First Evident Generation of Purin-2-yllithium: Lithiation of an 8-Silyl-Protected 6-Chloropurine Riboside as a Key Step for the Synthesis of 2-Carbon-Substituted Adenosines†

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Received April 20, 1999

Lithiation at the 2-position of purine ring has been accomplished for the first time by using 6-chloro-9-(2,3-*O*-isopropylidene-5-*O*-trityl-*β*-D-ribofuranosyl)-8-(triisopropylsilyl)purine (**7**) as a substrate and LTMP as a lithiating agent. The 8-triisopropylsilyl group in **7** did not undergo anionic migration and, thus, allowed the ready generation of the C2-lithiated species by preventing deprotonation at the 8-position. The electron-withdrawing 6-chlorine atom plays an essential role to this C2-lithiation. Reactions of the lithiated species with electrophiles gave the 2-substituted products (Me, Et, *i*-Pr, $CH(OH)C_6H_{11}$, $C(OH)Me_2$, CHO, CO_2Me, and I) mostly in good yields. Ammonolysis of the 6-chlorine atom of these products (heating at 110 °C in a sealed tube with NH_3/MeOH) effected simultaneous desilylation at the 8-position to give the corresponding adenosine analogues. The whole sequence provides a new and highly general method for the synthesis of 2-substituted adenosines.

Introduction

Synthetic methods for the base-modified nucleosides can be classified into the following three categories: (1) condensation of the modified bases with appropriately protected sugar derivatives, (2) cyclization of ribosyl precursors (N-substituted ribosylamines for pyrimidine analogues and ribosylimidazoles for purine analogues), and (3) manipulation of the base moieties of naturally occurring nucleosides.[1] In the third category, halogenation and subsequent nucleophilic substitution have been employed in many occasions. This approach is particularly useful for the introduction of heteroatom-substituents, while there seems to be a considerable limitation in introducing carbon-substituents.

Lithiation (hydrogen−lithium exchange) chemistry of nucleosides, which also falls into the third category, has been recognized to compensate the above-mentioned nucleophilic approach, since the lithiated species of nucleosides allow the reaction with a wide range of carbon-electrophiles, as exemplified already in the synthesis of 6-substituted uridines.[2] Lithiation of purine nucleosides started with the finding that N^6-methylated 2′,3′-*O*-isopropylideneadenosine undergoes exclusive deprotonation at the 8-position with BuLi.[3] This regiochemical outcome has been observed for a series of lithiation studies of adenosine, inosine, and 6-chloropurine riboside, in which LDA (lithium diisopropylamide) was used as a lithiating agent.[4,5]

Although the lithiation of 9-[2,3,5-tris-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]-6-chloropurine (**1**) recently reported from this laboratory also follows the same regioselectivity, reaction of its 8-lithiated species with TMSCl provides the 2-silylated product **2**, as a result of intermolecular anionic migration of the initially introduced 8-TMS group to the 2-position as depicted in Scheme 1 (**1**→**A**→**B**→**C**→**D**→**2**).[6]

This migration also takes place by using Bu_3SnCl as an electrophile. The resulting 2-stannylated product has been found to be useful for the synthesis of 2-substituted purine nucleosides by manipulation of its 2-stannyl group.[6] Although this method has made the introduction of halogen and certain types of carbon-functionalities possible, we thought it would be beneficial to develop an alternative method in which the 2-lithio intermediate reacts directly with added electrophiles.

This paper describes the first example of evident lithiation at the 2-position of purine ring by the use of an 8-silylated 6-chloropurine riboside. As a synthetic application, various types of 2-carbon-substituted adenosines were synthesized by employing the lithiation as a key reaction step.

Results and Discussion

Preparation and C2-lithiation of 9-[2,3,5-Tris-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]-6-chloro-8-(triisopropylsilyl)purine. The reaction mechanism given in Scheme 1 clearly indicates involvement of the 2-lithiated species (**B**) of a purine ring. It may also suggest that the difficulty in lithiating the 2-position could possibly be due to prior deprotonation at the

† This paper is dedicated to the memory of Professor Richard T. Walker (The University of Birmingham, U.K.) who died in November 1997.

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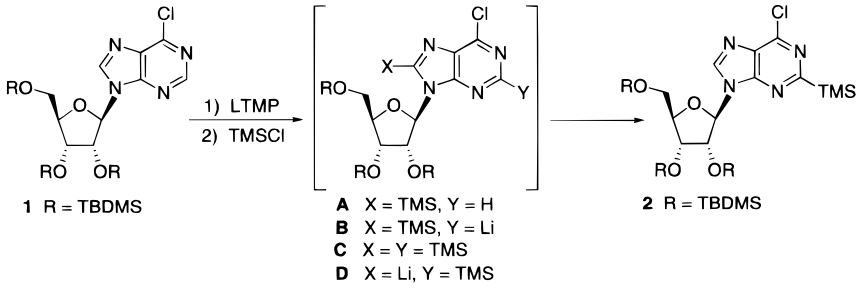
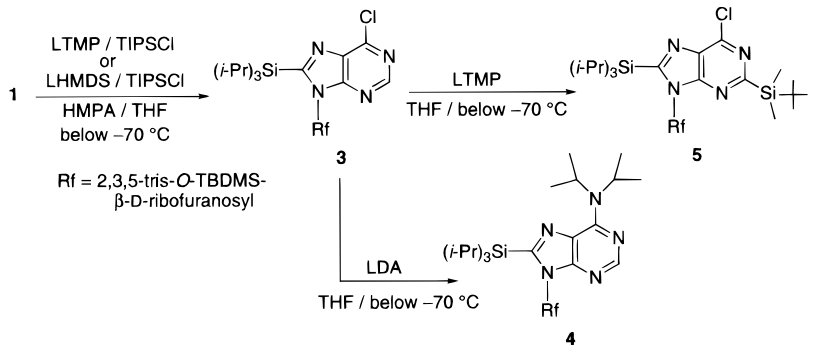
10.1021/jo9906577 CCC: $18.00
Published on Web 09/28/1999

Scheme 1



Scheme 2



8-position.[7] We considered, therefore, that C2-lithiation would be possible by introducing a more bulky silyl group, such as TIPS (triisopropylsilyl) group, to the 8-position, which is expected to prevent silaphilic attack of the 2-lithiated species.

Introduction of a TIPS group into the 8-position of **1** was first carried out based on LTMP (lithium 2,2,6,6-tetramethylpiperidide) lithiation, since the use of LDA in combination with TMSCl resulted in the displacement of the 6-chlorine atom with diisopropylamino group in our previous study.[6] When **1** was treated with LTMP (1.2 equiv) in THF below −70 °C and then reacted with TIPSCl (1.2 equiv), no reaction took place, showing that there is a significant difference in reactivity between TMSCl and TIPSCl. However, by adding HMPA (0.5 equiv) to the above reaction mixture, the 8-TIPS derivative **3** was formed and was isolated in 88% yield after silica gel column chromatography (Scheme 2). It should be mentioned that the corresponding 8-TMS derivative, prepared in our previous study,[6] is highly susceptible to protonolysis, forming **1** during silica gel column chromatography. It was found later that LHMDS in the presence of HMPA can also be employed for the preparation of **3** (99% yield).

The depicted regiochemistry of **3** was readily assumed by the ^{1}H NMR observation of a significant deshielding in H-2′ (δ 5.98 ppm) as compared with that of **2** (H-2′, δ 4.58 ppm).[8] It was also confirmed by HMBC (heteronuclear multiple bond connectivity) experiments: the H-1′ (δ 6.04 ppm) showed correlations with two quaternary carbon atoms (C-4, δ 153.4 ppm; C-8, δ 164.2 ppm).[9]

Lithiation of **3** at the 2-position was next examined by deuteration to see the efficiency of the lithiation as well as the compatibility of the 8-TIPS group to the reaction conditions. As anticipated, LDA was not a suitable reagent for the lithiation of **3**, it simply gave the *N*,*N*-diisopropyladenosine derivative **4** (88%). The use of LTMP (4 equiv), on the other hand, did not cause such displacement at the 6-position, but TLC analysis (hexane:EtOAc = 10:1) of the deuterated reaction mixture showed that an unexpected product **5** (R_f 0.85, isolated in 11% yield) was formed in addition to the deuterated **3** (R_f 0.65, isolated in 67% recovery, 92% D-incorporation as calculated by ^{1}H NMR spectroscopy).

The ^{1}H NMR spectrum of **5** showed no aromatic proton, and the presence of four TBDMS groups in addition to one TIPS group. Although unambiguous regiochemical assignment of **5** could not be made, and thus the depicted structure is tentative, it was confirmed that **5** was also formed upon reacting the lithiated species of **3** with TBDMSCl (90% yield) in the presence of HMPA. The formation of **5** clearly indicates that the C-2 lithiation of **3** had accompanied with an intermolecular migration of TBDMS group from the sugar to the base moiety.[10] Indeed, TLC analysis of the deuterated reaction mixture in more polar solvent system ($CHCl_3$:MeOH = 10:1) showed the presence of byproducts (R_f 0.45−0.60), which could not be isolated even by HPLC separation. This result led us to change the sugar protecting group of the substrate.

9-(2,3-*O*-Isopropylidene-5-*O*-trityl-*β*-D-ribofuranosyl)-6-chloro-8-(triisopropylsilyl)purine As a Suitable Substrate for C2-lithiation. As the hydroxyl-protecting groups of the sugar portion of 6-chloropurine

(7) The 2-lithio derivative of an 8-azapurine, 3*H*-1,2,3-triazolo-[4,5-*d*]pyrimidine, has been generated through a halogen−lithium exchange reaction: Tanji, K.; Kato, H.; Higashino, T. *Chem. Pharm. Bull.* **1991**, *39*, 3037−3040.

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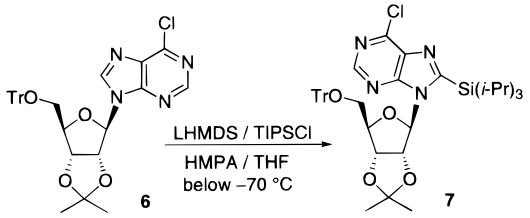
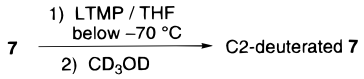
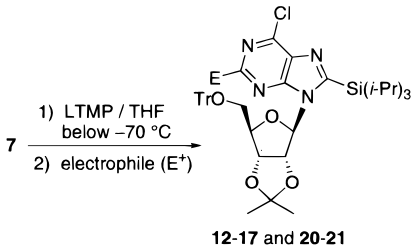
Scheme 3





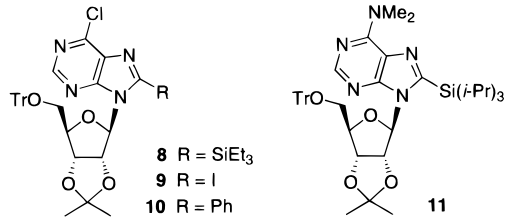
Scheme 4



riboside, isopropylidene, and trityl groups were selected. Compound **6** was prepared in 95% yield by tritylation ($TrCl/Et_3N/CH_2Cl_2$, reflux for 18 h) of 6-chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine.[4] Introduction of the 8-TIPS group to **6** was carried out by using LHMDS and TIPSCl as mentioned in the preparation of **3**, which gave **7** in 99% yield (Scheme 3).

The extent of LTMP lithiation of **7** was analyzed again by ^{1}H NMR measurement of the deuterated product. The results (entries 1−4) are given in Table 1. As can be seen in entry 4 (Table 1), almost quantitative lithiation at the 2-position was attained by the use of 5 equiv of LTMP. It is apparent from the observed high level of recovery that no appreciable side reaction occurred during the lithiation, indicating that the 8-TIPS group in **7** did not undergo the anionic migration.

We also examined the possibility of using a less bulky TES (triethylsilyl) group. However, LTMP lithiation and subsequent deuteration of **8**, carried out under the conditions used in entry 3 in Table 1, resulted in the formation of a mixture of three products: 2,8-bis-TES derivative (11%), C2-deuterated **8** (36%, D-incorporation 76%), and the desilylated 6-chloropurine riboside (31%, D-incorporation at the 2- and 8-positions 56% and 34%, respectively).



To see if the 8-TIPS group has any beneficial effect on facilitating C2-deprotonation, the 8-phenyl derivative **10** was used as a substrate for the lithiation. Compound **10** was prepared from **6** in 2 steps: LDA lithiation-based iodination leading to **9** (90%); the Stille reaction[11] between **9** and Ph_4Sn (the yield of **10**, 83%).

Table 1. D-Incorporation to the 2-Position upon LTMP Lithiation of 7[a]

entry	LTMP (equiv)	D-incorporation	recovery (%)
1	1.2	11	99
2	3.0	56	89
3	4.0	86	93
4	5.0	96	99

[a] The extent of D-incorporation was calculated on the basis of ^{1}H NMR spectroscopy by integrating H-2 versus H-1′.

The deuteration reaction of **10** was performed under the identical conditions used for **7** in entry 3 in Table 1. Although the recovery (56%) was rather low due to the formation of several unidentified products, the ^{1}H NMR analysis of the deuterated **10** revealed a C2-lithiation level of 91%. Therefore, it can be assumed that, once dissociation at the 8-position is prevented, lithiation at the 2-position of a purine ring becomes a feasible event.

An additional question would be whether the electron-withdrawing 6-chlorine atom plays an important role in the C2-lithiation of **7** or not. When *N*,*N*-dimethyladenosine derivative **11** was lithiated with 5 equiv of LTMP and then quenched by adding CD_3OD, no appreciable deuterium incorporation was observed in the recovered **11** (recovery 98%). Therefore, the successful C2-lithiation of **7** is a likely consequence of the presence of an electronegative chlorine atom at the 6-position which renders H-2 more acidic.

Synthesis of 2-Carbon-Substituted Adenosines. Unlike the 8-substituted analogues of purine nucleosides, the 2-substituted counterparts adopt an *anti*-glycosidic conformation, which mimics naturally occurring purine nucleosides, due to the absence of a substituent ortho to the glycosidic bond.[12] This fact when combined with well appreciated diverse biological properties of adenosine[13] provides an appeal to 2-substituted adenosines as a biologically attractive group of nucleoside anlogues.

The precedent of the first synthesis of 2-carbon-substituted adenosines goes back to 1952, which deals with that of 2-methyladenosine by classical condensation method.[14,15] An alternative method, the cyclization of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide or its 4-carbonitrile,[16] has been used for the synthesis of 2-methyl,[17,18] 2-aryl,[18] and 2-formyl[19] analogues of adenosine.[20]

Approaches that utilize naturally occurring purine nucleosides as starting materials involve a homolytic methylation of adenosine,[21] nucleophilic substitution of

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Table 2. Reactions of the C2-Lithiated Species of 7 with Electrophiles[a]

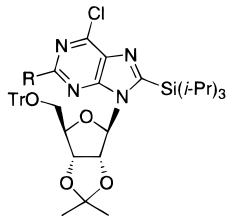
entry	electrophile	product	E	isolated yield (%)
1	MeI	**12**	Me	28
		13	Et	37
		14	*i*-Pr	15
2	$C_6H_{11}CHO$	**15**[b]	$CH(OH)C_6H_{11}$	58
3[c]	$C_6H_{11}CHO$	**15**[b]	$CH(OH)C_6H_{11}$	97
4	Me_2CO	**16**	$C(OH)Me_2$	67
5	HCO_2Me	**17**	CHO	98
6	$ClCO_2Me$	**20**	CO_2Me	46
7	iodine	**21**	I	78

[a] All reactions were carried out with 5.0 equiv of LTMP. After the respective electrophile (10 equiv) was added, the reaction mixture was stirred for 5 min below −70 °C. [b] A mixture of two diastereomers (ca 5:3). [c] The reaction was carried out in the presence of HMPA.

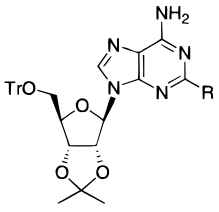
2-(methylsulfonyl)adenosine with cyanide,[22] and more recent cross-coupling reaction of 2-iodoadenosine.[23] Vasodilating activity has been reported for the 2-alkynyl derivatives of adenosine,[23c] 5′-*N*-(ethylcarboxamido)adenosine,[24] and 3′-deoxyadenosine.[25]

As an application of the present lithiation study, reactions of the C2-lithiated species of **7** with carbon electrophiles, as well as with iodine, were carried out. The results are summarized in Table 2. Also investigated here is the conversion of the resulting 2-substituted products to adenosine analogues.

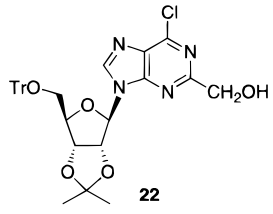
When MeI was used as an electrophile (entry 1, Table 2), the 2-methylated product **12** was accompanied by the 2-ethyl (**13**) and 2-isopropyl (**14**) derivatives, the formation of which is apparently a consequence of further *C*-methylation of the intially formed **12**. In the reaction with cyclohexanecarboxaldehyde (entries 2 and 3, Table 2), the presence of HMPA as an additive appeared to be effective to improve the yield of product (**15**). As shown in entry 4 (Table 2) by the reaction with acetone, an enolizable ketone also works satisfactorily to yield a tertiary alcohol **16**. The reaction with HCO_2Me (entry 5, Table 2) gave the 2-formyl derivative **17** in high yield. As all of the attempts to get its correct elemental analysis data failed, the purity of **17** was proved by its high-yield coversion (92%) to the 2-hydroxymethyl derivative **18** with $NaBH_4$ in MeOH. Compound **17** can also be used



18 R = CH_2OH
19 R = (*E*)-CH=$CHCO_2Me$



23 R = Me
24 R = Et
25 R = $CH(OH)C_6H_{11}$
26 R = $CH(OH)Me_2$
27 R = CH_2OH
28 R = $CONH_2$
29 R = I



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as a substrate for the Wittig reaction, as exemplified by the preparation of **19** (95%, Ph_3PCHCO_2Me in THF). The use of $ClCO_2Me$ in the reaction with the lithiated species of **7** gave a complex mixture of products, from which the methoxycarbonyl derivative **20** was isolated only in a poor yield (entry 6, Table 2). Entry 7 (Table 2) demonstrates, by the preparation of the 2-iodo derivative (**21**), that this reaction is also applicable to the introduction of heteroatom-substituents.

At this stage, by using **18**, we intended to confirm the regiochemical outcome of the present lithiation-based electrophilic substitution. Thus, desilylation of **18** was effected with TBAF in THF to give **22** in 99% yield.

Among the five purine-ring-carbon atoms of **22**, the C-5 resonates at the highest field of δ 131.1 ppm, because this is the sole carbon atom that is bound to only one electronegative atom (N-7). The fact that this C-5 showed a correlation with an aromatic proton (δ 8.21 ppm) in the HMBC spectrum clearly supports the regiochemistry of **22**. An additional support came also from the HMBC spectrum: correlations of H-1′ (δ 6.19 ppm) were seen with two carbon atoms, one of which was tertiary (C-8, δ 144.1 ppm) and the other quaternary (C-4, δ 151.1 ppm).

Finally, conversion of these 2-substituted products to the corresponding adenosine analogues was carried out. It appeared that the reaction conditions required for the ammonolysis of the 6-chlorine atom, heating at 110 °C in a sealed tube with NH_3/MeOH, effect simultaneous desilylation at the 8-position, and the 2-substituted adenosines **23**-**29** were obtained uniformly in good yields (65−99%). In the case of the 2-methoxycarbonyl derivative **20**, ammonolysis of the ester also occurred to give the 2-carbamoyladenosine **28**.

Conclusion

By protecting the 8-position of a 6-chloropurine riboside with TIPS group,[26] lithiation of purine ring at the 2-position has become possible for the first time. As the actual substrate and lithiating agent, 6-chloro-9-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-8-(triisopropylsilyl)purine (**7**) and LTMP were found to be suitable.

Since the lithiated species of **7** showed reactivity toward a variety of electrophiles and since ammonolysis of the resulting 2-substituted products afforded the corresponding adenosine analogues with simultaneous desilylation, the present method constitutes a highly general approach to the synthesis of 2-substituted adenosines. The likely possibility that the synthesis of 2-substituted analogues of inosine, 6-mercaptopurine riboside, and nebularine can also be accomplished, by manipulation of desilylated intermediates such as **22**, makes the present method more attractive.

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Experimental Section

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were measured at 23 °C (internal standard, Me_4Si) at 500 MHz. ^{13}C NMR chemical shifts are shown only for purine ring carbons. Mass spectra (MS) were taken in FAB mode (*m*-nitrobenzyl alcohol as a matrix). For compounds containing Cl, ion peaks corresponding to ^{35}Cl are shown. Column chromatography was carried out on silica gel (Silica Gel 60, Merck). Thin-layer chromatography (TLC) was performed on silica gel (precoated silica gel plate F_{254}, Merck).

9-[2,3,5-Tris-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]-6-chloro-8-triisopropylsilylpurine (3). Method A. To a THF (10 mL) solution containing LTMP (2.39 mmol) and TIPSCl (450 μL, 2.39 mmol) was added dropwise **1** (1.0 g, 1.59 mmol) dissolved in THF (5 mL) under positive pressure of dry Ar, while the temperature was maintained below −70 °C. After 3 min of stirring, HMPA (140 μL, 0.80 mmol) was added and the whole mixture was stirred for 5 min. The reaction was quenched by adding saturated aqueous NH_4Cl. Extraction with EtOAc followed by column chromatography (hexane:EtOAc = 80:1) gave **3** (1.10 g, 88%) as an oil. **Method B.** To a THF (10 mL) solution containing **1** (400 mg, 0.64 mmol), TIPSCl (205 μL, 0.95 mmol), and HMPA (1.1 mL, 6.40 mmol) was added LHMDS (1.0 M THF solution, 1.6 mL, 1.6 mmol) under positive pressure of dry Ar, while the temperature was maintained below −70 °C. After 5 min of stirring, the reaction mixture was worked up as described in Method A to give **3** (496 mg, 99%): UV (MeOH) λ_{max} 274 nm (ϵ 13900), λ_{min} 238 nm (ϵ 3700); ^{1}H NMR ($CDCl_3$) δ −0.35, −0.91, 0.07, 0.10, 0.14, and 0.16 (18H, each as s), 0.69, 0.93, and 0.95 (27H, each as s), 1.09, 1.17, and 1.20 (18H, each as d, J = 7.4 Hz), 1.61−1.67 (3H, m), 3.68 (1H, dd, J = 4.6 and 10.4 Hz), 3.95 (1H, t, J = 10.4 Hz), 4.03 (1H, dd, J = 4.6 and 10.4 Hz), 4.34 (1H, d, J = 4.0 Hz), 5.98 (1H, dd, J = 8.2 and 4.0 Hz), 6.04 (1H, d, J = 8.2 Hz), 8.64 (1H, s); ^{13}C NMR ($CDCl_3$) δ 134.0, 150.6, 150.7, 153.4, 164.2; FAB-MS *m*/*z* 785 (M^+ + H). Anal. Calcd for $C_{37}H_{73}ClN_4O_4Si_4$: C, 56.55; H, 9.36; N, 7.13. Found: C, 56.60; H, 9.67; N, 7.11.

2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)-*N*,*N*-diisopropyl-8-(triisopropylsilyl)adenosine (4). Physical data of this compound obtained as an oil are as follows: UV (MeOH) λ_{max} 299 nm (ϵ 12300) and 250 nm (ϵ 11300), λ_{min} 274 nm (ϵ 8300) and 233 nm (ϵ 9200); ^{1}H NMR ($CDCl_3$) δ −0.11, −0.04, 0.04, 0.11, and 0.13 (18H, each as s), 0.82, 0.89, and 0.93 (12H, each as s), 1.11−1.18 (18H, m), 1.22, 1.23, 1.35, and 1.36 (12H, each as d, J = 7.0 Hz), 1.47−1.60 (3H, m), 3.51 (1H, t, J = 10.7 Hz), 3.62 (1H, sept, J = 6.7 Hz), 3.69 (1H, dd, J = 4.6 and 10.7 Hz), 3.85 (1H, dd, J = 4.6 and 10.7 Hz), 4.86 (1H, sept, J = 7.0 Hz), 4.13 (1H, d, J = 3.3 Hz), 5.46 (1H, dd, J = 3.3 and 8.3 Hz), 5.73 (1H, d, J = 8.3 Hz), 8.18 (1H, s); FAB-MS *m*/*z* 850 (M^+ + H). Anal. Calcd for $C_{43}H_{87}N_5O_4Si_4$: C, 60.72; H, 10.31; N, 8.23. Found: C, 60.93; H, 10.54; N, 8.17.

LTMP Lithiation and Subsequent Deuteration of 3. Formation of 5. To a THF (10 mL) solution containing LTMP (4.53 mmol) was added dropwise **3** (712 mg, 0.91 mmol) dissolved in THF (5 mL) under positive pressure of dry Ar, while the temperature was maintained below −70 °C. After 5 min of stirring, the reaction mixture was treated with CD_3OD (0.75 mL). The reaction mixture was partitioned between saturated aqueous NH_4Cl and EtOAc. Column chromatography (hexane:EtOAc = 100:1 to 70:1) of the organic layer gave **5** (oil, 88 mg, 11%) and the deuterated **3** (oil, 474 mg, 67%). Physical data of **5** are as follows: UV (MeOH) λ_{max} 279 nm (ϵ 16 300), λ_{min} 243 nm (ϵ 5500); ^{1}H NMR ($CDCl_3$) δ −0.41, −0.16, 0.07, 0.10, 0.14, 0.18, 0.37, and 0.39 (24H, each as s), 0.68, 0.91, 0.96, and 1.01 (36H, each as s), 1.15−1.22 (18H, m), 1.57−1.67 (3H, m), 3.71 (1H, dd, J = 4.6 and 10.1 Hz), 3.89 (1H, t, J = 10.1 Hz), 4.00 (1H, dd, J = 4.6 and 10.1 Hz), 4.29 (1H, d, J = 3.9 Hz), 5.89 (1H, dd, J = 3.9 and 8.2 Hz), 6.05 (1H, d, J = 8.2 Hz); FAB-MS *m*/*z* 900 (M^+ + H). Anal. Calcd for $C_{43}H_{87}ClN_4O_4Si_5$: C, 57.38; H, 9.74; N, 6.22. Found: C, 57.51; H, 9.95; N, 6.19.

6-Chloro-9-(2,3-*O*-isopropylidene-5-*O*-trityl-*β*-D-ribofuranosyl)purine (6). A mixture of 6-chloro-(2,3-*O*-isoprpylidene-*β*-D-ribofuranosyl)purine (500 mg, 1.53 mmol), trityl chloride (853 mg, 3.06 mmol), and Et_3N (2.13 mL, 15.3 mmol) in CH_2Cl_2 (10 mL) was heated under reflux for 20 h. Evaporation of the reaction mixturte followed by column chromatography (hexane:EtOAc = 2:1) gave **6** (830 mg, 95%) as a foam: UV (MeOH) λ_{max} 264 nm (ϵ 6500), λ_{min} 244 nm (ϵ 4900); ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, s), 1.63 (3H, s), 3.27−3.29 (2H, m), 4.58−4.60 (1H, m), 4.96 (1H, dd, J = 2.7 and 6.0 Hz), 5.47 (1H, dd, J = 2.2 and 6.0 Hz), 6.17 (1H, d, J = 2.2 Hz), 7.18−7.20 (9H, m), 7.29−7.31 (6H, m), 8.21 (1H, s), 8.60 (1H, s); ^{13}C NMR ($CDCl_3$) δ 132.4, 144.3, 150.8, 151.3, 151.9; FAB-MS *m*/*z* 569 (M^+ + H). Anal. Calcd for $C_{32}H_{29}ClN_4O_4 \cdot 1/5H_2O$: C, 67.12; H, 5.17; N, 9.78. Found: C, 67.12; H, 5.04; N, 9.71.

6-Chloro-9-(2,3-*O*-isopropylidene-5-*O*-trityl-*β*-D-ribofuranosyl)-8-(triisopropylsilyl)purine (7). This compound was obtained from **6** by the procedure (Method B) described for the preparation of **3**. Column chromatography (hexane:EtOAc = 20:1) of the reaction mixture gave **7** as a foam in 99% yield: UV (MeOH) λ_{max} 274 nm (ϵ 8700), λ_{min} 245 nm (ϵ 4200); ^{1}H NMR ($CDCl_3$) δ 1.21−1.24 (18H, m), 1.36 (3H, s), 1.57 (3H, s), 1.60−1.67 (3H, m), 3.29 (1H, dd, J = 4.9 and 9.9 Hz), 3.34 (1H, dd, J = 7.7 and 9.9 Hz), 4.52−4.58 (1H, m), 5.09 (1H, dd, J = 3.4 and 6.5 Hz), 5.53 (1H, dd, J = 2.1 and 6.5 Hz), 6.13 (1H, d, J = 2.1 Hz), 7.11−7.18 (9H, m), 7.31−7.34 (6H, m), 8.30 (1H, s); ^{13}C NMR ($CDCl_3$) δ 133.5, 150.7, 150.7, 152.3, 162.3; FAB-MS *m*/*z* 725 (M^+ + H). Anal. Calcd for $C_{41}H_{49}ClN_4O_4Si$: C, 67.89; H, 6.81; N, 7.72. Found: C, 67.92; H, 6.51; N, 7.74.

LTMP Lithiation and Subsequent Deuteration of 7. This reaction was carried out with the procedure described for the LTMP lithiation of **3**.

6-Chloro-9-(2,3-*O*-isopropylidene-5-*O*-trityl-*β*-D-ribofuranosyl)-8-(triethylsilyl)purine (8). This compound was obtained from **6** by the procedure (Method B) described for the preparation of **3**, except that TESCl was used instead of TIPSCl. Purification was carried out by Florisil (Merck) column chromatography (hexane:EtOAc = 6:1), in this particular case. Compound **8** was isolated as a foam in 97% yield: UV (MeOH) λ_{max} 273 nm (ϵ 12 100), λ_{min} 245 nm (ϵ 5200); ^{1}H NMR ($CDCl_3$) δ 1.07−1.08 (15H, m), 1.37 (3H, s), 1.62 (3H, s), 3.20−3.26 (2H, m), 4.53−4.56 (1H, m), 5.08 (1H, dd, J = 3.1 and 6.4 Hz), 5.63 (1H, dd, J = 2.1 and 6.4 Hz), 6.14 (1H, d, J = 2.1 Hz), 7.12−7.18 (9H, m), 7.26−7.33 (6H, m), 8.30 (1H, s); FAB-MS *m*/*z* 683 (M^+ + H). Anal. Calcd for $C_{38}H_{43}ClN_4O_4Si$: C, 66.79; H, 6.34; N, 8.20. Found: C, 66.67; H, 6.20; N, 8.18.

6-Chloro-8-iodo-9-(2,3-*O*-isopropylidene-5-*O*-trityl-*β*-D-ribofuranosyl)purine (9). To a THF (5 mL) solution containing LDA (5.28 mmol), **6** (1.0 g, 1.76 mmol) dissolved in THF (5 mL) was added dropwise under positive pressure of dry Ar, while the temperature was maintained below −70 °C. After 5 min stirring, the lithiated mixture was treated with iodine (1.34 g, 5.28 mmol as I_2) in THF (5 mL). The reaction mixture was stirred for 5 min and then partitioned between aqueous $Na_2S_2O_3$ and $CHCl_3$. Column chromatography (hexane:EtOAc = 5:1) of the organic layer gave **9** (1.1 g, 90%) as a foam: UV (MeOH) λ_{max} 277 nm (ϵ 14 000), λ_{min} 245 nm (ϵ 6300); ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, s), 1.65 (3H, s), 3.12−3.18 (2H, m), 4.58−4.61 (1H, m), 5.12 (1H, dd, J = 3.1 and 6.4 Hz), 5.69 (1H, dd, J = 1.8 and 6.4 Hz), 6.17 (1H, d, J = 1.8 Hz), 7.17−7.19 (9H, m), 7.28−7.32 (6H, m), 8.31 (1H, s); FAB-MS *m*/*z* 694 (M^+ + H). Anal. Calcd for $C_{32}H_{28}ClIN_4O_4$: C, 55.31; H, 4.06; N, 8.06. Found: C, 55.21; H, 3.90; N, 7.98.

6-Chloro-9-(2,3-*O*-isopropylidene-5-*O*-trityl-*β*-D-ribofuranosyl)-8-phenylpurine (10). A dioxane (40 mL) solution containing **9** (950 mg, 1.37 mmol), $(Ph_3P)_2PdCl_2$ (96 mg, 0.14 mmol), CuI (52 mg, 0.27 mmol), and Ph_4Sn (1.47 g, 3.43 mmol) was heated at 110 °C for 15 h under positive pressure of dry Ar. The reaction mixture was diluted by adding EtOH (50 mL), and the resulting precipitate was removed by filtration. Column chromatography (hexane:EtOAc = 9:1) of the filtrate gave **10** (730 mg, 83%) as a foam: UV (MeOH) λ_{max} 283 nm (ϵ 16 700), λ_{min} 249 nm (ϵ 6400); ^{1}H NMR ($CDCl_3$) δ 1.34 (3H, s), 1.55 (3H, s), 3.26−3.33 (2H, m), 4.62−4.65 (1H, m), 5.18 (1H, dd, J = 2.8 and 6.1 Hz), 5.60 (1H, dd, J = 1.5 and 6.1 Hz),

6.10 (1H, d, J = 1.5 Hz), 7.14−7.16 (9H, m), 7.31−7.35 (6H, m), 7.57−7.63 (3H, m), 7.93−7.95 (2H, m), 8.39 (1H, s); FAB-MS m/z 645 ($M^+ + H$). Anal. Calcd for $C_{38}H_{33}ClN_4O_4$: C, 70.75; H, 5.16; N, 8.68. Found: C, 70.63; H, 5.12; N, 8.73.

LTMP Lithiation and Subsequent Deuteration of 10. This reaction was carried out by the procedure described for the LTMP lithiation of **3**.

***N,N*-Dimethyl-2′,3′-*O*-isopropylidene-5′-*O*-trityl-8-(triisopropylsilyl)adenosine (11).** To a THF (5 mL) solution of LDA (1.56 mmol) was added dropwise *N,N*-dimethyl-2′,3′-*O*-isopropylidene-5′-*O*-trityladenosine (300 mg, 0.52 mmol) dissolved in THF (5 mL) under positive pressure of dry Ar, while the temperature was maintained below −70 °C. To the resulting solution was added TIPSCl (225 μL, 1.04 mmol) neat, and the reaction mixture was stirred for 5 min. Quenching with saturated aqueous NH_4Cl was followed by extraction with EtOAc. Column chromatography (hexane:EtOAc = 10:1) of the extract gave **11** (313 mg, 82%) as a foam: UV (MeOH) λ_{max} 282 nm (ϵ 17 400), λ_{min} 245 nm (ϵ 3700); ^{1}H NMR ($CDCl_3$) δ 1.18−1.21 (18H, m), 1.35 (3H, s), 1.52−1.58 (3H, m), 1.58 (3H, s), 3.27 (1H, dd, J = 5.9 and 9.8 Hz), 3.44 (1H, dd, J = 7.8 and 9.8 Hz), 3.55 (6H, br), 4.41−4.44 (1H, m), 5.09 (1H, dd, J = 3.6 and 6.4 Hz), 5.59 (1H, dd, J = 2.1 and 6.4 Hz), 6.03 (1H, d, J = 2.1 Hz), 7.10−7.16 (9H, m), 7.33−7.36 (6H, m), 7.95 (1H, s); FAB-MS m/z 734 ($M^+ + H$). Anal. Calcd for $C_{43}H_{55}N_5O_4Si$: C, 70.36; H, 7.55; N, 9.54. Found: C, 70.64; H, 7.58; N, 9.62.

Reaction of the C2-Lithiated Species of 7 with MeI. Formation of 2-Methyl (12), 2-Ethyl (13), and 2-Isopropyl (14) Derivatives of 6-Chloro-9-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-8-(triisopropylsilyl)purine. To a THF (5 mL) solution of LTMP (4.0 mmol), **7** (580 mg, 0.8 mmol) dissolved in THF (5 mL) was added dropwise under positive pressure of dry Ar, while the temperature was maintained below −70 °C. To this was added MeI (280 μL, 4.0 mmol) neat. After 5 min of stirring, the reaction mixture was quenched by adding saturated aqueous NH_4Cl. Extraction with EtOAc followed by column chromatography gave **14** (eluted with hexane:EtOAc = 25:1, foam, 145 mg, 24%), **13** (eluted with hexane:EtOAc = 20:1, foam, 320 mg, 53%), and **12** (eluted with hexane:EtOAc = 5:1, oil, 130 mg, 22%).

Physical data of **12** are as follows: UV (MeOH) λ_{max} 278 nm (ϵ 13 200), λ_{min} 246 nm (ϵ 5600); ^{1}H NMR ($CDCl_3$) δ 1.20−1.24 (18H, m), 1.34 (3H, s), 1.60 (3H, s), 1.61−1.67 (3H, m), 2.41 (3H, s), 3.20 (1H, dd, J = 4.0 and 9.8 Hz), 3.45 (1H, t, J = 9.8 Hz), 4.51−4.54 (1H, m), 5.02 (1H, dd, J = 3.7 and 6.4 Hz), 5.40 (1H, dd, J = 1.9 and 6.4 Hz), 6.14 (1H, d, J = 1.9 Hz), 7.06−7.15 (9H, m), 7.30−7.34 (6H, m); FAB-MS m/z 739 ($M^+ + H$). Anal. Calcd for $C_{42}H_{51}ClN_4O_4Si·H_2O$: C, 66.66; H, 7.05; N, 7.40. Found: C, 66.47; H, 6.77; N, 7.27.

Physical data of **13** are as follows: UV (MeOH) λ_{max} 277 nm (ϵ 8900), λ_{min} 246 nm (ϵ 4600); ^{1}H NMR ($CDCl_3$) δ 1.11 (3H, t, J = 7.3 Hz), 1.21−1.25 (18H, m), 1.34 (3H, s), 1.61 (3H, s), 1.63−1.70 (3H, m), 2.60−2.80 (2H, m), 3.16 (1H, dd, J = 3.7 and 9.8 Hz), 3.42 (1H, t, J = 9.8 Hz), 4.49−4.54 (1H, m), 5.04 (1H, dd, J = 4.0 and 6.3 Hz), 5.48 (1H, dd, J = 1.5 and 6.3 Hz), 6.17 (1H, d, J = 1.5 Hz), 7.05−7.09 (6H, m), 7.11−7.14 (3H, m), 7.26−7.29 (6H, m); FAB-MS m/z 753 ($M^+ + H$). Anal. Calcd for $C_{43}H_{53}ClN_4O_4Si$: C, 68.55; H, 7.09; N, 7.44. Found: C, 68.73; H, 7.18; N, 7.46.

Physical data of **14** are as follows: UV (MeOH) λ_{max} 277 nm (ϵ 9100), λ_{min} 245 nm (ϵ 4400); ^{1}H NMR ($CDCl_3$) δ 1.06 (3H, d, J = 6.7 Hz), 1.15 (3H, d, J = 6.7 Hz), 1.22−1.25 (18H, m), 1.34 (3H, s), 1.60 (3H, s), 1.65−1.72 (3H, m), 2.97−3.07 (1H, m), 3.12 (1H, dd, J = 3.3 and 9.8 Hz), 3.39 (1H, t, J = 9.8 Hz), 4.48−4.51 (1H, m), 5.06 (1H, dd, J = 3.9 and 6.4 Hz), 5.51 (1H, dd, J = 1.2 and 6.4 Hz), 6.19 (1H, d, J = 1.2 Hz), 7.03−7.09 (6H, m), 7.10−7.13 (3H, m), 7.23−7.28 (6H, m); FAB-MS m/z 767 ($M^+ + H$). Anal. Calcd for $C_{44}H_{55}ClN_4O_4Si$: C, 68.86; H, 7.22; N, 7.30. Found: C, 68.68; H, 7.37; N, 7.23.

6-Chloro-2-(cyclohexyl)hydroxymethyl-9-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-8-(triisopropylsilyl)purine (15). This compound was prepared with the procedure described for the preparation of **12**−**14**, except that HMPA was added to a THF solution of LTMP. The following amounts of reagents and **7** (600 mg, 0.83 mmol) were used: LTMP (4.14 mmol), HMPA (1.45 mL, 8.27 mmol), cyclohexanecarbaldehyde (500 μL, 4.14 mmol). Column chromatography (hexane:EtOAc = 20:1) gave **15** (foam, 675 mg, 97%) as a mixture of two diastereomers (ca. 5:3): UV (MeOH) λ_{max} 278 nm (ϵ 14 100), λ_{min} 245 nm (ϵ 5900); ^{1}H NMR of the major diastereomer ($CDCl_3$) δ 1.20−1.25 (18H, m), 1.31 (3H, s), 1.60 (3H, s), 1.56−1.69 (11H, m), 1.65−1.68 (3H, m), 3.14 (1H, dd, J = 3.4 and 9.8 Hz), 3.37 (1H, dd, J = 9.2 and 9.8 Hz), 3.44 (1H, d, J = 6.4 Hz, D_2O exchangeable), 4.19 (1H, dd, J = 4.9 and 6.4 Hz), 4.49−4.53 (1H, m), 4.92 (1H, dd, J = 4.0 and 6.4 Hz), 5.40 (1H, dd, J = 1.8 and 4.0 Hz), 6.17 (1H, d, J = 1.8 Hz), 7.06−7.14 (9H, m), 7.27−7.36 (6H, m); ^{1}H NMR of the minor diastereomer ($CDCl_3$) δ 0.88−0.92 (11H, m), 1.16−1.25 (18H, m), 1.32 (3H, s), 1.59 (3H, s), 1.48−1.54 (3H, m), 2.65 (1H, d, J = 5.8 Hz, D_2O exchangeable), 3.21 (1H, dd, J = 3.4 and 9.8 Hz), 3.35 (1H, dd, J = 9.5 and 9.8 Hz), 4.39−4.43 (2H, m), 4.93 (1H, dd, J = 4.6 and 6.4 Hz), 5.49 (1H, dd, J = 1.8 and 6.4 Hz), 6.14 (1H, d, J = 1.8 Hz), 7.07−7.13 (9H, m), 7.28−7.32 (6H, m); FAB-MS m/z 837 ($M^+ + H$). Anal. Calcd for $C_{48}H_{61}ClN_4O_4Si·H_2O$: C, 67.38; H, 7.42; N, 6.55. Found: C, 67.36; H, 7.36; N, 6.51.

6-Chloro-2-(1-hydroxy-1-methyl)ethyl-9-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-8-(triisopropylsilyl)purine (16). This compound was prepared with the procedure described for the preparation of **12**−**14**. The following amounts of reagents and **7** (300 mg, 0.41 mmol) were used: LTMP (2.07 mmol), acetone (305 μL, 4.14 mmol). Column chromatography (hexane:EtOAc = 20:1) gave **16** (foam, 218 mg, 67%): UV (MeOH) λ_{max} 277 nm (ϵ 13 600), λ_{min} 245 nm (ϵ 5700); ^{1}H NMR ($CDCl_3$) δ 1.20−1.28 (18H, m), 1.25 (3H, s), 1.33 (3H, s), 1.44 (3H, s), 1.60 (3H, s), 1.66−1.71 (3H, m), 3.12 (1H, dd, J = 3.6 and 9.6 Hz), 3.34(1H,t, J = 9.6 Hz), 4.08 (1H, br), 4.46−4.50 (1H, m), 4.94 (1H, dd, J = 4.0 and 6.4 Hz), 5.52 (1H, dd, J = 1.6 and 6.4 Hz), 6.20 (1H, d, J = 1.6 Hz), 7.04−7.22 (9H, m), 7.27−7.30 (6H, m); FAB-MS m/z 783 ($M^+ + H$). Anal. Calcd for $C_{44}H_{55}ClN_4O_5Si$: C, 67.45; H, 7.08; N, 7.15. Found: C, 67.60; H, 7.23; N, 7.18.

6-Chloro-2-formyl-9-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-8-(triisopropylsilyl)purine (17). This compound was prepared with the procedure described for the preparation of **12**−**14**. The following amounts of reagents and **7** (327 mg, 0.45 mmol) were used: LTMP (2.25 mmol), HCO_2-Me (140 μL, 2.25 mmol). Column chromatography (hexane:EtOAc = 10:1) gave **17** (oil, 331 mg, 98%). Partial physical data of **17** are as follows: ^{1}H NMR ($CDCl_3$) δ 0.12−0.26 (18H, m), 1.34 (3H, s), 1.62 (3H, s), 1.65−1.89 (3H, m), 3.25 (1H, dd, J = 3.7 and 9.2 Hz), 3.51 (1H, t, J = 9.2 Hz), 4.61 (1H, dt, J = 4.0 and 9.2 Hz), 5.13 (1H, dd, J = 4.0 and 6.5 Hz), 5.39 (1H, dd, J = 1.8 and 6.5 Hz), 6.23 (1H, d, J = 1.8 Hz), 7.03−7.11 (10H, m), 7.23−7.24 (5H, m), 9.72 (1H, s); FAB-MS m/z 753 ($M^+ + H$).

6-Chloro-2-(hydroxymethyl)-9-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-8-(triisopropylsilyl)purine (18). To a MeOH (10 mL) solution of **17** (217 mg, 0.29 mmol), $NaBH_4$ (33 mg, 0.87 mmol) was added. The reaction mixture was stirred for 20 min at room temperature and filtrated. Column chromatography (hexane:EtOAc = 10:1) of the filtrate gave **18** (foam, 202 mg, 92%): UV (MeOH) λ_{max} 278 nm (ϵ 9000), λ_{min} 245 nm (ϵ 4400); ^{1}H NMR ($CDCl_3$) δ 1.21−1.24 (18H, m), 1.34 (3H, s), 1.60 (3H, s), 1.61−1.69 (3H, m), 2.89 (1H, t, J = 5.4 Hz, D_2O exchangeable), 3.19 (1H, dd, J = 4.0 and 10.0 Hz), 3.41 (1H, dd, J = 8.6 and 10.0 Hz), 4.42 (1H, dd, J = 5.4 and 15.8 Hz), 4.50−4.53 (1H, m), 4.55 (1H, dd, J = 5.4 and 15.8 Hz), 4.96 (1H, dd, J = 4.0 and 6.4 Hz), 5.43 (1H, dd, J = 2.0 and 6.4 Hz), 6.14 (1H, d, J = 2.0 Hz), 7.07−7.16 (9H, m), 7.29−7.32 (6H, m); FAB-MS m/z 755 ($M^+ + H$). Anal. Calcd for $C_{42}H_{51}ClN_4O_5Si$: C, 66.78; H, 6.81; N, 7.24. Found: C, 66.53; H, 6.80; N, 7.42.

6-Chloro-9-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-2-[(*E*)-2-(methoxycarbonyl)vinyl]-8-(triisopropylsilyl)purine (19). A mixture of **17** (290 mg, 0.38 mmol) and (carbomethoxymethylene)triphenylphosphorane (191 mg, 0.57 mmol) in THF (10 mL) was stirred for 4 h at room temperature. The reaction mixture was partitioned between

H_2O and $CHCl_3$. Column chromatography (hexane:EtOAc = 25:1) of the organic layer gave **19** (foam, 293 mg, 95%): UV (MeOH) λ_{max} 302 nm (ϵ 22 500), λ_{min} 264 nm (ϵ 7200); ^{1}H NMR ($CDCl_3$) δ 1.20−1.28 (18H, m), 1.35 (3H, s), 1.61 (3H, s), 1.63−1.70 (3H, m), 3.14 (1H, dd, J = 3.2 and 10.0 Hz), 3.47 (1H, dd, J = 9.6 and 10.0 Hz), 3.87 (3H, s), 4.55−4.59 (1H, m), 4.99 (1H, dd, J = 3.6 and 6.4 Hz), 5.46 (1H, dd, J = 1.6 and 6.4 Hz), 6.19 (1H, d, J = 1.6 Hz), 6.94 (1H, d, J = 16.0 Hz), 7.01−7.15 (10H, m), 7.23−7.25 (5H, m), 7.42 (1H, d, J = 16.0 Hz); FAB-MS m/z 809 (M^+ + H). Anal. Calcd for $C_{45}H_{53}ClN_4O_6Si\cdot 1/2H_2O$: C, 66.03; H, 6.65; N, 6.85. Found: C, 65.98; H, 6.58; N, 6.85.

6-Chloro-9-(2,3-*O*-isopropylidene-5-*O*-trityl-*β*-D-ribofuranosyl)-2-(methoxycarbonyl)-8-(triisopropylsilyl)purine (20). This compound was prepared with the procedure described for the preparation of **12**−**14**. The following amounts of reagents and **7** (608 mg, 0.84 mmol) were used: LTMP (4.2 mmol), $ClCO_2Me$ (325 μL, 4.2 mmol). Column chromatography (hexane:EtOAc = 10:1) gave **20** (foam, 303 mg, 46%): UV (MeOH) λ_{max} 283 nm (ϵ 14 200), λ_{min} 250 nm (ϵ 7100); ^{1}H NMR ($CDCl_3$) δ 1.12−1.26 (18H, m), 1.33 (3H, s), 1.61 (3H, s), 1.65−1.71 (3H, m), 3.25 (1H, dd, J = 2.7 and 10.4 Hz), 3.54 (1H, dd, J = 2.7 and 10.4 Hz), 3.92 (3H, s), 4.59−4.62 (1H, m), 5.20 (1H, dd, J = 4.0 and 6.4 Hz), 5.29 (1H, dd, J = 1.0 and 4.0 Hz), 6.26 (1H, d, J = 1.0 Hz), 7.00−7.03 (6H, m), 7.06−7.10 (3H, m), 7.22−7.23 (6H, m); FAB-MS m/z 783 (M^+ + H). Anal. Calcd for $C_{43}H_{51}ClN_4O_6Si\cdot 3/2H_2O$: C, 63.73; H, 6.71; N, 6.91. Found: C, 63.84; H, 6.33; N, 6.89.

6-Chloro-2-iodo-9-(2,3-*O*-isopropylidene-5-*O*-trityl-*β*-d-ribofuranosyl)-8-(triisopropylsilyl)purine (21). This compound was prepared with the procedure described for the preparation of **12**−**14**. The following amounts of reagents and **7** (500 mg, 0.69 mmol) were used: LTMP (3.44 mmol), iodine (880 mg, 0.69 mmol as I_2) in THF (5 mL). Column chromatography (hexane:EtOAc = 30:1) gave **21** (foam, 458 mg, 78%): UV (MeOH) λ_{max} 291 nm (ϵ 11 900), λ_{min} 252 nm (ϵ 5600); ^{1}H NMR ($CDCl_3$) δ 1.20−1.25 (18H, m), 1.34 (3H, s), 1.60 (3H, s), 1.61−1.68 (3H, m), 3.23 (1H, dd, J = 3.0 and 10.0 Hz), 3.44 (1H, t, J = 10.0 Hz), 4.53−4.57 (1H, m), 4.92 (1H, dd, J = 3.9 and 6.4 Hz), 5.26 (1H, dd, J = 1.3 and 6.4 Hz), 6.15 (1H, d, J = 1.3 Hz), 7.04−7.13 (9H, m), 7.32−7.36 (6H, m); FAB-MS m/z 851 (M^+ + H). Anal. Calcd for $C_{41}H_{48}ClIN_4O_4Si$: C, 57.85; H, 5.68; N, 6.58. Found: C, 58.23; H, 5.89; N, 6.47.

6-Chloro-2-(hydroxymethyl)-9-(2,3-*O*-isopropylidene-5-*O*-trityl-*β*-D-ribofuranosyl)purine (22). To a solution of **18** (315 mg, 0.42 mmol) in THF (5 mL) was added TBAF (1 M THF solution, 500 μL, 0.50 mmol), and the reaction mixture was stirred for 0.5 h at room temperature. Evaporation of the solvent followed by column chromatography ($CHCl_3$) gave **22** (foam, 250 mg, 99%): UV (MeOH) λ_{max} 267 nm (ϵ 8400), λ_{min} 246 nm (ϵ 6200); ^{1}H NMR ($CDCl_3$, after addition of D_2O) δ 1.39 (3H, s), 1.63 (3H, s), 3.27 (1H, dd, J = 6.4 and 10.4 Hz), 3.34 (1H, dd, J = 6.4 and 10.4 Hz), 4.56−4.59 (1H, m), 4.71 (1H, d, J = 16.2 Hz), 4.77 (1H, d, J = 16.2 Hz), 4.90 (1H, dd, J = 2.8 and 6.3 Hz), 5.35 (1H, dd, J = 2.5 and 6.3 Hz), 6.19 (1H, d, J = 2.5 Hz), 7.19−7.20 (9H, m), 7.31−7.32 (6H, m), 8.21 (1H, s); ^{13}C NMR ($CDCl_3$) δ 131.1, 144.1, 151.1, 151.4, 162.9; FAB-MS m/z 599 (M^+ + H). Anal. Calcd for $C_{33}H_{31}ClN_4O_5\cdot 1/2H_2O$: C, 65.18; H, 5.30; N, 9.21. Found: C, 64.99; H, 4.92; N, 9.14.

2′,3′-*O*-Isopropylidene-2-methyl-5′-*O*-trityladenosine (23). A mixture of **12** (218 mg, 0.29 mmol) in THF (10 mL) and saturated NH_3/MeOH (40 mL) was placed in a sealed tube and heated at 110 °C for 95 h. Column chromatography (5% MeOH in $CHCl_3$) of the reaction mixture gave **23** (oil, 165 mg, 99%): UV (MeOH) λ_{max} 262 nm (ϵ 9900), λ_{min} 240 nm (ϵ 6400); ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, s), 1.61 (3H, s), 2.36 (3H, s), 3.21 (1H, dd, J = 4.3 and 10.1 Hz), 3.42 (1H, dd, J = 7.0 and 10.1 Hz), 4.50−4.52 (1H, m), 4.97 (1H, dd, J = 3.2 and 6.1 Hz), 5.39 (1H, dd, J = 2.1 and 6.1 Hz), 5.59 (2H, br), 6.10 (1H, d, J = 2.1 Hz), 7.15−7.20 (9H, m), 7.31−7.34 (6H, m), 7.81 (1H, s); FAB-MS m/z 564 (M^+ + H). Anal. Calcd for $C_{33}H_{33}N_5O_4\cdot 1/2H_2O$: C, 69.21; H, 5.98; N, 12.23. Found: C, 69.51; H, 5.97; N, 12.14.

2-Ethyl-2′,3′-*O*-isopropylidene-5′-*O*-trityladenosine (24). Compound **13** (174 mg, 0.23 mmol) was reacted with NH_3/MeOH in a similar manner as described in the preparation of **23**. The reaction was continued for 84 h. Column chromatography (4% MeOH in $CHCl_3$) of the reaction mixture gave **24** (foam, 122 mg, 91%): UV (MeOH) λ_{max} 261 nm (ϵ 11 500), λ_{min} 241 nm (ϵ 6600); ^{1}H NMR ($CDCl_3$) δ 1.14 (3H, t, J = 7.5 Hz), 1.37 (3H, s), 1.61 (3H, s), 2.57−2.70 (2H, m), 3.17 (1H, dd, J = 4.0 and 10.1 Hz), 3.40 (1H, dd, J = 7.9 and 10.1 Hz), 4.49−4.52 (1H, m), 5.01 (1H, dd, J = 3.4 and 6.4 Hz), 5.46 (1H, dd, J = 1.8 and 6.4 Hz), 6.11 (1H, d, J = 1.8 Hz), 7.13−7.16 (9H, m), 7.29−7.32 (6H, m), 7.81 (1H, s); FAB-MS m/z 578 (M^+ + H). Anal. Calcd for $C_{34}H_{35}N_5O_4\cdot 1/2H_2O$: C, 69.61; H, 6.19; N, 11.94. Found: C, 69.96; H, 5.98; N, 11.71.

2-((Cyclohexyl)hydroxymethyl)-2′,3′-*O*-isopropylidene-5′-*O*-trityladenosine (25). Compound **15** (400 mg, 0.48 mmol) was reacted with NH_3/MeOH in a similar manner as described in the preparation of **23**. The reaction was continued for 90 h. Column chromatography (2% MeOH in $CHCl_3$) of the reaction mixture gave **25** (foam, 305 mg, 96%) as a mixture of two diastereomers (ca. 5:3): UV (MeOH) λ_{max} 261 nm (ϵ 9200), λ_{min} 241 nm (ϵ 5400); ^{1}H NMR of the major diastereomer ($CDCl_3$, after addition of D_2O) δ 1.05−1.36 (11H, m), 1.35 (3H, s), 1.61 (3H, s), 3.21 (1H, dd, J = 3.8 and 10.2 Hz), 3.37 (1H, dd, J = 7.0 and 10.2 Hz), 4.22 (1H, d, J = 4.0 Hz), 4.48−4.52 (1H, m), 4.89 (1H, dd, J = 3.6 and 6.4 Hz), 5.36 (1H, dd, J = 2.0 and 6.4 Hz), 6.13 (1H, d, J = 2.0 Hz), 7.15−7.23 (9H, m), 7.29−7.37 (6H, m), 7.87 (1H, s); ^{1}H NMR of the minor diastereomer ($CDCl_3$, after addition of D_2O) δ 1.36 (3H, s), 1.67 (3H, s), 1.67−1.84 (11H, m), 3.30−3.31 (2H, m), 4.41 (1H, d, J = 4.0 Hz), 4.41−4.47 (1H, m), 4.84 (1H, dd, J = 3.0 and 6.4 Hz), 5.32 (1H, dd, J = 2.4 and 6.4 Hz), 6.15 (1H, d, J = 2.4 Hz), 7.15−7.24 (9H, m), 7.29−7.37 (6H, m), 7.88 (1H, s); FAB-MS m/z 662 (M^+ + H). Anal. Calcd for $C_{39}H_{43}N_5O_5$: C, 70.78; H, 6.55; N, 10.58. Found: C, 70.96; H, 6.59; N, 10.55.

2-[(1-Hydroxy-1-methyl)ethyl]-2′,3′-*O*-isopropylidene-5′-*O*-trityladenosine (26). Compound **16** (473 mg, 0.61 mmol) was reacted with NH_3/MeOH in a similar manner as described in the preparation of **23**. The reaction was continued for 69 h. Column chromatography (2% MeOH in $CHCl_3$) of the reaction mixture gave **26** (foam, 317 mg, 87%): UV (MeOH) λ_{max} 261 nm (ϵ 13 300), λ_{min} 241 nm (ϵ 7500); ^{1}H NMR ($CDCl_3$) δ 1.34 (3H, s), 1.36 (3H, s), 1.46 (3H, s), 1.61 (3H, s), 3.21 (1H, dd, J = 4.0 and 10.0 Hz), 3.34 (1H, dd, J = 7.6 and 10.0 Hz), 4.47−4.51 (1H, m), 4.73 (1H, br), 4.90 (1H, dd, J = 3.2 and 6.2 Hz), 5.41 (1H, dd, J = 2.0 and 6.2 Hz), 5.63 (2H, br), 6.15 (1H, d, J = 2.0 Hz), 7.13−7.19 (9H, m), 7.27−7.35 (6H, m), 7.89 (1H, s); FAB-MS m/z 608 (M^+ + H). Anal. Calcd for $C_{37}H_{37}N_5O_5\cdot 1/2H_2O$: C, 68.16; H, 6.21; N, 11.35. Found: C, 67.79; H, 5.90; N, 11.03.

2-(Hydroxymethyl)-2′,3′-*O*-isopropylidene-5′-*O*-trityladenosine (27). Compound **18** (432 mg, 0.57 mmol) was reacted with NH_3/MeOH in a similar manner as described in the preparation of **23**. The reaction was continued for 80 h. Column chromatography (5% MeOH in $CHCl_3$) of the reaction mixture gave **27** (foam, 304 mg, 92%): UV (MeOH) λ_{max} 261 nm (ϵ 12 300), λ_{min} 241 nm (ϵ 6800); ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, s), 1.62 (3H, s), 3.25 (1H, dd, J = 4.0 and 10.1 Hz), 3.37 (1H, dd, J = 6.4 and 10.1 Hz), 4.45 (1H, d, J = 15.5 Hz), 4.53 (1H, d, J = 15.5 Hz), 4.50−4.53 (1H, m), 4.88 (1H, dd, J = 3.1 and 6.4 Hz), 5.35 (1H, dd, J = 2.4 and 6.4 Hz), 6.13 (1H, d, J = 2.4 Hz), 5.75 (2H, br), 7.17−7.21 (15H, m), 7.88 (1H, s); FAB-MS m/z 580 (M^+ + H). Anal. Calcd for $C_{33}H_{33}N_5O_5\cdot 1/2H_2O$: C, 67.33; H, 5.82; N, 11.90. Found: C, 67.12; H, 6.16; N, 11.51.

2-Carbamoyl-2′,3′-*O*-isopropylidene-5′-*O*-trityladenosine (28). Compound **20** (340 mg, 0.43 mmol) was reacted with NH_3/MeOH in a similar manner as described in the preparation of **23**. The reaction was continued for 79 h. Column chromatography (5% MeOH in $CHCl_3$) of the reaction mixture gave **28** (foam, 166 mg, 65%): UV (MeOH) λ_{max} 265 nm (ϵ 10 600) and 294 nm (ϵ 5500), λ_{min} 245 nm (ϵ 6000) and 275 nm (ϵ 4400); ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, s), 1.63 (3H, s), 3.31 (1H, dd, J = 4.0 and 10.4 Hz), 3.37 (1H, dd, J = 5.8 and 10.4 Hz), 4.51−4.54 (1H, m), 4.93 (1H, dd, J = 3.1 and 6.1 Hz), 5.33 (1H, dd, J = 2.7 and 6.1 Hz), 5.92 (2H, br), 6.10 (2H, br), 6.18 (1H, d, J = 2.7 Hz), 7.17−7.22 (9H, m), 7.30−7.35 (6H, m), 8.01 (1H, s); FAB-MS m/z 593 (M^+ + H). Anal. Calcd for

$C_{33}H_{32}N_6O_5 \cdot 5/4H_2O$: C, 64.43; H, 5.65; N, 13.66. Found: C, 64.14; H, 5.25; N, 13.60.

2-Iodo-2′,3′-*O*-isopropylidene-5′-*O*-trityladenosine (29). Compound **21** (300 mg, 0.35 mmol) was reacted with NH_3/MeOH in a similar manner as described in the preparation of **23**. The reaction was continued for 90 h. Column chromatography (3% MeOH in $CHCl_3$) of the reaction mixture gave **29** (foam, 187 mg, 79%): UV (MeOH) λ_{max} 265 nm (ϵ 12 900), λ_{min} 243 nm (ϵ 7400); ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, s), 1.62 (3H, s), 3.22 (1H, dd, J = 3.7 and 10.4 Hz), 3.46 (1H, dd, J = 7.7 and 10.4 Hz), 4.50−4.53 (1H, m), 4.90 (1H, dd, J = 3.4 and 6.4 Hz), 5.27 (1H, dd, J = 1.8 and 6.4 Hz), 5.80 (2H, br), 6.09 (1H, d, J = 1.8 Hz), 7.15−7.18 (9H, m), 7.33−7.37 (6H, m), 7.78 (1H, s); FAB-MS m/z 676 ($M^+ + H$). Anal. Calcd for $C_{32}H_{30}IN_5O_4$: C, 56.90; H, 4.48; N, 10.37. Found: C, 57.13; H, 4.45; N, 10.11.

Acknowledgment. Financial support from the Ministry of Education, Science and Culture (Grant-in-Aid No. 09672159 to H.T.) is gratefully acknowledged. Part of this work has been supported by Japan Society for the Promotion of Science (to H.T.). The authors thank Dr. Martin J. Slater (Glaxo-Wellcome Medicine Research Centre, U.K.) for proof-reading this manuscript.

JO9906577