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Synthetic Utility of an Isolable Nucleoside Phosphonium Salt

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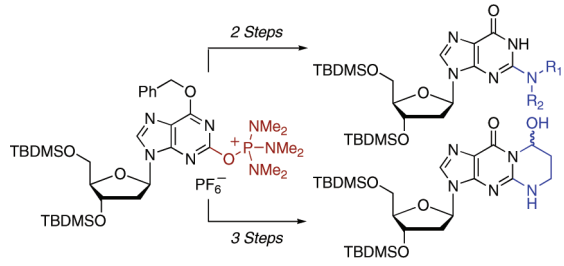
ABSTRACT



The reaction of O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyxanthosine with 1*H*-benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) yielded the nucleoside C-2 tris(dimethylamino)phosphonium hexafluorophosphate salt as a stable, isolable species. This is in contrast to reactions of inosine nucleosides with BOP, where the in situ formed phosphonium salts undergo subsequent reaction to yield O^6-(benzotriazol-1-yl)inosine derivatives. The phosphonium salt obtained from the 2′-deoxyxanthosine derivative can be effectively used to synthesize N^2-modified 2′-deoxyguanosine analogues. Using this salt, a new synthesis of an acrolein-2′-deoxyguanosine adduct has also been accomplished.

The ability to modify natural nucleosides translates to novel applications in biochemistry, biology, and medicine.[1] A classical method for nucleoside modification is via displacement chemistry. For modification at the C-2 position various protected or unproteced 2-halo-2′-deoxyinosines, namely fluoro,[2] bromo,[3] and chloro[4] derivatives, have been used. In addition, use of triflate[5] and tosylate[4a] derivatives have also been reported.

Phosphonium salts have been proposed as intermediates in the reactions of inosine nucleosides with $Ph_3P{\bullet}I_2$[6,7] or with 1*H*-benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP).[8,9] These salts can be converted to adenine derivatives via reaction with various amines.[6,8] In this context, we demonstrated that in reactions of hypoxanthine nucleosides with BOP, the inosine-derived phosphonium salts undergo reaction with BtO^- that is released. This results in the formation of O^6-(benzotriazol-1-yl)inosine derivatives.[9] More recently, we demonstrated that the inosine-derived phoshonium salt formed via reaction with $Ph_3P{\bullet}I_2$ can also be converted to O^6-(benzotriazol-1-yl)inosine derivatives in good yields.[7] These new O^6-(benzotriazol-1-yl)inosine derivatives possess excellent reactivity for a variety of transformations, leading to modification at the C-6 position of the purine (Scheme 1).[7,9]

On the basis of our prior work on inosine nucleosides, we became interested in studying the reaction of *O*6-protected 2′-deoxyxanthosine with BOP. This paper describes our preliminary results on the reaction of O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyxanthosine with BOP. In the course of these studies we have identified the nucleoside C-2 phosphonium salt as an isolable compound that can be readily utilized for S_NAr displacement chemistry with a broad range of amines. Finally, the C-2 phosphonium

(1) (a) *Nucleic Acids in Chemistry and Biology*, 3rd ed.; Blackburn, G. M., Gait, M. J., Loakes, D., Williams, D. M., Eds.; RSC Publishing: Cambridge, UK, 2006. (b) Simons, C. *Nucleoside Mimetics: Their Chemistry and Biological Properties*; Gordon and Breach: Amsterdam, 2001. (c) *Perspectives in Nucleoside and Nucleic Acid Chemistry*; Kisakürek, M. V., Rosemeyer, H., Eds.; Verlag Helvetica Chimica Acta: Zürich and Wiley-VCH: Weinheim, 2000. (d) Suhadolnik, R. J. *Nucleosides as Biological Probes*; Wiley: New York, 1979.

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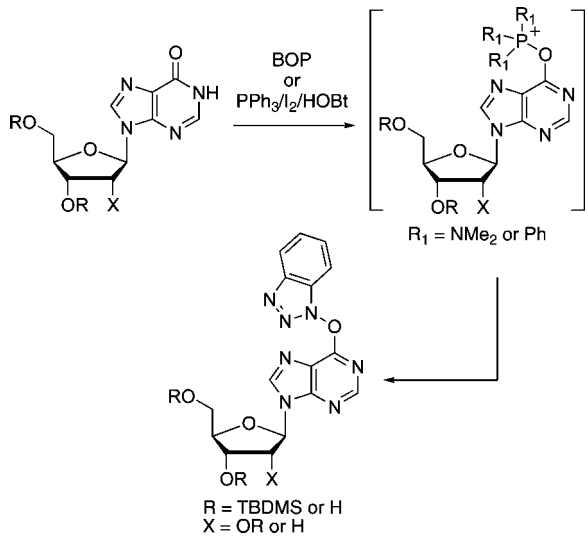
Scheme 1. Synthesis of O^6-(Benzotriazol-1-yl) Derivatives of Inosine and 2′-Deoxyinosine via Reaction with BOP or Ph_3P/I_2/HOBt

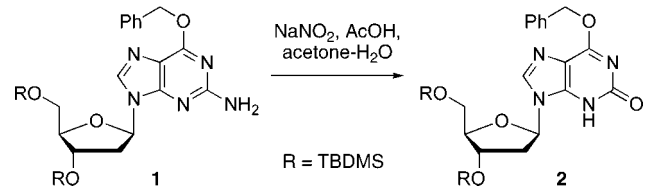


salt has been utilized in a new synthesis of an acrolein adduct with 2′-deoxyguanosine.

O^6-Benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (**1**) can be readily synthesized on the multigram scale via a Mitsunobu etherification of 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine.[2b,3a,10] Diazotization−hydrolysis of **1** as described[4a,11] yielded O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyxanthosine (**2** in Scheme 2, 64% yield).

Under conditions similar to those we have described previously,[9] (2 molar equiv of BOP/1.5−2.0 molar equiv (*i*-Pr)$_2$NEt, anhydrous CH_2Cl_2, room temperature), the reaction of **2** with BOP was evaluated (Scheme 3). A fairly rapid

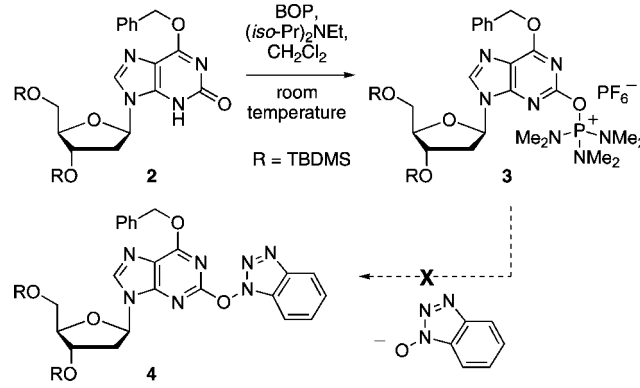
Scheme 2. Synthesis of O^6-Benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyxanthosine



reaction was observed (4−5 h at room temperature) with the predominant formation of a new material that was isolated by chromatography on silica gel.

Analysis of this new product indicated that it was the phosphonium salt **3** and not the benzotriazol-1-yl compound **4**. From this reaction, two noteworthy points emerged: (a) the greater difficulty in S_NAr displacement of HMPA by BtO^- from the C-2 position, in contrast to reactions at the C-6 of purines[9] and (b) the relative stability of phosphonium salt **3**, which could be readily obtained by chromatographic purification.

Scheme 3. Reaction of O^6-Benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyxanthosine with BOP



The ^{1}H NMR spectrum of **3** ($CDCl_3$) showed a characteristic doublet at δ 2.83 ppm for the NMe_2 resonance (J_{P-H} = 10.7 Hz). The ^{31}P NMR of **3** ($CDCl_3$) showed a singlet at δ 34.11 ppm as well as a septet centered at δ −143.27 ppm (J_{P-F} = 712.7 Hz) for the PF_6 anion. The synthesis of phosphonium salt **3** is reproducible and scalable, usually returning product yields of 88−92%.[12]

Given the high isolated yield of phosphonium salt **3** and the relative simplicity of its synthesis, we were interested in evaluating its utility in displacement reactions with amines. Such reactions would involve HMPA as a neutral leaving group, and this would lead to a simple approach to *N*-modified 2′-deoxyguanosine analogues. A variety of amines were selected for this purpose (Table 1).

The displacement reactions on **3** were conducted in 1,2-dimethoxyethane (DME) at room temperature or at 85 °C

(2) Some examples for the synthesis of 2-fluoro-2′-deoxyinosine derivatives: (a) Woo, J.; Sigurdsson, S. T.; Hopkins, P. B. *J. Am. Chem. Soc.* **1993**, *115*, 3407–3415. (b) Zajc, B.; Lakshman, M. K.; Sayer, J. M.; Jerina, D. M. *Tetrahedron Lett.* **1992**, *33*, 3409–3412. (c) Kim, S. J.; Stone, M. P.; Harris, C. M.; Harris, T. M. *J. Am. Chem. Soc.* **1992**, *114*, 5480–5481.

(3) Some examples for the synthesis of *O*6-protected and unprotected 2-bromo-2′-deoxyinosine derivatives: (a) Harwood, E. A.; Sigurdsson, S. T.; Edfeldt, N. B. F.; Reid, B. R.; Hopkins, P. B. *J. Am. Chem. Soc.* **1999**, *121*, 5081–5082. (b) Jhingan, A. K.; Meehan, T. *Synth. Commun.* **1992**, *22*, 3129–3135.

(4) Some examples for the synthesis of 2-chloro-2′-deoxyinosine derivatives: (a) Pottabathini, N.; Bae, S.; Pradhan, P.; Hahn, H.-G.; Mah, H.; Lakshman, M. K. *J. Org. Chem.* **2005**, *70*, 7188–7195. (b) Ramasamy, K. S.; Zounes, M.; Gonzalez, C.; Freier, S. M.; Lesnik, E. A.; Cummins, L. L.; Griffey, R. H.; Monia, B. P.; Cook, P. D. *Tetrahedron Lett.* **1994**, *35*, 215–218.

(5) Some examples of an *O*6-protected C-2 triflate: (a) Edwards, C.; Boche, G.; Steinbrecher, T.; Scheer, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1887–1893. (b) Steinbrecher, T.; Wameling, C.; Oesch, F.; Seidel, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 404–406.

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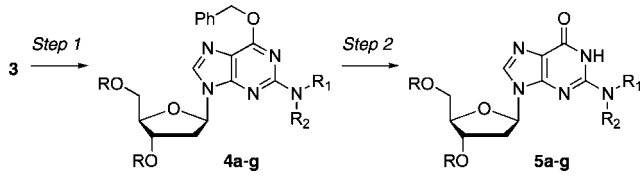
(8) Wan, Z.-K.; Binnun, E.; Wilson, D. P.; Lee, J. *Org. Lett.* **2005**, *7*, 5877–5880.

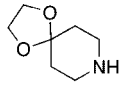
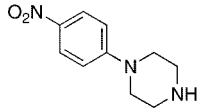
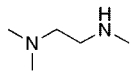
(9) Bae, S.; Lakshman, M. K. *J. Am. Chem. Soc.* **2007**, *129*, 782–789.

(10) Himmelsbach, F.; Schulz, B S.; Trichtinger, T.; Charubala, R.; Pfleiderer, W. *Tetrahedron* **1984**, *40*, 59–72.

(11) (a) Jurczyk, S. C.; Horlacher, J.; Devined, K. G.; Benner, S. A.; Battersby, T. R. *Helv. Chim. Acta* **2000**, *83*, 1517–1524. (b) Kodra, J. T.; Benner, S. A. *Synlett* **1997**, 939–940.

Table 1. Synthesis of N^2-Modified 2′-Deoxyguanosine Analogues from **3**



entry	amine	displacement (*step 1*) yield	debenzylation (*step 2*) yield[e]
1		**4a:** 65%[a] **4a:** 90%[b]	**5a:** 95%
2		**4b:** 96%[b]	**5b:** 91%
3		**4c:** 100%[b]	**5c:** 97%
4		**4d:** 83%[c]	**5d:** 97%
5		**4e:** 65%[c]	**5e:** --[f]
6		**4f:** 71%[c]	**5f:** 66%
7		**4g:** 78%[d]	**5g:** 98%

[a] Reaction using 5.7 molar equiv of amine, 2.0 molar equiv of Cs_2CO_3, DME, room temperature. [b] Reaction using 4 molar equiv of amine, DME, room temperature. [c] Reaction using 4 molar equiv of amine, DME, room temperature and then 85 °C. [d] Reaction using 7.5 molar equiv of amine, DME, room temperature and then 85 °C. [e] Debenzylation was performed using H_2 (1 atm)/10% Pd−C, 1:1 THF−MeOH, room temperature. [f] Debenzylation was accompanied by nitro group reduction, no attempt was made at finding selective debenzylation conditions.

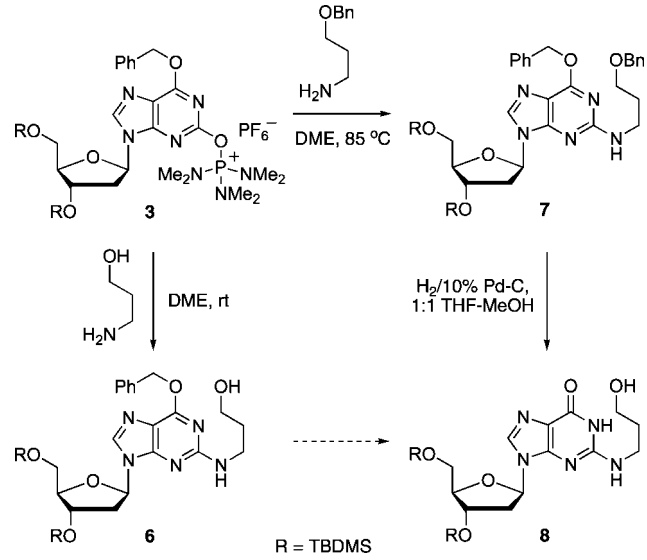
when reactions were slow or incomplete at room temperature. Subsequent to the displacement, the *O*6-benzyl group was removed by catalytic hydrogenolysis at room temperature. The fact that the *O*6-protected derivative **3** could be used in these reactions makes **3** a substrate for S_NAr displacement. This is different in comparison to the displacement reactions on 2-chloro-2′-deoxyinosine which were addition−elimination-type processes on a conjugated system.[4a] Also, no degradation of **3** was observed with the primary amine (entry 7) and this contrasts to what has been reported in the reaction of O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2-bromo-2′-deoxyinosine.[13] All of these features bode well for the utility of **3** in S_NAr displacement reactions.

With the simple displacement reactions completed, we then considered the use of **3** for the synthesis of a more complex, biologically relevant compound. Of several possibilites, we chose to evaluate the synthesis of the 2′-deoxyguanosine-acrolein adduct. This compound has been important in studies aimed at understanding the structure and biological implications of acrolein-induced DNA damage.

Typically compounds of this type have been synthesized by fluoride displacement from 2-fluoro-2′-deoxyinosine derivatives.[14,15] However, this fluoro nucleoside requires a multistep synthesis and involves the use of HF−pyridine in the diazotization-fluorination step. In comparison, **3** offers significant advantages.

For our synthesis, we reasoned that ready access to the acrolein adduct with 2′-deoxyguanosine could be attained from commercially available 3-amino-1-propanol and **3**. Initial experiments were therefore directed toward displacement of HMPA from **3** by 3-amino-1-propanol (Scheme 4). However, the yield of **6** via this approach was low (ca. 30%).

Scheme 4. Approaches to 3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-*N*-(3-hydroxypropyl)-2′-deoxyguanosine



By analysis of the byproducts formed in the synthesis of **6**, protection of the hydroxyl group in 3-amino-1-propanol was deemed necessary to suppress the undesired side reactions.

(12) **Synthesis of O^6-Benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-O^2-tris(dimethylamino)phosphonium-2′-deoxyxanthosine hexafluorophosphate** (**3**). In a clean, dry flask equipped with stirring bar were placed O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyxanthosine (**2**) (0.588 g, 1.00 mmol) and BOP (0.885 g, 2.00 mmol). CH_2Cl_2 (10.0 mL) and $(i\text{-Pr})_2NEt$ (0.35 mL, 2.01 mmol) were added. The mixture was flushed with nitrogen gas and allowed to stir at room temperature. After 5 h, the reaction was complete and the mixture was concentrated. Chromatographic purification (SiO_2, eluted with 50% EtOAc in hexanes followed by 30% acetone in CH_2Cl_2) afforded 0.785 g (88% yield) of compound **3** as a beige foam. R_f (5% MeOH in CH_2Cl_2) = 0.40. ^1H NMR (500 MHz, $CDCl_3$): δ 8.36 (s, 1H, H-8), 7.46 (d, 2H, Ar-H, J = 6.8), 7.38−7.31 (m, 3H, Ar-H), 6.38 (t, 1H, H-1′, J = 6.4), 5.67 (s, 2H, OCH_2), 4.58 (app q, 1H, H-3′, $J \sim 4.2$), 4.02 (br q, 1H, H-4′, J = 2.9), 3.85 (dd, 1H, H-5′, J = 11.7, 3.2), 3.78 (dd, 1H, H-5′, J = 11.7, 2.4), 2.83 (d, 18H, NCH_3, $J_{H\text{-}P}$ = 10.7), 2.44 (t, 2H, H-2′, J = 5.9), 0.91 (s, 18H, *t*-Bu), 0.10 (br s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.9, 152.7, 152.6, 141.5, 135.3, 128.6, 128.5, 127.8, 120.2, 88.0, 84.0, 71.6, 69.7, 62.6, 41.9, 37.0 (d, $J_{C\text{-}P}$ = 4.5), 26.0, 25.7, 18.4, 17.9, −4.7, −4.8, −5.4, −5.5. $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 34.11 (s, $P[N(CH_3)_2]_3$), −143.27 (septet, PF_6, $J_{P\text{-}F}$ = 712.7). ESI HRMS: calcd for $C_{35}H_{63}N_7O_5PSi_2^+$ 748.4161, found 748.4151.

(13) Harwood, E. A.; Hopkins, P. B.; Sigurdsson, S. T. *J. Org. Chem.* **2000**, *65*, 2959–2964.

(14) Acrolein: (a) Khullar, S.; Varaprasad, C. V.; Johnson, F. *J. Med. Chem.* **1999**, *42*, 947–950. (b) Nechev, L. V.; Harris, C. M.; Harris, T. M. *Chem. Res. Toxicol.* **2000**, *13*, 421–429.

(15) Cinnamaldehyde: Rezaei, M.; Harris, T. M.; Rizzo, C. M. *Tetrahedron Lett.* **2003**, *44*, 7513–7516.

Based upon a literature procedure,[16] 3-amino-1-propanol was selectively converted to the *O*-benzyl ether. The reaction of **3** with this benzyl-protected 3-amino-1-propanol (Scheme 4) proceeded smoothly at 85 °C in DME to provide the bis-benzyl ether protected nucleoside **7** in 82% yield.

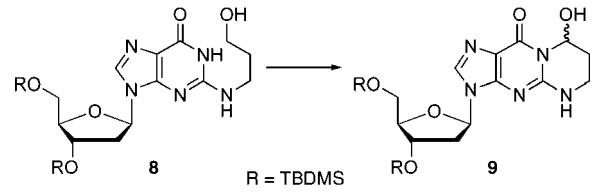
At this stage, removal of the two benzyl protecting groups in **7** followed by mild oxidation of the primary hydroxyl should result in the requisite cyclized acrolein-2′-deoxyguanine adduct as its bis-TBDMS ether. Along these lines, exposure of **7** to 1 atm H_2 and 10% Pd−C in 1:1 THF−MeOH resulted in the debenzylated product **8** (89% yield). Upon monitoring this reduction carefully, it was observed that the nucleoside benzyl ether underwent rapid deprotection (within 4 h), whereas the alkyl benzyl ether required prolonged exposure to the reductive conditions (23 h).

With **8** in hand, the final oxidative cyclization to **9** was explored. This proved to be nontrivial and both TPAP/NMO[17,18] as well as PCC[19,20] gave modest to low yields of **9** (Table 2). In the presence of silica gel, 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate has been shown to be an excellent mild oxidant.[21,22] Application of this reagent resulted in successful synthesis of the desired **9** in 69% yield.

The in situ formation of phosphonium salts in the reactions of peptide coupling agents with amide and urea functionalities have been reported.[23] However, in this letter we have shown that the C-2 tris(dimethylamino)phosphonium hexafluorophosphate salt **3** is formed in a high-yield reaction of O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyxanthosine (**2**) with BOP, and is a readily isolated species. This reactivity contrasts to that of inosine nucleosides with BOP, where the final products are the O^6-(benzotriazol-1-yl) derivatives.[9]

Salt **3** is a good substrate for S_NAr displacement reactions with primary and secondary amines, providing a facile approach to N^2-modified 2′-deoxyguanosine analogues. As demonstrated with the synthesis of the acrolein-2′-deoxyguanosine adduct **9**, it appears that **3** can be used for the synthesis of other biologically important compounds. Thus, these C-2 nucleoside phosphonium salts can be considered as a new family of reactive nucleosides. Given the simplicity in synthesis, a variety of *O*6 protecting groups can be readily utilized in order to accommodate for a wide range of reactions. Other reactions of the C-2 tris(dimethyl)phosphonium hexafluorophosphate salt **3** and related compounds are currently under investigation in our laboratories.

Table 2. Conditions Tested for the Oxidative Cyclization of **8** as Well as the Yields of **9** in These Reactions



entry	conditions	result[a]
1	TPAP (0.16 molar equiv), NMO (1.9 molar equiv), 4 Å molecular sieves, CH_2Cl_2, room temperature, 8 h	Incomplete reaction, 41% yield
2	PCC (3.0 molar equiv), 4 Å molecular sieves, CH_2Cl_2, room temperature, 16 h	23% yield
3	4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (1.2 molar equiv), silica gel, CH_2Cl_2, room temperature, 16 h	69% yield

[a] Yield of isolated, purified product.

Acknowledgment. Support of this work by NSF Grant No. CHE-0640417 and a PSC CUNY-38 award are gratefully acknowledged. Acquisition of a mass spectrometer was funded by NSF Grant No. CHE-0520963. Infrastructural support at CCNY was provided by NIH RCMI Grant No. G12 RR03060. We thank Prof. James. M. Bobbitt (University of Connecticut) for a generous sample of 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate.

Note Added after ASAP Publication. In the version published May 29, 2008 the compound named O^6-Benzyl-2′,3′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyxanthosine was changed to O^6-Benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyxanthosine in three places.

Supporting Information Available: Experimental procedures, ^1H and ^{13}C NMR spectra of **3**, **4a**−**g**, and **7**−**9**. ^1H NMR spectra of **5a**−**d**,**f**,**g** and $^{31}P\{^1H\}$ NMR spectrum of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) For examples, see: (a) Wan, Z.-K.; Wacharasindhu, S.; Levins, C. G.; Lin, M.; Tabei, K.; Mansour, T. S. *J. Org. Chem.* **2007**, *72*, 10194–10210. (b) Kang, F.-A.; Kodah, J.; Guan, Q.; Li, X.; Murray, W. V. *J. Org. Chem.* **2005**, *70*, 1957–1960.