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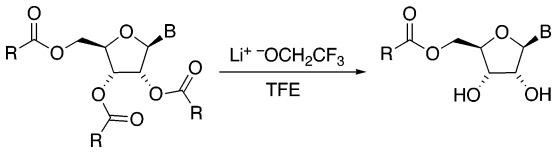
Selective Removal of the 2′- and 3′-*O*-Acyl Groups from 2′,3′,5′-Tri-*O*-acylribonucleoside Derivatives with Lithium Trifluoroethoxide[1]

Ireneusz Nowak, Carl T. Jones, and Morris J. Robins*

Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602-5700

morris_robins@byu.edu

Received January 3, 2006



Selective cleavage of O2′ and O3′ ester groups from ribonucleoside derivatives has been accomplished with Dowex 1 × 2 ($CF_3CH_2O^-$) in 2,2,2-trifluoroethanol (TFE) or lithium trifluoroethoxide/TFE. Deacylations with Li^+ $^-OCH_2CF_3$/TFE proceed at ambient temperature (or with mild heating) to give the 5′-*O*-acyl derivatives in superior yields and higher purity than prior approaches for selective O2′ and O3′ ester deprotection.

Introduction

Selective protection of the primary hydroxyl group in nucleosides is often required, and development of convenient new procedures for O5′-protected derivatives can benefit synthesis of biomedically important compounds. Good selectivity for O5′ monoprotection[2] can usually be achieved with acid-labile trityl and substituted trityl groups, but their reactivity with amino groups on the nucleobases is often encountered. The *tert*-butyldimethylsilyl and *tert*-butyldiphenylsilyl groups are more selective, but the reagents are costly. Base-labile protecting groups allow deprotection of deoxyoligonucleotides without deglycosylation and other troublesome side reactions.[3]

Acylation of the primary hydroxyl group in sugars has been achieved with thioesters and BOP-derived mixed anhydrides.[4] Selective acylations of nucleosides have been reported,[5] but problems involved with chemical procedures stimulated development of alternative enzyme-catalyzed processes.[6]

Two-step procedures that involve selective deacylation of di- and triacetates have been reported,[7−9] but the lack of general applicability, problems with reproducibility, and less than desirable overall yields leave ample room for improvement. For example, Ishido and co-workers reported three methods for selective deacylation at O2′ and O3′ of ribonucleosides.[9] They first employed buffered hydroxylamine acetate (anhydrous hydroxylamine is neither stable for storage nor commercially available) with extended reaction times (1 day), and characterization of the four final products was not described.[9a] Their second method used a strong base (2.5 equiv of solid NaOMe in THF),[9b] and our attempted repetition of that procedure gave a mixture of deacylation products with low selectivity. Hydrazine hydrate was used in their third method,[9c] but extended reaction times were employed and only two examples (benzoylated adenosine and uridine) were reported. An additional problem with the hydroxylamine and hydrazine procedures results from the potential addition of these nitrogen nucleophiles

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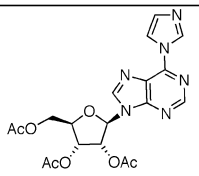
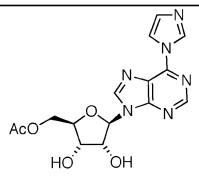
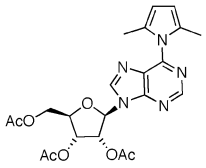
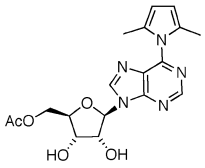
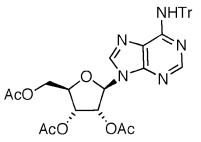
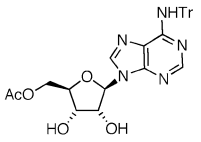
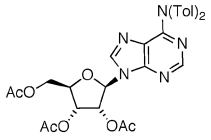
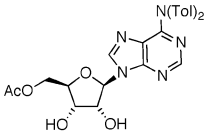
10.1021/jo0600104 CCC: $33.50
Published on Web 03/17/2006

TABLE 1. Deacylations (Dowex/TFE)[a]

entry	substrate	product[b]
1	 **1a**	 **2a** (75)
2	 **1b**	 **2b** (71)
3	 **1c**	 **2c** (66)
4	 **1d**	 **2d** (39)

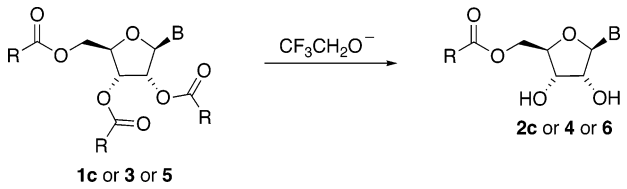
[a] Reactions performed by general procedure A (Experimental Section). [b] Isolated yields in parentheses.

at C4 and C6 of cytosine nucleosides.[9a,10] We now report selective base-promoted O2′ and O3′ deacylation with solutions of polyacylated nucleosides in 2,2,2-trifluoroethanol. A number of nucleobase-protecting groups are stable under these conditions.

Results and Discussion

We had employed S_NAr replacement of (1,2,4-triazol-4-yl)[11] and (imidazol-1-yl)[12] groups by alkoxides on purine nucleosides using Dowex 1 × 2 (OH^-) resin washed with and suspended in primary alcohols. Such treatment of **1a** (Table 1) with Dowex 1 × 2 (OH^-) in methanol gave efficient conversion to 6-methoxy-9-(β-D-ribofuranosyl)purine (with concomitant removal of the three acetyl groups). However, selective removal of the acetyl groups from O2′ and O3′ without S_NAr replacement of the imidazole group occurred upon treatment of **1a** with Dowex 1 × 2 (OH^-) in 2,2,2-trifluoroethanol (TFE). We then began a systematic investigation of selective deprotection of polyacylated nucleosides in TFE to capitalize on the lower pK_a values and distinctive solvation properties of fluorinated alcohols.[13] Adenosine derivatives with nonpolar groups on the adenine base facilitated analysis and separation of the polyacylated and selectively deprotected pairs (Table 1). Yields were reasonable with base-stable N6-protecting groups (entries 1−3), but partial removal of an acyl group from the 6-*N*,*N*-bis(4-methylbenzoyl) imide in **1d** lowered the yield of **2d** (entry 4).

SCHEME 1. Selective Deacylation



The acidities and relative reactivities of the 2′-, 3′-, and 5′-hydroxyl groups in ribonucleosides are affected by changes that withdraw electron density from the oxyanions. Subtle differences in these pK_a values and reactivities can have major implications for the recognition, processing, and catalytic properties of RNAs.[14] Acidity data measured under uniform noninvasive conditions[15] indicate that the 2′-hydroxyl group is most acidic (pK_a = 12.31) for the adenosine moiety in **A**pG and slightly less acidic in **G**pG, **C**pG, and **U**pG (pK_a = 12.73−12.77). The pK_a values for the 2′- and 3′-hydroxyl groups in ribonucleosides were shown to be very similar in different solvents,[16] although they (or the anions derived therefrom) display different reactivities in a number of reactions.[17] Primary (5′-OH) alcohol groups are least acidic (pK_a ≅ 14.8[18]), which results in the lowest reactivity of O5′ esters toward base-promoted solvolysis. This usually is not apparent unless a base weak enough to promote subtle discrimination is used. Additional stabilization of a 2′/3′-oxyanion results from the proximity of the vicinal diol oxygens and the electron-withdrawing nature of the nucleobase at C1′. The acidities of TFE (pK_a = 12.37)[18] and heptafluoropropanol (pK_a ≅ 11)[19] are close to those of the 2′- and 3′-hydroxyl groups of nucleosides—and quite distinct from the pK_a values (∼15) of the 5′-hydroxyl group. Thus, selective attack of $CF_3CH_2O^-$ at the ester carbonyl group attached at O2′ and O3′, relative to attack on 5′-*O*-acyl groups, would be expected with this weaker nucleophile.

Our studies with Dowex 1 × 2 (OH^-)/TFE (method A) were extended to include adenosine **1c**, **3a**−**c**, cytidine **3d**−**g**, and uridine **3h**−**k** derivatives with more diverse ester groups (Scheme 1). The more sterically hindered propionyl (70 °C) and isobutyryl (90−110 °C) [and *p*-toluyl (4-methylbenzoyl) (90−110 °C)] esters required elevated temperatures to achieve rates of deprotection of O2′ and O3′ equivalent to those for acetyl esters at ambient temperature (complete in ∼2 h, TLC). However, the deacylations promoted by Dowex 1 × 2 (OH^-)

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TABLE 2. Selective Deacylations[a]

entry[b]	B[c]	method	R	T[d]	t[e]	yield[f]
1 (**1c**)	TrAde	A	Me	amb	2.0	66
2 (**1c**)	TrAde	B	Me	amb	0.5	88
3 (**3a**)	TrAde	A	Et	70	2.0	75
4 (**3a**)	TrAde	B	Et	amb	2.0	86
5 (**3b**)	TrAde	A	^{i}Pr	110	2.0	51
6 (**3b**)	TrAde	B	^{i}Pr	60	0.5	65
7 (**3c**)	TrAde	A	Tol	110	2.0	54
8 (**3c**)	TrAde	B	Tol	60	0.5	76
9 (**3d**)	TrCyt	B	Me	amb	0.5	93
10 (**3e**)	TrCyt	B	Et	amb	2.5	94
11 (**3f**)	TrCyt	B	^{i}Pr	60	0.5	87
12 (**3g**)	TrCyt	B	Tol	60	0.5	80
13 (**3h**)	BnUra	A	Me	amb	2.0	69
14 (**3h**)	BnUra	B	Me	amb	0.5	91
15 (**3i**)	BnUra	A	Et	80	2.0	61
16 (**3i**)	BnUra	B	Et	amb	2.0	79
17 (**3j**)	BnUra	A	^{i}Pr	90	2.0	52
18 (**3j**)	BnUra	B	^{i}Pr	60	0.5	71
19 (**3k**)	BnUra	A	Tol	90	4.0	65
20 (**3k**)	BnUra	B	Tol	60	0.5	90

[a] See the Results and Discussion and Experimental Section for methods A and B. [b] Starting material in parentheses. [c] TrAde: 6-*N*-tritylladenin-9-yl, TrCyt: 4-*N*-tritylcytosin-1-yl, BnUra: 3-benzyluracil-1-yl. [d] Amb: ambient, other temperatures in °C. [e] Time in hours. [f] Isolated % yield.

produced results that were less than desirable because partially (di-O-acylated) and completely deprotected byproducts were formed. Addition of the hydrogen bond-accepting cosolvent THF (THF/TFE, 10:1) resulted in more extensive conversion of **3b** to the fully deacylated product, whereas addition of toluene (toluene/TFE, 5:1) markedly retarded the rate of deacylation. We then examined replacement of the two-phase system of Dowex resin (which contains traces of water and OH^- anions) and TFE with homogeneous solutions of metal trifluoroethoxides in TFE.

A solution of sodium trifluoroethoxide (generated with excess TFE and 1 M sodium hexamethyldisilazide/THF) gave rapid deacylation. However, the above-noted effect of THF-promoted removal of the O5′ ester gave a lower yield of **4i** (52%, compared with Table 2 entry 16, 79%). Lithium trifluoroethoxide/TFE (generated with excess TFE and 1.6 M butyllithium/hexanes) (method B) caused rapid deacylation, and the selectively deprotected 5′-*O*-acyl products were isolated in higher yields (entries 2, 4, 6, 8−12, 14, 16, 18, 20).

Nucleoside derivatives **5** without N-protection (containing mobile NH and/or OH protons) also were examined (Table 3). Despite their increased polarity, products **6** and byproducts were resolved by TLC and purified by column chromatography. An additional equivalent of $LiOCH_2CF_3$ was used with the uridine, **5i**−**l**, hypoxanthine, **5m**, and guanine, **5n**, derivatives (which have an acidic imide or amide proton). The deprotections with **5** were slightly less selective than those with the less polar derivatives **3**. Treatment of 2′,3′,5′-tri-*O*-acetylformycin (**5o**) with 3 equiv of $LiOCH_2CF_3$/TFE by method B gave formycin as the major product. The loss of selectivity (the desired product **6o** was a minor component) was accompanied by yellow coloration of the reaction mixture. The proximal pyrazole ring nitrogen (N2) of the base moiety (For, Figure 1) might participate in solvolysis of the acetyl group from O5′.

A demanding application of our method involved removal of the benzoyl-protecting groups from the sensitive furo[2,3-*d*]pyrimidin-2(3*H*)-one derivative **5p**. The fused furan moiety (FuPym) in **5p** is susceptible to nucleophilic attack and undergoes ring opening upon attempted deprotection with NH_3/MeOH or NaOMe/MeOH. We were pleased that the decreased nucleophilicity of $LiOCH_2CF_3$/TFE accommodates selective cleavage of the benzoate esters at O2′ and O3′ (62% isolated yield, entry 16). Prolonged treatment resulted in removal of the 5′-*O*-benzoyl group without problematic opening of the furan ring.

TABLE 3. Deacylations of 5 (Method B)

entry[a]	B[b]	R	T[c]	t[d]	yield[e]
1 (**5a**)	Ade	Me	amb	0.5	70
2 (**5b**)	Ade	Et	amb	2.0	71
3 (**5c**)	Ade	^{i}Pr	60	1.0	64
4 (**5d**)	Ade	Tol	60	1.5	81
5 (**5e**)	Cyt	Me	amb	0.5	88
6 (**5f**)	Cyt	Et	amb	2.5	84
7 (**5g**)	Cyt	^{i}Pr	60	1.0	83
8 (**5h**)	Cyt	Tol	60	1.0	66
9 (**5i**)[f]	Ura	Me	amb	0.5	80[c]
10 (**5j**)[f]	Ura	Et	amb	2.0	83[c]
11 (**5k**)[f]	Ura	^{i}Pr	60	1.0	62[c]
12 (**5l**)[f]	Ura	Tol	60	1.5	73[c]
13 (**5m**)[f]	Hpx	Tol	60	1.0	75[c]
14 (**5n**)[f]	AcGua	Me	amb	1.5	84
15 (**5o**)[f]	For	Me	amb	2.0	*g*
16 (**5p**)	FuPym	Ph	amb	0.5	62[h]

[a] Starting material in parentheses. [b] Ade: adenin-9-yl, Cyt: cytosin-1-yl, Ura: uracil-1-yl, Hpx: hypoxanthin-9-yl, AcGua: 2-*N*-acetylguanin-9-yl, For: 7-aminopyrazolo[4,3-*d*]pyrimidin-3(1*H*)-yl, FuPym: furo[2,3-*d*]pyrimidin-2-(3*H*)-on-3-yl. [c] Amb: ambient, other temperatures in °C. [d] Time in hours. [e] Isolated % yield. [f] $LiOCH_2CF_3$ (3 equiv). [g] Complex mixture. [h] TFE was used for chromatography in place of MeOH.

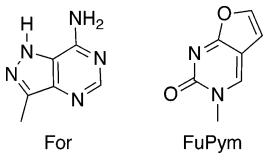
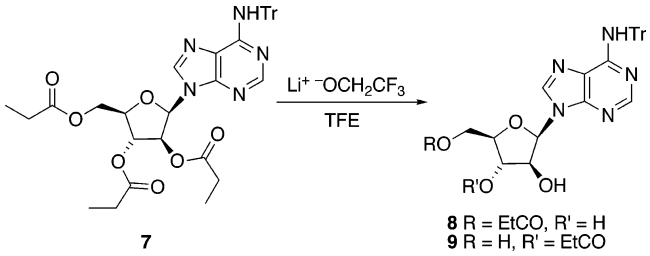


FIGURE 1. Structures of For and FuPym.

SCHEME 2. Deacylation of 7



Replacement of the 2′-hydroxyl group by hydrogen caused dramatic decreases in deacylation rates and loss of selectivity for cleavage of O3′ versus O5′ esters in 2′-deoxynucleoside derivatives. For example, 2′-deoxy-3′,5′-di-*O*-(4-methylbenzoyl)uridine remained unchanged after 3 h at 60 °C. Treatment of 3′,5′-di-*O*-acetyl-2′-deoxyadenosine (method B, 3.5 h, ambient temperature) produced a mixture of starting material, 3′-*O*-acetyl-2′-deoxyadenosine, 5′-*O*-acetyl-2′-deoxyadenosine, and 2′-deoxyadenosine (∼3:2:2:1).

Further probing of the effects of sugar structure on our selective deprotection with $LiOCH_2CF_3$/TFE (method B) was pursued with 9-(2,3,5-tri-*O*-propanoyl-β-D-arabinofuranosyl)-6-*N*-tritylladenine (**7**) (Scheme 2). Inversion of configuration at C2′ to give the arabino epimer **7** does not significantly alter the acidity of the vicinal secondary hydroxyl groups, but makes acyl transfer between the trans O2′ and O3′ termini highly

unfavorable. However, acyl transfer between the cis O5′ and O2′ oxygens is possible. Treatment of **7** under the usual conditions gave the 5′-ester **8** as the major product accompanied by the 3′-ester **9** (~3:2 ratio) in a combined yield of 81%. A 5:1 ratio of **8**/**9** (39% combined) was obtained with Dowex/TFE (method A). These results are consistent with more rapid solvolysis of the 2′-ester followed by migration of the acyl group from O5′ to O2′. The second cleavage from O2′ is in competition with solvolysis of the 3′-ester. Migration is dependent on the acyl group and occurred to a lesser extent with the 2′,3′,5′-tri-*O*-(4-methylbenzoyl) analogue (i.e., a larger 5′-/3′-ester ratio was observed (^{1}H NMR)).

Our methodology with $LiOCH_2CF_3$/TFE (readily prepared with quantitative stoichiometry from TFE and commercial 1.6 M BuLi/hexanes) employs a solvent with unique pK_a and physicochemical properties. The nucleoside derivatives we examined are readily soluble, and a variety of ester derivatives **1c**, **3**, and **5** underwent selective deacylation readily (most reactions were completed in 0.5−2.0 h at ambient temperature or 60 °C). This procedure is superior to method A (Dowex 1 × 2 [OH^-]/TFE), which requires higher temperatures with hindered alkyl and 4-methylbenzoyl esters and is often less selective. Others have noted the loss of selectivity for cleavage of esters of deoxynucleosides. For example, hydrazinolysis of esters of 2′- and 3′-deoxyadenosine[9c] and treatment of such derivatives with ethanolic morpholine (pK_a = ~8.4)[20] gave mixtures.

Conclusions

We have demonstrated that solutions of O-peracylated ribonucleosides in lithium trifluoroethoxide/trifluoroethanol undergo selective deacylation at O2′ and O3′. Increased reaction times and/or temperatures are required for esters with greater steric demands in the acyl group. One equivalent of $LiOCH_2CF_3$ is neutralized by the acidic amide/imide proton on certain nucleobases, but addition of a further equivalent of $LiOCH_2CF_3$ results in a negligible effect on the selectivity and yields of most reactions. The method is mild and rapid (complete within 3 h in the slowest cases) and provides the 5′-*O*-acyl products in 60−90% yields. It is noteworthy that the low nucleophilicity of $CF_3CH_2O^-$ makes this methodology tolerant of a 4-amino group and the 5,6-double bond in pyrimidines, the 6-(imidazol-1-yl) group on purines, and the fused furan moiety in a furo[2,3-*d*]pyrimidin-2(3*H*)-one derivative. A broad variety of 5′-*O*-acyl nucleoside derivatives are now readily available as intermediates for synthesis of deoxynucleosides,[21] cyclic nucleosides,[17] oligoribonucleotides,[22] and nucleoside prodrugs. They also can be functionalized into numerous other compounds via 2′,3′-*O*-(dibutylstannylene) derivatives.[23] By the proper choice of 5′-*O*-acyl groups, the polarity and crystallinity of ribonucleoside derivatives can be fine-tuned for purification and other purposes.

Experimental Section

Dowex 1 × 2 [$CF_3CH_2O^-$] Resin. Commercial Dowex 1 × 2 [Cl^-] resin was washed with four column volumes of 1 M HCl/H_2O and then with distilled H_2O until the eluant was neutral. The resin was next washed with 1 M NaOH/H_2O until an aliquot (after acidification with HNO_3/H_2O) showed no cloudiness upon addition of $AgNO_3$/H_2O, and then it was washed with distilled H_2O until the eluate was neutral. The Dowex 1 × 2 [OH^-] resin, collected by suction filtration and air-dried, can be stored indefinitely in a bottle protected from light at refrigerator temperature.

Air-dried Dowex 1 × 2 [OH^-] resin was suspended in dried TFE, stirred for 30 min, filtered with suction, and resuspended in TFE. This cycle was repeated several times, and the resin was then dried in vacuo at ambient temperature overnight and stored in a bottle protected from light in a desiccator.

Method A. Selective Deacylation of Peracylated Nucleosides with Dowex 1 × 2 [$CF_3CH_2O^-$] Resin in TFE. Dried Dowex 1 × 2 [$CF_3CH_2O^-$] resin (0.5 g, ~0.5 mmol exchange capacity) was added to a solution of nucleoside **1** or **3** (1 mmol) in TFE (2 mL), and the suspension was stirred vigorously for the time (and at the temperature) specified. Reactions at temperatures greater than the boiling point of TFE (74 °C) were performed in a pressure flask equipped with a Teflon valve. When selective deprotection was judged complete (TLC), the suspension was filtered and the resin was washed thoroughly with EtOAc and then MeOH. The combined filtrates were concentrated and subjected to silica column chromatography to give the purified products **2** or **4**.

Method B. Selective Deacylation of O-Peracylated Nucleosides with $LiOCH_2CF_3$/TFE. Butyllithium/hexanes (1.6 M, 0.8 mL, 1.28 mmol) were added dropwise to stirred trifluoroethanol (2 mL), and moderate evolution of heat occurred. The resulting solution was added to compound **1** (or **3** or **7**) (0.64 mmol) in a separate flask, and the reaction mixture was stirred at ambient temperature (or 60 °C) until selective deacylation was judged to be complete (TLC). Acetic acid (0.5 mL, 8.33 mmol) was added, and volatiles were evaporated. A suspension of the residue in CH_2Cl_2 was subjected to silica column chromatography to give the purified compound **4** (or **6** or **8** or **9**).

Preparation of 2′,3′,5′-Tri-*O*-acyl-*N*-trityl Nucleosides (1c, 3a−g, 7). A solution of the adenine or cytosine 2′,3′,5′-tri-*O*-acyl nucleoside and trityl chloride (2 equiv) in dried pyridine was stirred overnight at 100 °C. Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes) to give purified **1c**, **3a**−**g**, and **7** in 80−90% yields.

2′,3′,5′-Tri-*O*-acetyl-6-*N*-trityladenosine[24] (1c). ^{1}H NMR δ 2.08, 2.10, 2.12 (3 × s, 3 × 3H), 4.33−4.46 (m, 3H), 5.68 (t, J = 5.1 Hz, 1H), 5.91 (t, J = 5.4 Hz, 1H), 6.14 (d, J = 4.9 Hz, 1H), 6.94 (s, 1H), 7.23−7.35 (m, 15H), 7.90 (s, 1H), 8.04 (s, 1H); ^{13}C NMR δ 20.06, 20.14, 20.4, 62.7, 70.2, 71.0, 72.8, 79.7, 86.0, 121.0, 126.6, 127.5, 128.6, 138.2, 144.5, 148.3, 152.2, 153.8, 169.0, 169.2, 169.9; MS *m*/*z* 658 (100%, M + Na^+); HMRS Calcd for $C_{35}H_{33}N_5O_7Na$: 658.2277, Found: 658.2375.

2′,3′,5′-Tri-*O*-acetyl-6-*N*,*N*-di(4-methylbenzoyl)adenosine (1d). *p*-Toluyl chloride (0.50 mL, 0.58 g, 3.78 mmol) was added to a solution of 2′,3′,5′-tri-*O*-acetyladenosine (0.17 g, 0.43 mmol) in dried pyridine (1 mL), and the solution was stirred for 1 h at 80 °C. Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes 10:1 → EtOAc) to give **1d** (0.23 g, 84%): ^{1}H NMR δ 2.09, 2.10, 2.14 (3 × s, 3 × 3H), 2.35 (s, 6H), 4.36−4.48 (m, 3H), 5.69 (t, J = 2.7 Hz, 1H), 5.94 (t, J = 5.2 Hz, 1H), 6.25 (d, J = 4.9 Hz, 1H), 7.16 (d, J = 7.8 Hz, 4H), 7.76 (d, J = 7.8 Hz, 4H), 8.21 (s, 1H), 8.65 (s, 1H); ^{13}C NMR δ 20.0, 20.2, 20.4, 21.3, 62.7, 70.2, 72.7, 80.1, 86.3, 127.4, 129.2, 129.3, 130.8, 143.1, 143.7, 152.0, 152.2, 169.0, 169.2, 169.9, 171.8; MS *m*/*z* 652 (100%, M + Na^+); HMRS Calcd for $C_{32}H_{31}N_5O_9Na$: 652.2019; Found: 652.2017.

9-(5-*O*-Acetyl-β-D-ribofuranosyl)-6-(imidazol-1-yl)purine (2a). Treatment of 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6-(imidazol-

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1-yl)purine[25] (**1a**) by method A at ambient temperature for 2 h gave **2a** (75%): ^{1}H NMR (CD_3OD) δ 2.08 (s, 3H), 4.29−4.45 (m, 4H), 4.84 (t, J = 4.9 Hz, 1H), 6.15 (d, J = 4.4 Hz, 1H), 7.18 (d, J = 1.0 Hz, 1H), 8.35 (t, J = 1.5 Hz, 1H), 8.58 (s, 1H), 8.73 (s, 1H), 9.09 (s, 1H); ^{13}C NMR δ 20.9, 65.0, 72.0, 75.2, 83.7, 90.9, 118.9, 124.3, 130.6, 138.8, 146.3, 146.4, 153.3, 154.8, 172.5; MS *m*/*z* 383 (100%, M + Na^+); HMRS Calcd for $C_{15}H_{16}N_6O_5Na$: 383.1080, Found: 383.1088.

9-(5-*O*-Acetyl-β-D-ribofuranosyl)-6-(2,5-dimethylpyrrol-1-yl)-purine (2b). Treatment of 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6-(2,5-dimethylpyrrol-1-yl)purine[26] (**1b**) by method A at ambient temperature for 1.5 h gave **2b** (71%): ^{1}H NMR δ 2.05 (s, 3H), 2.16 (s, 6H), 4.02 (br s, 1H), 4.33−4.43 (m, 4H), 4.60 (t, J = 4.2 Hz, 1H), 4.99 (br s, 1H), 5.94 (s, 2H), 6.10 (t, J = 3.9 Hz, 1H), 8.33 (s, 1H), 8.89 (s, 1H); ^{13}C NMR δ 13.4, 20.7, 63.5, 70.7, 74.6, 82.7, 90.0, 109.1, 129.1, 129.8, 143.7, 150.2, 152.1, 152.7, 170.7; MS *m*/*z* 410 (100%, M + Na^+); HMRS Calcd for $C_{18}H_{21}N_5O_5Na$: 410.1440, Found: 410.1436.

5′-*O*-Acetyl-6-*N*-trityladenosine (2c). Method A. Treatment of **1c** by method A at ambient temperature for 2 h gave **2c** (66%): ^{1}H NMR δ 1.98 (s, 3H), 4.12−4.48 (m, 7H), 5.89 (d, J = 4.9 Hz, 1H), 6.18 (br s, 1H), 7.14 (s, 1H), 7.20−7.34 (m, 15H), 7.95 (s, 1H); ^{13}C NMR δ 20.6, 63.2, 70.5, 71.3, 74.8, 82.3, 89.8, 120.8, 126.8, 127.7, 128.8, 138.1, 144.5, 147.6, 151.7, 153.9, 170.4; MS *m*/*z* 574 (100%, M + Na^+); HMRS Calcd for $C_{31}H_{29}N_5O_5Na$: 574.2066, Found: 574.2053.

Method B. Treatment of **1c** by method B at ambient temperature for 0.5 h gave **2c** (88%) with identical spectral data.

5′-*O*-Acetyl-6-*N*,*N*-di(4-methylbenzoyl)adenosine (2d). Treatment of **1d** by method A at ambient temperature for 1 h gave **2d** (39%): ^{1}H NMR δ 2.00 (s, 3H), 2.34 (s, 6H), 3.67 (d, J = 3.9 Hz, 1H), 4.24−4.36 (m, 4H), 4.57 (m, 1H), 4.95 (d, J = 3.9 Hz, 1H), 6.00 (d, J = 4.9 Hz, 1H), 7.14 (d, J = 7.8 Hz, 4H), 7.73 (d, J = 7.8 Hz, 4H), 8.18 (s, 1H), 8.58 (s, 1H); ^{13}C NMR δ 20.7, 21.6, 63.6, 70.7, 74.4, 82.4, 89.6, 127.5, 129.47, 129.54, 130.9, 143.6, 144.2, 151.9, 152.0, 152.3, 170.7, 172.3; MS *m*/*z* 568 (100%, M + Na^+); HMRS Calcd for $C_{28}H_{27}N_5O_7Na$: 568.1808, Found: 568.1804.

2′,3′,5′-Tri-*O*-propionyl-4-*N*-tritylcytidine (3e). ^{1}H NMR δ 1.06 (t, J = 7.3 Hz, 3H), 1.13 (t, J = 7.3 Hz, 6H), 2.17−2.48 (m, 6H), 4.25−4.38 (m, 3H), 5.04 (d, J = 7.8 Hz, 1H), 5.26 (t, J = 5.6 Hz, 1H), 5.34 (t, J = 4.6 Hz, 1H), 6.11 (d, J = 3.9 Hz, 1H), 6.93 (br s, 1H), 7.20−7.36 (m, 16H); ^{13}C NMR δ 8.49, 8.56, 26.79, 26.89, 62.1, 69.0, 70.6, 73.3, 78.9, 88.3, 94.5, 127.3, 128.1, 128.3, 139.7, 143.4, 154.3, 165.1, 172.5, 172.6, 173.1; MS *m*/*z* 676 (100%, M + Na^+); HMRS Calcd for $C_{37}H_{39}N_3O_8Na$: 676.2635, Found: 676.2637.

5′-*O*-Propionyl-4-*N*-tritylcytidine (4e). Treatment of **3e** by method B at ambient temperature for 2.5 h gave **4e** (94%): ^{1}H NMR δ 1.00 (t, J = 7.3 Hz, 3H), 2.04−2.19 (m, 2H), 3.61 (br s, 1H), 4.10−4.44 (m, 5H), 5.09 (d, J = 7.8 Hz, 1H), 5.73 (d, J = 2.9 Hz, 1H), 6.11 (br s, 1H), 7.02 (br s, 1H), 7.22−7.35 (m, 15H), 7.37 (d, J = 7.8 Hz, 1H); ^{13}C NMR δ 8.9, 27.2, 63.3, 70.8, 71.0, 75.9, 82.9, 92.4, 94.6, 127.6, 128.4, 128.6, 140.0, 143.5, 156.2, 165.5, 173.6; MS *m*/*z* 564 (100%, M + Na^+); HMRS Calcd for $C_{31}H_{31}N_3O_6Na$: 564.2110, Found: 564.2124.

5′-*O*-Propionylcytidine (6f). Treatment of **5f** by method B at ambient temperature for 2.5 h gave **6f** (84%): ^{1}H NMR (DMSO-d_6) δ 1.04 (t, J = 7.6 Hz, 3H), 2.37 (q, J = 7.5 Hz, 2H), 3.89−4.00 (m, 3H), 4.18 (dd, J = 5.4, 11.8 Hz, 1H), 4.27 (dd, J = 2.9, 11.8 Hz, 1H), 5.22 (br s, 1H), 5.43 (br s, 1H), 5.74 (d, J = 7.8 Hz, 1H), 5.76 (d, J = 3.9 Hz, 1H), 7.19 (br s, 1H), 7.24 (br s, 1H), 7.59 (d, J = 7.9 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 9.0, 26.7, 63.7, 69.7, 73.4, 80.4, 90.0, 94.2, 141.3, 155.2, 165.6, 173.5; MS *m*/*z* 322 (100%, M + Na^+); HMRS Calcd for $C_{12}H_{17}N_3O_6Na$: 322.1010, Found: 322.1014.

5′-*O*-Isobutyrylcytidine (6g). Treatment of **5g** by method B at 60 °C for 1 h gave **6g** (83%): ^{1}H NMR (DMSO-d_6) δ 1.10 (t, J = 6.8 Hz, 6H), 2.54−2.62 (m, 1H), 3.89−4.00 (m, 3H), 4.19 (dd, J = 3.9, 12.2 Hz, 1H), 4.26 (dd, J = 2.9, 12.2 Hz, 1H), 5.21 (d, J = 6.4 Hz, 1H), 5.43 (d, J = 5.4 Hz, 1H), 5.73 (d, J = 7.3 Hz, 1H), 5.76 (d, J = 3.9 Hz, 1H), 7.18 (br s, 1H), 7.22 (br s, 1H), 7.59 (d, J = 7.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 19.3, 19.4, 34.6, 64.5, 71.2, 76.1, 82.6, 92.0, 95.8, 142.0, 157.4, 167.2, 177.0; MS *m*/*z* 314 (100%, M + H^+); HMRS Calcd for $C_{13}H_{20}N_3O_6$: 314.1347, Found: 314.1352.

5′-*O*-(4-Methylbenzoyl)uridine (6l). Treatment of **5l** by method B at 60 °C for 1.5 h gave **6l** (73%): ^{1}H NMR (DMSO-d_6) δ 2.40 (s, 3H), 4.06−4.18 (m, 3H), 4.44 (dd, J = 5.4, 11.7 Hz, 1H), 4.54 (dd, J = 2.9, 11.7 Hz, 1H), 5.39 (br s, 1H), 5.54 (d, J = 8.3 Hz, 1H), 5.56 (br s, 1H), 5.79 (d, J = 4.4 Hz, 1H), 7.37 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 7.8 Hz, 2H), 11.40 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.2, 64.1, 69.7, 72.8, 81.1, 89.0, 101.9, 126.7, 129.3, 129.5, 140.8, 144.0, 150.6, 163.1, 165.6; MS *m*/*z* 363 (100%, M + H^+); HMRS Calcd for $C_{17}H_{19}N_2O_7$: 363.1187, Found: 363.1183.

3-(5-*O*-Benzoyl-β-D-ribofuranosyl)furo[2,3-*d*]pyrimidin-2(3*H*)-one (6p). Treatment of **5p** by method B at ambient temperature for 0.5 h gave **6p** (62%): ^{1}H NMR (DMSO-d_6) δ 4.09−4.14 (m, 2H), 4.28−4.32 (m, 1H), 4.58 (dd, J = 5.4, 12.7 Hz, 1H), 4.71 (dd, J = 2.4, 12.2 Hz, 1H), 5.66 (br s, 1H), 5.87 (s, 1H), 5.96 (br s, 1H), 6.39 (dd, J = 1.0, 2.4 Hz, 1H), 7.54 (t, J = 7.3 Hz, 2H), 7.68−7.71 (m, 1H), 8.01 (d, J = 8.3 Hz, 2H), 8.50 (s, 1H), 8.57 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 63.9, 68.9, 74.7, 79.2, 80.7, 92.6, 105.0, 128.8, 129.3, 133.5, 138.9, 144.9, 153.8, 165.6, 166.0, 171.4; MS *m*/*z* 373 (100%, M + H^+); HMRS Calcd for $C_{18}H_{17}N_2O_7$: 373.1030, Found: 373.1035.

Acknowledgment. We gratefully acknowledge pharmaceutical company unrestricted gift funds (M.J.R.), and Brigham Young University for support of this research.

Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and mass spectral data for less accessible polyacylated starting materials and selective deacylation products; representative ^{1}H NMR spectra (for **4a**, **4h**, **6h**, **6k**, **6m**, **9**); ^{13}C NMR spectra (for **1c**, **1d**, **2a**−**d**, **3a**−**g**, **3i**−**k**, **4a**−**k**, **5m**, **5n**, **5p**, **6a**−**n**, **6p**, **7**−**9**). This material is available free of charge via the Internet at http://pubs.acs.org.

JO0600104

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