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A Novel Polymer Supported Approach to Nucleoside Modification

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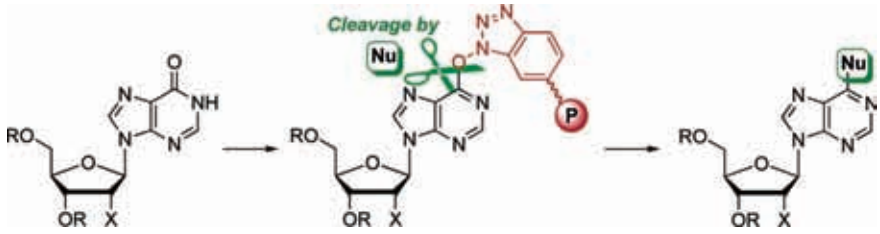


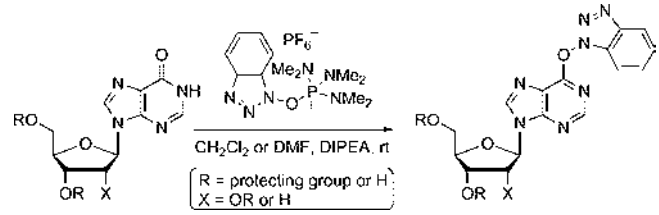
Polymer-supported O^6-(benzotriazol-1-yl)inosine derivatives (**Pol-I** and **Pol-dI**) have been synthesized reasonably effectively via reaction of nucleoside phosphonium salts with polymer-linked HOBt (Pol-HOBt). In constast to solution chemistry, use of polymer-supported BOP (Pol-BOP) did not lead to efficient nucleoside loading. Presence of the nucleosides on the support could be readily detected by MAS NMR. Exposure of the polymer-supported nucleosides, **Pol-I** and **Pol-dI**, to alcohol, phenol, thiol and amine nucleophiles caused cleavage from the support leading directly to the C-6 modified nucleoside analogues. To our knowledge, these are the first examples of the application of such technology for nucleoside modification. Where possible, results of reactions with the polymer-supported nucleosides are compared to those from solution chemistry, providing insight into the differences between the two techniques. These new polymer-supported nucleosides can be conveniently utilized for diversity-oriented synthesis.

Introduction

The significance of chemical routes to nucleoside modification resides in the biochemical, biological, and medicinal importance of nucleoside analogues.[1] A classical method for altering nucleoside structure is via the S_NAr displacement of leaving groups from the heterocylic base by nucleophiles.[2] For this, a wide assortment of electrophilic nucleosides have been developed such as halo,[3–6] phenoxy,[7] aryl or alkyl sulfonyl,[8] pyridyl,[9] sulfone,[10] and imidazolyl.[10,11] However, in most of these cases, nontrivial chemistry and use of protecting groups are often necessary for their syntheses.

Recently, we have reported that either hydroxyl protected or unprotected inosine (I) and 2′-deoxyinosine (dI) can be readily converted to O^6-(benzotriazol-1-yl) derivatives (Scheme 1) via a simple reaction with 1*H*-benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP).[12] These com-

SCHEME 1. Synthesis of O^6-(benzotriazol-1-yl) Inosine Derivatives via a Straightforward Methodology



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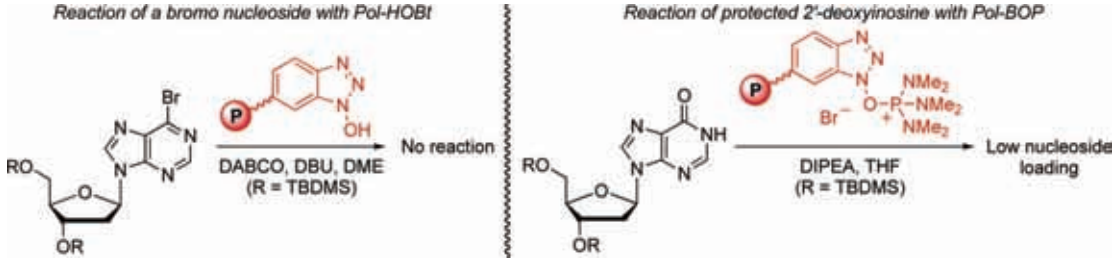
SCHEME 2. Methods Tested for the Synthesis of Polymer-Supported O^6-(Benzotriazol-1-yl)-2′-deoxyinosine (Pol-dI)



pounds were superb reagents that underwent smooth reactions with a range of nucleophiles.[12] The O^6-(benzotriazol-1-yl)-2′-deoxyinosine derivative could also be incorporated into DNA for site-specific modification.[12]

Attachment of nucleosides to a polymer support offers convenience for diversity-oriented chemical synthesis of nucleoside analogues. Although attachment of the hydroxyl goups of nucleosides to polymer supports can be envisioned, such a strategy would entail two discrete chemical steps: one for base modification and a second for cleavage from the support. On the other hand, attachment of the base to the polymeric support would yield polymer-supported nucleosides wherein the chemical transformation on the base can also release the product from the support, essentially leaving no trace of the support itself. Such an approach appeared feasible because polymer-supported 1-hydroxybenzotriazole (HOBt) is commercially available.[13] In this context it should be noted that a 6-chloro purine has been attached to a polymer-linked HOBt (Pol-HOBt).[14] However, synthesis of 6-chloropurine nucleosides, and particularly that of the 2′-deoxy derivative, is not trivial.[3] On the basis of these reasons, we set out to explore the development of polymer-supported O^6-(benzotriazol-1-yl) inosine nucleosides and to test their applicability in displacement reactions.

Results and Discussion

Since chemistry to support 6-chloro purine on a polymer has been reported,[14] we initially made an unsuccessful attempt to directly link 6-bromo-9-[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine to Pol-HOBt via a direct halide displacement (Scheme 2).[15] The choice of the silyl protecting group for the sugar in this case as well as in subsequent experimentation was to not only avoid any undesired reactions but also because it offered the possibility for solid-state NMR.

Next, in a parallel to the solution chemistry, synthesis of polymer-supported BOP (Pol-BOP) was pursued (Scheme 2).[16] It was soon discovered that reaction of Pol-BOP with 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (**1a**) was not a viable route to loading the nucleosides onto the support, as only low levels of polymer functionalization occurred (11% nucleoside loading). In this and subsequent experiments, actual nucleoside loading was estimated by exposure of polymer-supported nucleoside (**Pol-dI**) to morpholine/Cs_2CO_3 in DME at room temperature and determination of the actual yield of the morpholino nucleoside.

Because the approach using Pol-BOP was not very successful, we reasoned that it might be possible to generate nucleoside O^6-phosphonium salts in solution, followed by reaction with Pol-HOBt. We have previously shown by $^{31}P\{^1H\}$ NMR that BOP reacts with **1a** to form a O^6-[tris(dimethylamino)]phosphonium salt. The in situ generated BtO^- then displaces HMPA from the purinyl C-6 to yield the O^6-(benzotriazol-1-yl) derivatives.[12] Therefore, several methods were tested via this approach for activation of the amide carbonyl followed by reaction with Pol-HOBt, and the results are summarized in Table 1.

From these experiments, it became clear that the use of BroP for formation of a nucleoside phosphonium salt was quite effective, but BroP is not inexpensive. In attempts at cost efficiency, the combination PPh_3/I_2 was evaluated but without success.[17] On the other hand, the combination HMPT/I_2 gave nearly the same loading efficiency as BroP, and therefore this combination was used to prepare both **Pol-I** and **Pol-dI**.

The conversion of **1a** to **Pol-dI** could be readily monitored by $^{31}P\{^1H\}$ NMR (Figure 1, referenced to 85% H_3PO_4). Mixing HMPT (δ 123.1 ppm) and I_2 in $CDCl_3$ resulted in the formation of a major broad resonance at δ 55.7 ppm (a signal corresponding to HMPA was also visible at δ 26.6 ppm possibly due to

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(5) Examples of iodo nucleoside synthesis: (a) Cosstick, R.; Douglas, M. E. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1035–1040. (b) van der Wenden, E. M.; von Frijtag Drabbe Künzel, J. K.; Mathôt, R. A. A.; Danhof, M.; IJzerman, A. P.; Soudijn, W. *J. Med. Chem.* **1995**, *38*, 4000–4006. (c) Liu, J.; Janeba, Z.; Robins, M. J. *Org. Lett.* **2004**, *6*, 2917–2919.

(6) Examples of fluoro nucleoside synthesis: ref 3a and Robins, M. J.; Uznański, B. *Can. J. Chem.* **1981**, *59*, 2608–2611.

(7) O^6-(Pentafluorophenyl)-2′-deoxyguanosine: (a) Gao, H.; Fathi, R.; Gaffney, B. L.; Goswami, B.; Kung, P.-P.; Rhee, Y.; Jin, R.; Jones, R. A *J. Org. Chem.* **1992**, *57*, 6954–6959. O^6-(4-Bromophenyl)-2′-deoxyinosine and O^6-(phenyl)-2′-deoxyinosine: (b) Lakshman, M. K.; Zajc, B. *Nucleosides Nucleotides* **1996**, *15*, 1029–1039. O^6-(4-Chlorophenyl)inosine: (c) Allerson, C. R.; Chen, S. L.; Verdine, G. L *J. Am. Chem. Soc.* **1997**, *119*, 7423–7433.

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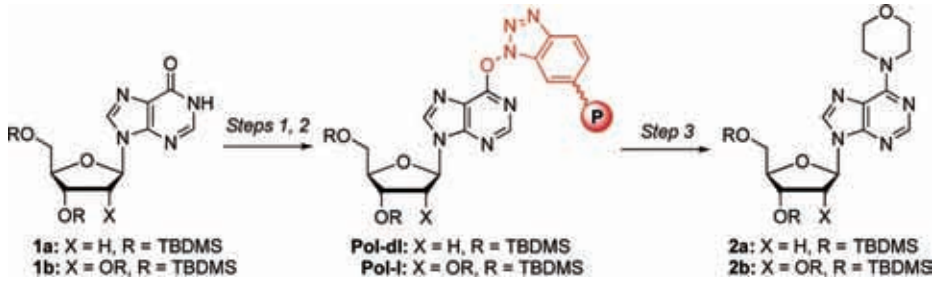
(17) Bae, S.; Lakshman, M. K. *J. Org. Chem.* **2008**, *73*, 1311–1319.

TABLE 1. Determining the Optimal Method for Synthesis of Polymer-Supported dI (Pol-dI) and I (Pol-I)[a]



entry	conditions for steps 1, 2, and 3	yield[b]
1	*Step 1:* **1a**/BroP/DIPEA (1:1.1:4 mol equiv), CH_2Cl_2, rt 7 h *Step 2:* Pol-HOBt (1.5 mol equiv), rt 24 h, 40 °C 30 h *Step 3:* morpholine/Cs_2CO_3 (2.8:2 mol equiv), DME, rt 20 h	**2a**: 58%
2	*Step 1:* **1a**/BroP/DIPEA (1:1.1:4 mol equiv), THF, rt 7 h *Step 2:* Pol-HOBt (1.5 mol equiv), rt 24 h, 40 °C 30 h *Step 3:* morpholine/Cs_2CO_3 (2.8:2 mol equiv), DME, rt 20 h	**2a**: 65%[c]
3	*Step 1:* PPh_3/I_2 (3:3 mol equiv), CH_2Cl_2, rt 0.5 h, then **1a**/DIPEA (1:8 mol equiv), rt 19 h *Step 2:* Pol-HOBt (1.5 mol equiv), rt 72 h, reflux 4 h *Step 3:* morpholine (3.8 mol equiv), DME, rt 23 h	**2a**: 8%
4	*Step 1:* HMPT/I_2 (1.5:1.5 mol equiv), CH_2Cl_2, rt 10 min, then **1a**/DIPEA (1:4 mol equiv), rt 2 h *Step 2:* Pol-HOBt (1.5 mol equiv), rt 22 h *Step 3:* morpholine/Cs_2CO_3 (2:2 mol equiv), DME, rt 20 h	**2a**: 55%
5	*Step 1:* **1a**/PyBroP/DIPEA (1:1.1:4 mol equiv), CH_2Cl_2, rt 17 h	**2a**: --[d]
6	*Step 1:* HMPT/I_2 (1.5:1.5 mol equiv), CH_2Cl_2, rt 10 min, then **1b**/DIPEA (1:4 mol equiv), rt 1 h *Step 2:* Pol-HOBt (1.5 mol equiv), rt 22 h *Step 3:* morpholine/Cs_2CO_3 (2:2 mol equiv), DME, rt 22 h	**2b**: 58%

[a] BroP, bromotris(dimethylamino)phosphonium hexafluorophosphate; PyBroP, bromotris(pyrrolidino)phosphonium hexafluorophosphate; HMPT, hexamethylphosphorus triamide. [b] Yield is based upon **1a** or **1b** as limiting reagent and is of isolated and purified **2a** or **2b**. [c] ^{1}H NMR indicated ~5% impurity. [d] ^{1}H NMR indicated ~48% unreacted **1a**.

hydrolysis of the iodo phosphonium salt formed, by water in the NMR solvent). Addition of **1a** and DIPEA resulted in the formation of a new resonance at δ 35.0 ppm corresponding to the nucleoside phosphonium salt (comparable to that of the corresponding PF_6 salt[12]). Then, upon addition of Pol-HOBt, this resonance disappeared to a trace over 40 h, and the only remaining signal was that of HMPA.

Presence of the nucleosides on the polymer support could be readily identified by MAS NMR. The ^{1}H MAS NMR spectra (Figure 2, Panel A) of **Pol-dI** and **Pol-I** clearly showed the presence of comparable resonances in both. However, upon comparison to Pol-HOBt, there are new resonances in both that are absent in Pol-HOBt. More strikingly, the ^{29}Si CP/MAS NMR (Figure 2, Panel B) showed the presence of ^{29}Si resonances of the TBDMS protecting groups in both Pol-dI and Pol-I that are absent in Pol-HOBt.

Having established a reasonable method for the synthesis of the polymer- supported O^6-(benzotriazol-1-yl)-2′-deoxyinosine (**Pol-dI**) and inosine (**Pol-I**), the stage was set for the evaluation of these compounds for the synthesis of C-6 modified purine nucleosides. Table 2 is a listing of the various nucleophiles that were used in this assessment as well as conditions and product yields based upon the polymer loading (0.336 mmol/g for **Pol-dI** and 0.244 mmol/g for **Pol-I**).

From Table 2 some interesting points emerge. In contrast to solution chemistry,[12] elevated temperature was needed for reaction with EtOH (entries 2, 3), whereas *i*-PrOH (entry 4) did not react. Reactions with phenols were lower yielding, requiring longer reaction times (entries 5−9). On the other hand, reactions with 1° and 2° amines proceeded in excellent yields (entries 12−20). Imidazole also produced a satisfactory reaction (entry 21). In the reactions of phenols and benzyl mercaptan, ~8−30% of 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethyl-2′-deoxyadenosine was observed. This indicates some residual source of Me_2NH such as contamination with HMPT (despite extensive washing of the polymer), or the presence of some covalently linked source such as Pol-BOP that could be formed in the polymer loading process. Thus, in these cases, careful chromatography of products on silica gel was necessary. In reactions with benzyl mercaptan, the reason for the difference in yields obtained with **Pol-dI** and **Pol-I** is not immediately clear. However, among nucleosides, remote protecting groups have been shown to influence reactivity.[4c] In the present case, one obvious difference is the added steric factor associated with **Pol-I** in comparison to **Pol-dI**. In reactions with alcohols and amines, the dimethylamino adenine byproduct was not observed and in these cases simple, rapid filtration through a silica gel column was adequate to obtain pure products.

Conclusions

In this paper we have demonstrated that inosine and 2′-deoxyinosine can be conveniently appended to polymer-supported HOBt. Best results were obtained via formation of a nucleoside O^6-phosphonium salt followed by displacement with the hydroxyl group of Pol-HOBt. In contrast, direct displacement[15,16] of bromide from 6-bromo-9-[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine with Pol-HOBt as well as reaction of dI with Pol-BOP proved to be unsuccessful for loading onto the support. Due to the silyl protecting groups on the nucleosides, their presence on the polymer could be readily detected by MAS NMR techniques. The polymer-

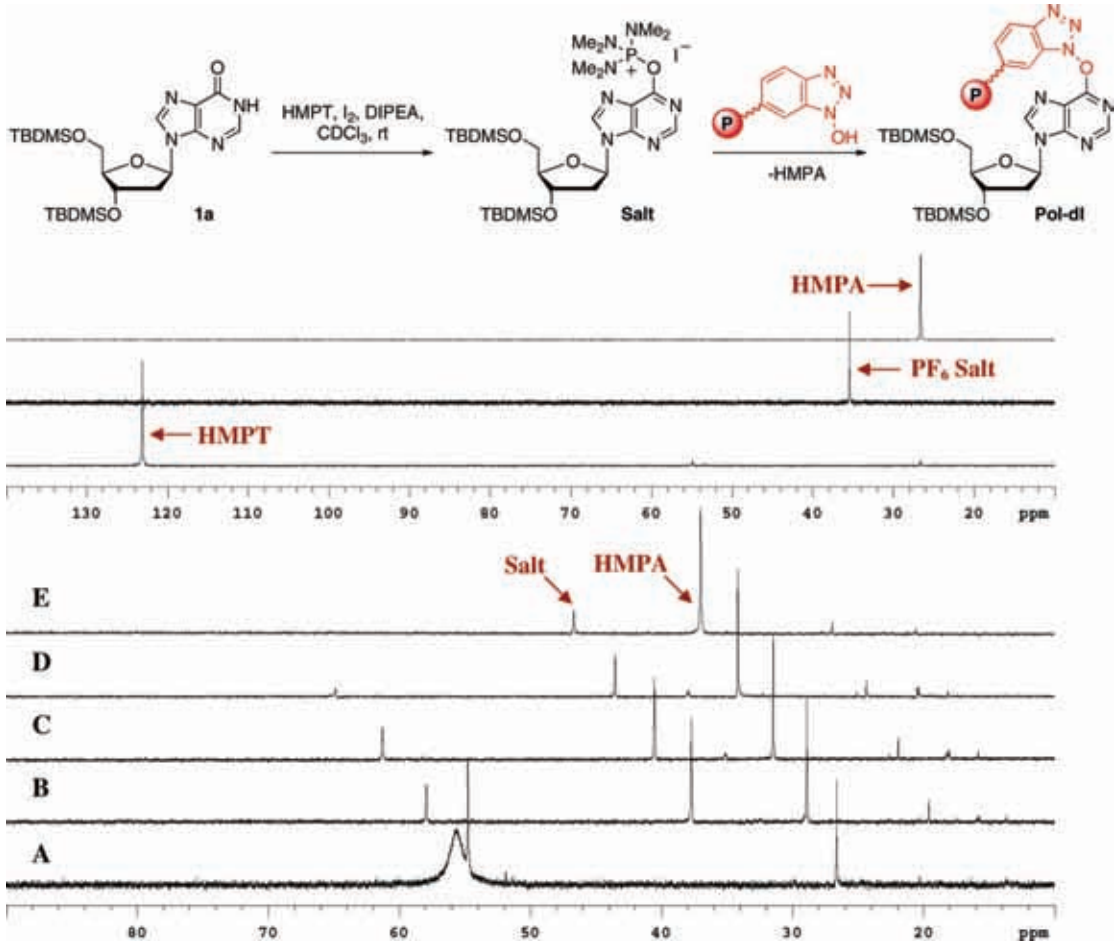


FIGURE 1. Monitoring the conversion of **1a** to **Pol-dI** by $^{31}P\{^{1}H\}$ NMR in $CDCl_3$ (spectra offset to the left). (**A**) HMPT and I_2; (**B**) 10 min after addition of DIPEA and **1a** at room temperature; (**C**) same as **B** but after 1.5 h; (**D**) 30 min after addition of Pol-HOBt at room temperature; (**E**) same as **D** but after 40 h.

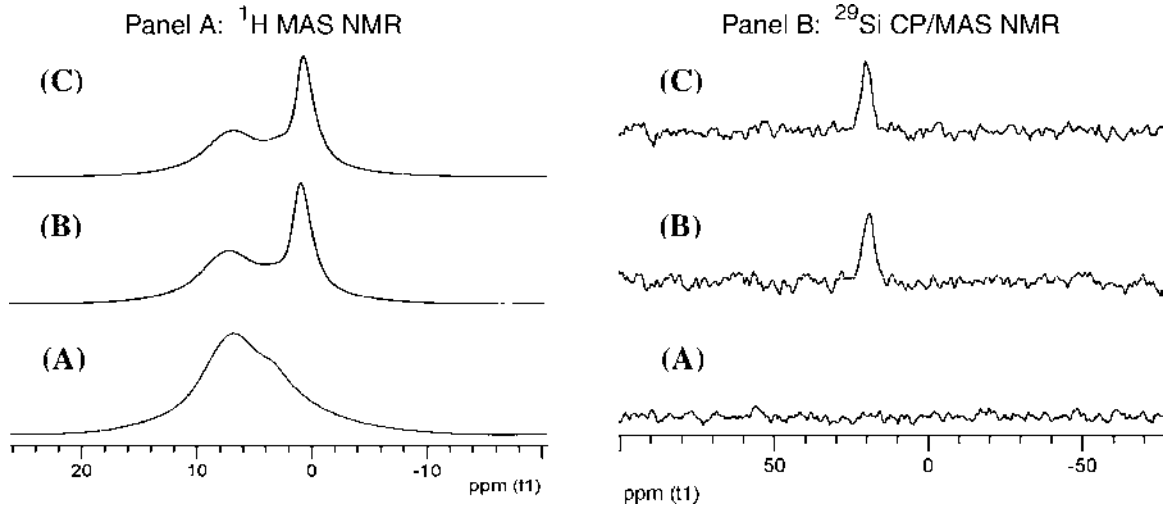
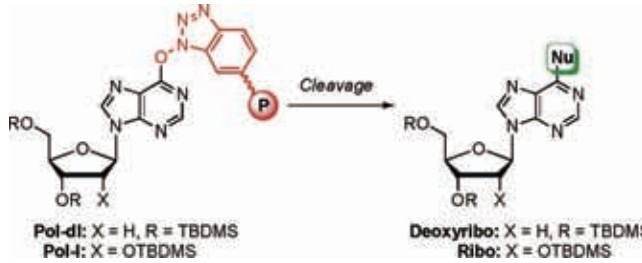
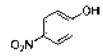
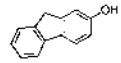


FIGURE 2. ^{1}H and ^{29}Si MAS NMR spectra. (**A**) Pol-HOBt, (**B**) **Pol-dI**, and (**C**) **Pol-I**.

supported reagents are quite stable at −5 °C (based upon their reactions in a one year span). Results obtained herein indicate that they are stable to routine organic solvents such as CH_2Cl_2 and Et_2O that were used for washing, in some cases even at elevated temperatures. In solution chemistry, O^6-(benzotriazol-1-yl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine was stable to $(i\text{-Pr})_2NEt$ and reasonably stable to Cs_2CO_3 (2 mol equiv each) in THF, although moisture can cause hydrolysis. We have also previously shown that this derivative remained intact to an extent of 80% in the presence of Cs_2CO_3 in toluene at 100 °C over 15 h.[17] These results combined with the lowered reactivity of the polymer-supported reagents with alcohols (vide

TABLE 2. Synthesis of the Modified Nucleosides Using the Polymer-Supported Nucleosides (Pol-N)



entry	Pol-N	nucleophile	conditions (experimental procedure)	chromatography (SiO_2)	yield[a,b]
1	**Pol-dI**	MeOH	Cs_2CO_3, rt 24 h (A)	Filtered through a bed of SiO_2 using EtOAc	91% (77%)
2	**Pol-dI**	EtOH	Cs_2CO_3, rt 36 h (A)	No purification required	51% (95%)
3	**Pol-dI**	EtOH	Cs_2CO_3, 80 °C 15 h (A)	No purification required	87%
4	**Pol-dI**	*i*-PrOH	Cs_2CO_3, 80 °C 15 h (A)	—	NR[c] (84%)
5	**Pol-dI**		DME, Cs_2CO_3, 85 °C 1 h (B)	5% EtOAc hexanes then 10% EtOAc-hexanes	41% (86%)
6	**Pol-dI**		DME, Cs_2CO_3, 85 °C 15 h (B)	10% acetone-hexanes	54% (78%)
7	**Pol-dI**		DME, Cs_2CO_3, 85 °C 15 h (B)	20% acetone hexanes	68% (82%)
8	**Pol-dI**		DME, Cs_2CO_3, 85 °C 15 h (B)	5% EtOAc-hexanes then 20% EtOAc-hexanes	49% (81%)
9	**Pol-dI**		DME, Cs_2CO_3, 85 °C 8 h (B)	5% EtOAc-hexanes then 20% EtOAc-hexanes	39% (87%)
10	**Pol-dI**		DME, Cs_2CO_3, rt 24 h then 85 °C 20 h (B)	5% EtOAc hexanes then 20% EtOAc-hexanes	87% (85%)
11	**Pol-I**		DME, Cs_2CO_3, rt 24 h (B)	5% EtOAc-hexanes	46% (93%)
12	**Pol-dI**	Me_2NH	DME, rt 24 h (C)	Filtered through a bed of SiO_2 using EtOAc	Quant[d]
13	**Pol-I**	Me_2NH	DME, rt 24 h (C)	Filtered through a bed of SiO_2 using EtOAc	Quant[d,18]
14	**Pol-dI**		DME, rt 24 h (C)	Filtered through a bed of SiO_2 using EtOAc	Quant[d]
15	**Pol-dI**		DME, rt 24 h (C)	Filtered through a bed of SiO_2 using EtOAc	Quant[d]
16	**Pol-I**		DME, rt 24 h (C)	Filtered through a bed of SiO_2 using EtOAc	Quant[d,e]
17	**Pol-dI**		DME, rt 24 h (C)	Filtered through a bed of SiO_2 using EtOAc	Quant[d,e] (82%)
18	**Pol-I**		DME, rt 24 h (C)	Filtered through a bed of SiO_2 using EtOAc	Quant[d] (90%)
19	**Pol-dI**		DME, rt 24 h (C)	10% acetone-hexanes	Quant[d] (75%)
20	**Pol-I**		DME, rt 24 h (C)	5% acetone hexanes then 30% acetone hexanes	92% (83%)
21	**Pol-dI**		DME, Cs_2CO_3, 85 °C 15 h (B)	10% acetone-hexanes	69% (60%)

[a] Yield of isolated and purified products. [b] Where available, the yield obtained via solution chemistry (ref 12) is shown in parentheses. [c] No reaction was observed. [d] Quantitative yield. [e] With added Cs_2CO_3 and either at room temperature (34 h) or at 85 °C (15 h), the yield was quantitative, indicating that typically base and increased temperature were not necessary.

supra) are indicators of stability toward solvents, to hydrolysis as well as bases. Due to the possibility of deglycosylation as well as desilylation, no tests were performed in the presence of acids.

As shown by the results, these new **Pol-dI** and **Pol-I** are good reagents for nucleoside modification, and to our knowledge these are the first such examples wherein the reaction leading to the C-6 modification also conveniently produces cleavage from the support. Although the unprotected nucleosides can potentially be loaded onto the polymer support, this would require polar solvents due to nucleoside solubility considerations. We have recently shown that solvents like DMF are not suitable when

the O^6 benzotriazolyl nucleosides are prepared via reaction with PPh_3/I_2 followed by displacement with HOBt.[17] Thus, in future developments and additional optimizations, we anticipate addressing the question of directly loading the unprotected nucleosides onto polymer supports. We are currently considering other applications of these reagents as well as the methodology itself and potential commercialization.[19]

Finally, while this work was under review, the isolation of HOBt and HOAt adducts of cyclic amides and ureas has been reported.[20] Thus, the approach described herein could potentially be used for attachment of such cyclic amides and ureas to a polymer support from which suitable derivatives can be released by reaction with nucleophiles. This may assist in rapid access to small molecule libraries in addition to nucleoside modification.

Experimental Section

Synthesis of Polymer-Supported O^6-(Benzotriazol-1-yl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (Pol-dI). In a 50 mL round-bottomed flask equipped with a stirring bar were placed I_2 (0.914 g, 3.60 mmol) and dry CH_2Cl_2 (30 mL). HMPT (0.65 mL, 3.60 mmol) was added slowly and the mixture was stirred at room temperature for 10 min. DIPEA (1.67 mL, 9.60 mmol) and 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine **1a** (1.154 g, 2.40 mmol) were added and the mixture was allowed to stir at room temperature for 1.5 h. Pol-HOBt (3.672 g, 3.75 mmol) was added to this solution and the suspension was allowed to stir at room temperature for 21 h. The resin was filtered, and sequentially washed with CH_2Cl_2, 5% MeOH in CH_2Cl_2, CH_2Cl_2, and Et_2O, and then dried under vacuum. **Pol-dI** was obtained as pale brownish resin (4.65 g). ^{1}H MAS NMR: δ 7.03 (br), 0.80 (br s). ^{29}Si CP/MAS NMR: δ 19.14 (br s).

Determination of Loading Capacity. In a clean, dry reaction vial equipped with a stirring bar were placed **Pol-dI** (0.150 g), Cs_2CO_3 (50.5 mg, 0.155 mmol), and dry DME (1.0 mL). Morpholine (25 μL, 0.286 mmol) was added; the reaction mixture was flushed with nitrogen gas and allowed to stir at room temperature for 34 h. The reaction mixture was filtered and the residue was washed with EtOAc. The filtrate was washed with 10% aq citric acid, sat aq $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness. No additional purification was needed and 27.7 mg of 6-(morpholin-4-yl)-9-[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine was obtained. The calculated loading capacity of **Pol-dI** was 0.336 mmol/g.

Synthesis of Polymer-Supported O^6-(Benzotriazol-1-yl)-2′,3′,5′-tris-*O*-(*tert*-butyldimethylsilyl)inosine (Pol-I). As described for the synthesis of **Pol-dI**, **Pol-I** was prepared by reaction between I_2 (0.571 g, 2.25 mmol), HMPT (0.41 mL, 2.25 mmol), DIPEA (1.05 mL, 6.00 mmol), and 2′,3′,5′-tris-*O*-(*tert*-butyldimethylsilyl)inosine **1b** (0.917 g, 1.50 mmol) and Pol-HOBt (2.206 g, 2.25 mmol) in dry CH_2Cl_2 (20 mL). **Pol-I** was obtained as yellow resin (2.793 g). ^{1}H MAS NMR: δ 6.98 (br), 0.85 (br s). ^{29}Si CP/MAS NMR: δ 20.40 (br s).

Determination of Loading Capacity. As described for **Pol-dI**, the loading capacity of **Pol-I** was determined by reaction between **Pol-I** (0.100 g), Cs_2CO_3 (35.2 mg, 0.108 mmol), and morpholine (18.9 μL, 0.216 mmol) in dry DME (0.6 mL). No additional purification was needed, and 16.6 mg of 6-(morpholin-4-yl)-9-[2,3,5-tris-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine was obtained. The calculated loading capacity of **Pol-I** was 0.244 mmol/g.

General Procedure A. Synthesis of O^6-Alkyl Ether Derivatives. In a clean, dry reaction vial equipped with a stirring bar were placed the polymer-supported nucleoside (1.0 mol equiv) and Cs_2CO_3 (2.0 mol equiv) in the alcohol (0.5−1.0 mL). The reaction mixture was flushed with nitrogen gas and was allowed to stir under the appropriate conditions. The reaction mixture was filtered and subjected to purification according to the method described in Table 2.

General Procedure B. Synthesis of O^6-Aryl Ether and O^6-Thio Ether Derivatives. In a clean, dry reaction vial equipped with a stirring bar were placed the polymer-supported nucleoside (1.0 mol equiv), Cs_2CO_3 (2.0 mol equiv), and the appropriate phenol (2.0 mol equiv). Dry DME (1.0 mL) was added, the reaction mixture was flushed with nitrogen gas and allowed to stir under the appropriate conditions. The reaction mixture was filtered, the residue was washed with EtOAc followed by CH_2Cl_2, and the filtrate was evaporated to dryness. The crude reaction product was purified by column chromatography on silica gel using appropriate solvents indicated in Table 2.

General Procedure C. Synthesis of N^6-Alkyl and N^6-Benzyl Derivatives. In a clean, dry reaction vial equipped with a stirring bar was placed the polymer-supported nucleoside (1.0 mol equiv) in dry DME (1.0 mL). The requisite amine (4.0 mol equiv) was added, the reaction mixture was flushed with nitrogen gas and allowed to stir under the appropriate conditions. In case of N^6-alkyl derivatives; the reaction mixtures were directly loaded onto a bed of SiO_2 and the products eluted with EtOAc. For the N^6-benzyl derivatives; the reaction mixtures was filtered, the residue in each case was washed with EtOAc followed by CH_2Cl_2 and the filtrates were evaporated to dryness. The crude reaction products were purified by column chromatography on silica gel using appropriate solvents indicated in Table 2.

3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethyl-2′-deoxyadenosine. Clear, yellowish gum. R_f (20% EtOAc in hexanes) = 0.35. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (s, 1H, Ar−H), 7.98 (s, 1H, Ar−H), 6.45 (t, 1H, H-1′, J = 6.4), 4.59 (app quint, 1H, H-3′, $J \approx$ 3.0), 4.00 (app q, 1H, H-4′, $J \approx$ 3.6), 3.82 (dd, 1H, H-5′, J = 11.0, 4.4), 3.76 (dd, 1H, H-5′, J = 11.0, 3.4), 3.52 (br s, 6H, NCH_3), 2.59 (quint, 1H, H-2′, J = 6.4), 2.41 (ddd, 1H, H-2′, J = 12.8, 6.0, 3.7), 0.91 (s, 18H, *tert*-Bu), 0.09, 0.073, 0.07 (2s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.9, 152.4, 150.2, 136.4, 120.5, 87.8, 84.0, 72.1, 62.9, 41.0, 38.5, 26.0, 25.8, 18.4, 18.0, −4.7, −4.8, −5.4, −5.5. FAB HRMS calcd for $C_{24}H_{46}N_5O_3Si_2$ (M^+ + H) 508.3139, found 508.3164.

6-(Pyrrolidin-1-yl)-9-[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine. Clear, yellowish gum. R_f (20% EtOAc in hexanes) = 0.23. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (s, 1H, Ar−H), 7.95 (s, 1H, Ar−H), 6.44 (t, 1H, H-1′, J = 6.7), 4.58 (app quint, 1H, H-3′, $J \approx$ 3.0), 4.15 (br, 2H, NCH_2), 4.00 (q, 1H, H-4′, J = 3.7), 3.81 (dd, 1H, H-5′, J = 11.0, 4.6), 3.76 (br, 2H, NCH_2), 3.75 (dd, 1H, H-5′, J = 11.0, 3.4), 2.61 (app quint, 1H, H-2′, $J \approx$ 6.5), 2.40 (ddd, 1H, H-2′, J = 13.1, 5.8, 3.4), 2.02 (br s, 4H, pyrrolidinyl CH_2), 0.90, 0.897 (2s, 18H, *tert*-Bu), 0.09, 0.07, 0.06 (3s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.1, 152.7, 149.8, 120.6, 87.8, 84.0, 72.2, 62.9, 48.9 (br), 47.3 (br), 40.9, 26.0, 25.8, 24.3 (br), −4.7, −4.8, −5.4, −5.5. FAB HRMS calcd for $C_{26}H_{48}N_5O_3Si_2$ (M^+ + H) 534.3296, found 534.3279.

6-(Piperidin-1-yl)-9-[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine. Clear, yellowish gum. R_f (20% EtOAc in hexanes) = 0.47. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (s, 1H, Ar−H), 7.97 (s, 1H, Ar−H), 6.44 (t, 1H, H-1′, J = 6.6), 4.58 (m, 1H, H-3′), 4.23 (br s, 4H, NCH_2), 4.00 (m, 1H, H-4′), 3.81 (dd, 1H, H-5′, J = 11.0, 4.6), 3.75 (dd, 1H, H-5′, J = 11.0, 3.2), 2.59 (quint, 1H, H-2′, J = 6.4), 2.40 (ddd, 1H, H-2′, J = 13.1, 5.8, 3.7), 1.73−1.68 (m, 6H, piperidinyl CH_2), 0.90 (s, 18H,

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tert-Bu), 0.09, 0.07, 0.066 (3s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.9, 152.4, 150.4, 136.1, 120.2, 87.8, 84.0, 72.1, 62.9, 46.4, 41.0, 26.1, 26.0, 25.8, 18.4, 18.0, −4.7, −4.8, −5.4, −5.5. FAB HRMS calcd for $C_{27}H_{50}N_5O_3Si_2$ ($M^+ + H$) 548.3452, found 548.3424.

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Supporting Information Available: General experimental protocols, ^1H and ^{13}C NMR spectra of 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethyl-2′-deoxyadenosine, 6-(pyrrolidin-1-yl)-9-[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)]-β-D-ribofuranosyl]purine and 6-(piperidin-1-yl)-9-[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)]-β-D-ribofuranosyl]purine as well as ^1H NMR spectra of other known products in Table 2 that were resynthesized in course of this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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