10 g, 0.19 mmol). *tert*-BuOH (1.5 mL) was added to the vial, followed by morpholine (86 μL , 0.98 mmol). The vial was flushed with N_2 and then sealed, and the mixture was allowed to stir at 85 $^\circ\text{C}$ for 24 h. The mixture was then evaporated under reduced pressure and dried under high vacuum. The crude product was applied to a silica gel column packed in CH_2Cl_2 . Sequential elution with CH_2Cl_2 , 1% MeOH in CH_2Cl_2 , and 2% MeOH in CH_2Cl_2 gave 0.093 g (84% yield) of **6a** as a white foam. R_f (5% MeOH in CH_2Cl_2) = 0.38. ^1H NMR (500 MHz, CDCl_3): δ 11.77 (s, 1H, NH), 7.79 (s, 1H, H-8), 6.25 (app t, 1H, H-1', $J = 6.9$), 4.55 (m, 1H, H-3'), 3.95 (app q, 1H, H-4', $J_{\text{app}} \sim 3.5$), 3.84–3.75 (m, 10H, 2H-5', 2 x OCH_2 , 2 x NCH_2), 2.49 (app quint, 1H, H-2', $J = 12.8$; 7.2; 5.8), 2.32 (ddd, 1H, H-2', $J = 12.8$; 6.9; 3.6), 0.91, 0.90 (2s, 18H, $\text{C}(\text{CH}_3)_3$), 0.1, 0.073, 0.07 (3s, 12H, SiCH_3). ^{13}C NMR (125 MHz, CDCl_3): δ 159.3, 152.6, 150.9, 136.3, 117.3, 87.6, 83.5, 72.06, 72.05, 66.4,

62.9, 45.6, 41.1, 25.9, 25.7, 18.4, 17.9, -4.7, -4.8, -5.4, -5.5. FAB HRMS calcd for $C_{26}H_{48}N_5O_5Si_2$ ($M^+ + H$) 566.3194, found 566.3205.

3',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-2-piperidinyl-2'-deoxyinosine (6b). As described for the synthesis of **6a**, **6b** was prepared by a reaction between **5a** (0.015 g, 0.03 mmol) and piperidine (15 μ L, 0.15 mmol) in *tert*-BuOH (0.23 mL) over 24 h. Chromatographically purified (SiO_2 , 2% MeOH in CH_2Cl_2) compound **6b** was obtained as a white foam (0.016 g, 98% yield). R_f (5% MeOH- CH_2Cl_2) = 0.45. 1H NMR (500 MHz, $CDCl_3$): δ 11.37 (br s, 1H, NH), 7.71 (s, 1H, H-8), 6.22 (app t, 1H, H-1', J = 6.9), 4.53 (m, 1H, H-3'), 3.94 (app q, 1H, H-4', J_{app} ~ 3.8), 3.77-3.73 (br m, 2H, 2H-5'), 3.73-3.69 (br m, 4H, NCH_2), 2.52 (app quint, 1H, H-2', J = 13.2; 7.2; 5.8), 2.30 (ddd, 1H, H-2', J = 13.2; 6.8; 3.6), 1.66 (br s, 6H, CH_2), 0.90, 0.89 (2s, 18H, $C(CH_3)_3$), 0.09, 0.06 (2s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 152.3, 151.3, 135.9, 116.7, 87.5, 83.5, 72.1, 62.9, 46.6, 40.8, 25.9, 25.7, 25.4, 24.3, 18.4, 17.9, -4.7, -4.8, -5.4, -5.5. FAB HRMS calcd for $C_{27}H_{50}N_5O_4Si_2$ ($M^+ + H$) 564.3401, found 564.3411.

3',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-2-pyrrolidinyl-2'-deoxyinosine (6c). As described for the synthesis of **6a**, **6c** was prepared by a reaction between **5a** (0.1 g, 0.194 mmol) and pyrrolidine (82 μ L, 0.97 mmol) in *tert*-BuOH (1.5 mL) over 8 h. Chromatographically purified (SiO_2 , 2% MeOH in CH_2Cl_2) compound **6c** was obtained as a light yellow foam (0.078 g, 73% yield). R_f (5% MeOH in CH_2Cl_2) = 0.32. 1H NMR (500 MHz, $CDCl_3$): δ 10.54 (br s, 1H, NH), 7.69 (s, 1H, H-8), 6.23 (app t, 1H, H-1', J = 6.9), 4.56 (m, 1H, H-3'), 3.95 (app q, 1H, H-4', J_{app} ~ 3.7), 3.80-3.75 (br m, 2H, 2H-5'), 3.65-3.61 (br m, 4H, NCH_2), 2.61 (app quint, 1H, H-2', J = 13.2; 7.2; 5.8), 2.28 (ddd, 1H, H-2', J = 13.2; 6.1; 3.6), 2.03-2.01 (br s, 4H, CH_2), 0.91, 0.90 (2s, 18H, $C(CH_3)_3$), 0.10, 0.09, 0.07, 0.06 (4s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 151.5, 150.9, 135.7, 116.6, 87.5, 83.8, 72.2, 62.9, 47.3, 40.3, 25.9, 25.7, 25.5, 18.1, 17.9, -4.7, -4.8, -5.53, -5.55. FAB HRMS calcd for $C_{26}H_{48}N_5O_6Si_2$ ($M^+ + H$): 550.3245, found 550.3247.

3',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-2-(1,4-dioxazaspiro[4.5]dec-8-yl)-2'-deoxyinosine (6d). As described for the synthesis of **6a**, **6d** was prepared by a reaction between **5a** (0.04 g, 0.078 mmol) and 1,4-dioxazaspiro[4.5]decane (51 μ L, 0.39 mmol) in *tert*-BuOH (0.6 mL) over 2 h. Chromatographically purified (SiO_2 , 2% MeOH in CH_2Cl_2) compound **6d** was obtained as a white solid (0.027 g, 56% yield). R_f (5% MeOH in CH_2Cl_2) = 0.28. 1H NMR (500 MHz, $CDCl_3$): δ 11.38 (br s, 1H, NH), 7.86 (s, 1H, H-8), 6.25 (app t, 1H, H-1', J = 6.5), 4.54 (m, 1H, H-3'), 4.10-3.95 (m, 4H, OCH_2), 3.96 (app q, 1H, H-4', J_{app} ~ 3.9), 3.88 (t, 4H, NCH_2 , J = 5.6), 3.77-3.74 (m, 2H, 2H-5'), 2.49 (app quint, 1H, H-2', J = 13.1; 6.9; 6.0), 2.32 (ddd, 1H, H-2', J = 13.1; 6.2; 3.6), 1.81 (t, 4H, CH_2 , J = 5.6), 0.91 (s, 18H, $C(CH_3)_3$), 0.10, 0.08 (2s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 152.0, 151.2, 136.0, 116.9, 106.9, 87.6, 83.6, 72.2, 64.4, 63.0, 43.8, 41.1, 34.6, 25.9, 25.7, 18.4, 18.0, -4.6, -4.7, -5.3, -5.5. FAB HRMS calcd for $C_{29}H_{52}N_5O_6Si_2$ ($M^+ + H$) 622.3456, found 622.3420.

3',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-2-[4-(4-nitrophenyl)piperizin-1-yl]-2'-deoxyinosine (6e). As described for the synthesis of **6a**, **6e** was prepared by a reaction between **5a** (0.04 g, 0.078 mmol) and 1-(4-

nitrophenyl)piperazine (0.04 g, 0.19 mmol) in *tert*-BuOH (0.6 mL) over 2 h. Chromatographically purified (SiO_2 , 2% MeOH in CH_2Cl_2) compound **6e** was obtained as a yellow solid (0.039 g, 73% yield). R_f (5% MeOH in CH_2Cl_2) = 0.32. 1H NMR (500 MHz, $CDCl_3$): δ 11.93 (br s, 1H, NH), 8.16 (d, 2H, Ar-H, J = 9.4), 7.86 (s, 1H, H-8), 6.85 (d, 2H, Ar-H, J = 9.4), 6.30 (app t, 1H, H-1', J = 6.8), 4.57 (m, 1H, H-3'), 4.07-4.00 (br m, 4H, NCH_2), 3.99 (app q, 1H, H-4', J_{app} ~ 3.4), 3.85-3.70 (m, 2H, 2H-5'), 3.64 (t, 4H, NCH_2 , J = 5.5), 2.48 (app quint, 1H, H-2', J = 13.2; 7.0; 6.1), 2.35 (ddd, 1H, H-2', J = 13.2; 6.1; 3.6), 0.93, 0.92 (2s, 18H, $C(CH_3)_3$), 0.12, 0.09 (2s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5, 154.3, 152.2, 151.0, 138.8, 136.4, 125.9, 117.1, 112.5, 87.8, 83.4, 72.1, 62.9, 46.2, 44.5, 41.4, 25.9, 25.7, 18.4, 18.1, -4.6, -4.7, -5.3, -5.5. FAB HRMS calcd for $C_{32}H_{52}N_7O_6Si_2$ ($M^+ + H$) 686.3518, found 686.3516.

3',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-*N*²-methyl-*N*²-(2-*N,N*-dimethylamino)ethyl)-2'-deoxyguanosine (6f). As described for the synthesis of **6a**, **6f** was prepared by a reaction between **5a** (0.04 g, 0.078 mmol) and *N,N,N'*-trimethylethylenediamine (76 μ L, 0.59 mmol) in *tert*-BuOH (0.6 mL) over 8 h. Chromatographically purified (SiO_2 , 2% MeOH in CH_2Cl_2) compound **6f** was obtained as a light yellow foam (0.032 g, 73% yield). R_f (5% MeOH in CH_2Cl_2) = 0.11. 1H NMR (500 MHz, $CDCl_3$): δ 7.71 (s, 1H, H-8), 6.25 (dd, 1H, H-1', J = 6.2; 7.3), 4.54 (m, 1H, H-3'), 3.95 (app q, 1H, H-4', J_{app} ~ 4.3), 3.79-3.72 (m, 2H, 2H-5'), J = 10.9; 3.9), 3.43 (t, 2H, CH_2 , J = 4.5), 3.14 (s, 3H, CH_3), 2.62 (t, 2H, CH_2 , J = 4.5), 2.53 (app quint, 1H, H-2', J = 13.3; 7.4; 6.0), 2.41 (s, 6H, $N(CH_3)_2$), 2.29 (ddd, 1H, H-2', J = 13.3; 6.2; 3.5), 0.90, 0.89 (2s, 18H, $C(CH_3)_3$), 0.09, 0.07, 0.06 (3s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.7, 154.2, 150.6, 135.3, 118.0, 87.5, 83.5, 72.2, 63.0, 59.1, 50.8, 45.1, 40.8, 37.8, 25.9, 25.7, 24.3, 8.4, 17.9, -4.7, -4.8, -5.4, -5.5. FAB HRMS calcd for $C_{27}H_{53}N_6O_4Si_2$ ($M^+ + H$) 581.3667, found 581.3678.

3',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-*N*²-propyl-2'-deoxyguanosine (6g). As described for the synthesis of **6a**, **6g** was prepared by a reaction between **5a** (0.04 g, 0.078 mmol) and *n*-propylamine (0.192 mL, 2.34 mmol) in *tert*-BuOH (0.6 mL) over 8 h. Chromatographically purified (SiO_2 , 2% MeOH in CH_2Cl_2) compound **6g** was obtained as a whitish yellow foam (0.029 g, 69% yield). R_f (5% MeOH in CH_2Cl_2) = 0.32. 1H NMR (500 MHz, $CDCl_3$): δ 12.01 (br s, 1H, NH), 7.70 (s, 1H, H-8), 7.01 (br s, 1H, NH), 6.25 (app t, 1H, H-1', J = 6.6), 4.55 (m, 1H, H-3'), 3.98 (app q, 1H, H-4', J_{app} ~ 3.9), 3.80-3.76 (m, 2H, 2H-5'), 3.37 (br m, 2H, $-NCH_2$), 2.56 (app quint, 1H, H-2', J = 13.2; 7.1; 5.9), 2.34 (ddd, 1H, H-2', J = 13.2; 6.4; 3.5), 2.02 (br s, 2H, $-CH_2$), 1.65 (app q, 2H, CH_2 , J = 6.9), 0.93 (t, 3H, CH_3 , J = 7.4), 0.92, 0.91 (2s, 18H, $C(CH_3)_3$), 0.11, 0.084, 0.08 (3s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.7, 152.8, 151.7, 135.5, 116.9, 87.7, 83.9, 72.2, 63.1, 43.0, 40.9, 25.9, 25.7, 22.5, 18.4, 17.9, 11.6, -4.8, -5.4, -5.5. FAB HRMS calcd for $C_{25}H_{48}N_5O_4Si_2$ ($M^+ + H$) 538.3245, found 538.3248.

Typical Procedure for the Amination of 5b. In a dry screw-cap vial, equipped with a stirring bar, were placed nucleoside sulfonate **5b** (0.03 g, 0.046 mmol), anhydrous *tert*-BuOH (0.3 mL), and amine (5 molar equiv). The vial was flushed with argon and sealed with a Teflon-lined cap, and the mixture was heated at 82-

83 °C with stirring. Upon completion of the reaction, evaporation of the mixture provided the crude products that were purified by column chromatography on silica gel as described for the individual compounds above.

Typical Procedure for the Two-Step, One-Pot Reaction of 4a with Amines: Synthesis of 3',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-2-morpholinyl-2'-deoxyinosine (6a). Compound **4a** (0.05 g, 0.09 mmol) was placed in a clean and dry vial equipped with a stirring bar. *tert*-BuOH (0.75 mL) was added followed by the amine (5 molar equiv), (±)-BINAP (1.1 mg, 1.76 μmol), and finally Pd₂(dba)₃ (0.7 mg, 0.76 μmol). The reaction mixture was flushed with N₂ and heated at 85 °C for 2.5–4 h with stirring. Upon completion of the reaction as indicated by TLC, the reaction mixture was evaporated under reduced pressure and dried under high vacuum. The product mixture was applied to silica gel column packed in CH₂Cl₂. Sequential elution with CH₂Cl₂, 1%

MeOH in CH₂Cl₂, and 2% MeOH in CH₂Cl₂ afforded 0.043 g (84% yield) of the desired **6a** as a white foamy solid. Data for **6a** have been reported above.

3',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-2-piperidinyl-2'-deoxyinosine (6b). White foam (0.048 g, 94% yield). Data for **6b** have been reported above.

3',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-2-pyrrolidinyl-2'-deoxyinosine (6c). Pale yellow foam (0.042 g, 85% yield). Data for **6c** have been reported above.

Acknowledgment. This work has been partially supported by NSF Grant CHE-0314326, NIH Grant 2S06 GM008168-24S1, and a PSC-CUNY 36 award. Acquisition of a 500 MHz NMR spectrometer was funded by NSF Grant CHE-0210295.

Supporting Information Available: Proton NMR spectra of **4a–d**, **5a**, **5b**, and **6a–g**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO050847J