Nucleosides and Nucleotides. 184. Synthesis and Conformational Investigation of Anti-Fixed 3-Deaza-3-halopurine Ribonucleosides[1,2]

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A versatile synthetic route to 3-deaza-3-haloinosines **6**−**8** and **46**, -adenosines **15**−**17** and **64**, and -guanosines **25**, **26**, and **52** is described. 3-Deaza-3-chloro-, -bromo-, and -iodopurine ribonucleosides can be synthesized by treating the 3-deazapurine ribonucleosides with *N*-halosuccinimides. For the synthesis of 3-deaza-3-fluoropurine ribonucleosides, 5-formylimidazole-4-carboxamide ribosides **34** and **35** prepared from 5-iodoimidazole-4-carboxamide derivatives **29** and **31** were used as the key intermediates. The reaction of **34** and **35** with lithium (trimethylsilyl)acetylide and sodium cyanide, respectively, followed by appropriate manipulations gave 3-deaza-3-fluoroinosine derivative **46** and 3-deaza-3-fluoroguanosine derivative **52**. 3-Deaza-3-fluoroadenosine (**64**) was also synthesized by selective reductive deamination of 4,6-diamino-7-fluoroimidazo[4,5-*c*]pyridine derivative **51**, followed by deprotection. A conformational analysis using ^{1}H NMR and NOE experiments showed that the introduction of halogens (chloro, bromo, and iodo) into the 3-position of 3-deazapurine ribonucleosides forced fixation of the glycosyl torsion angle in the anti region, but did not abnormally influence sugar puckering. On the other hand, 3-deaza-3-fluoropurine ribonucleosides should rotate freely around the glycosyl bond.

Introduction

The conformation of a nucleoside is defined by several parameters, i.e., sugar pucker modes, syn/anti conformation around the glycosyl bond, and orientation about the C4′−C5′ bond.[3] Concerning nucleoside−enzyme interactions when acting as substrates or inhibitors, the syn/anti conformation around the glycosyl bond is one of the most important conformational aspects. In this regard, several nucleosides with restricted conformation about glycosyl torsion angles have been synthesized and evaluated to understand the relationships between glycosyl torsion angles and nucleoside−enzyme interactions. The most straightforward fixation of glycosyl torsion angles is found in cyclonucleosides that possess an extra covalent linkage between the sugar and the nucleobase. These cyclonucleosides cover a wide range of glycosyl torsion angles, and the correlations between the direction of the sign and magnitude of their CD spectra and the glycosyl torsion angles have been well studied.[4] However, such fixation frequently results in a change in the sugar conformation that is not normally seen in unconstrained nucleosides. Like the syn/anti conformation around the glycosyl bond, it has been revealed that the sugar pucker is also an important conformational aspect in terms of its correlation with nucleoside−enzyme interactions.[5] Therefore, it would be interesting to devise a new way to lock the conformation of nucleosides where the nucleobase is still held in a particular region, but where the sugar ring is sufficiently flexible to adopt whatever puckering the enzyme normally imposes on its substrates. From this point of view, nucleosides that have a bulky substituent on a nucleobase or a sugar portion may be useful for fixing the nucleoside conformation. For example, 8-bromoadenosine and 8-bromoguanosine have been found to exist in the syn conformation in the solid state as well as in solution due to steric repulsion between the 8-bromo group and the sugar portion, and hence, 8-bromoguanosine 5′-triphosphate is not a substrate of Qβ replicase or *Escherichia coli* transcriptase, which prefer an anti rotational isomer either during or after the polymerization reaction.[6] On the other hand, 8-bromoadenosine 5′-diphosphoribose bound to horse liver alcohol dehydrogenase was found to assume an anti conformation in its cocrystal, in contrast to the syn conformation found in 8-bromoadenosine itself.[7] As can be seen from this result, the syn/anti conformation around the glycosyl bond may be forced to change when the nucleo(s/t)ide binds to certain enzymes or receptors, and therefore, the position of an introduced substituent would be important for such fixation. Iimori et al.[8] have attempted to restrict the conformation of sangivamycin

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(1) Part 183: Sugimoto, I.; Shuto, S.; Mori, S.; Shigeta, S.; Matsuda, A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 385−388.

(2) Purine numbering has been used for all nucleosides throughout the text except for the Experimental Section.

(3) Saenger, W. *Principles of Nucleic Acid Structure*; Springer-Verlag: New York, 1984; pp 51−81.

(4) Yoshimura, Y.; Otter, B. A.; Ueda, T.; Matsuda, A. *Chem. Pharm. Bull.* **1992**, *40*, 1761−1769 and references therein.

(5) For examples: (a) Parkanyi, L.; Kalman, A.; Czugler, M.; Walker, R. T. *Nucleic Acids Res.* **1987**, *15*, 4111−4121. (b) Rodriguez, J. B.; Marquez, V. E.; Mitsuya, H.; Barchi, J. J. *J. Med. Chem.* **1994**, *37*, 3389−3399. (c) Marquez, V. E.; Siddiqui, M. A.; Ezzitouni, A.; Russ, P.; Wang, J.; Wagner, R. W.; Matteucci, M. D. *J. Med. Chem.* **1996**, *39*, 3739−3747.

(6) Tavale, S. S.; Sobell, H. M. *J. Mol. Biol.* **1970**, *48*, 109−123.

(7) Abdallah, M. A.; Biellmann, J. F.; Nordstrom, B.; Branden, C. I. *Eur. J. Biochem.* **1975**, *50*, 475−481.

(8) Iimori, T.; Murai, Y.; Ohuchi, S.; Kodama, Y.; Ohtsuka, Y.; Oishi, T. *Tetrahedron Lett.* **1991**, *32*, 7273−7276.

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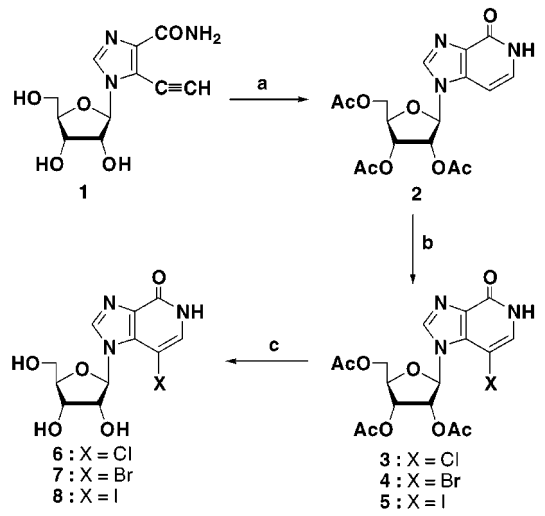
by introducing a methyl group on the sugar, but the steric repulsion between the sugar and the nucleobase moiety was insufficient. In addition, introduction of the methyl group changed the conformation of the sugar moiety. On the basis of these results, we envisioned the introduction of a bulky substituent at the 3-position of 3-deazapurine ribonucleosides to fix the conformation around the glycosyl linkage in the anti region without greatly affecting their sugar puckering. In our first approach, we previously reported the synthesis of 3-alkyl-3-deazainosines that were successfully fixed in the anti conformation, and the predominant sugar puckering was assigned to be C2′-endo in solution, as in inosine and 3-deazainosine (3-zI).[9,10] However, the physicochemical properties such as the pK_a value of the nucleobase moiety would be appreciably altered relative to those of 3-deazainosine itself and its alkylated derivatives. In our previous paper,[11] we reported the synthesis of 3-deaza-3-haloinosines and that such conformational fixation not only resulted in the usual sugar puckering but also only minimally changed the pK_a values. In this paper, we describe in detail the synthesis of 3-deaza-3-haloadenosines and -guanosines in addition to -inosines and conformational studies of these compounds using ^{1}H NMR and NOE experiments.

Results and Discussion

Chlorination, Bromination, and Iodination of 3-Deazapurine Ribonucleosides. 3-Deazapurine ribonucleosides have an imidazo[4,5-*c*]pyridine or imidazo-[4,5-*c*]pyridinone skeleton at the nucleobase moiety that could be expected to react with electrophilic reagents at the 3-position. Chloro, bromo, and iodo substituents can be easily introduced into the 3-position of 3-deazapurine ribonucleosides by treatment with *N*-halosuccinimides. When 3-deazainosine derivative **2**, which was prepared from 5-ethynyl-1-β-D-ribofuranosylimidazole-4-carboxamide (**1**)[12] in 89% yield, was treated with *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) in CH_2Cl_2 at room temperature, 3-chloro and 3-bromo derivatives **3** and **4** were obtained in yields of 71 and 78%, respectively. 3-Iodo derivative **5** was obtained by treatment of **2** with *N*-iodosuccinimide (NIS) in DMF in 75% yield (Scheme 1). The position of halogenation was established by comparing the ^{1}H NMR spectra of **2** and **3** and by NOE experiments. Thus, the vinylic protons of **2** at 7.36 (broad doublet) and 6.65 ppm (doublet) that correspond to H-2 and H-3, respectively, disappeared after chlorination, and a broad signal at 7.46 ppm due to H-2 was observed in **3**. Furthermore, an NOE was observed at the proton (12%) upon irradiation of the N^1H proton. On the basis of these results, it is likely that halogenation took place at the expected 3-position.

In contrast to 3-deazainosine **2**, 3-deazaadenosine and 3-deazaguanosine derivatives were much more reactive toward *N*-halosuccinimides. Although bromination and iodination of 3-deazaadenosine derivative **9**[13] achieved as described above to give **11** and **12** in yields of 74 and 71%, respectively, treatment of **9** with NCS in CH_2Cl_2 at −15 °C resulted in **10** in 16% yield.[14] Thus, the exocyclic amino group was protected by an acetyl group prior to the chlorination. Treatment of **9** with an excess amount of Ac_2O in the presence of Et_3N and (dimethylamino)-pyridine (DMAP) in CH_3CN, which gave a mixture of **13** and diacetylated derivative, followed by methanolic ammonia gave **13** in 94% yield. When **13** was subjected to chlorination, the desired product **14** was obtained in 75% yield. Deprotection of the acetyl group was achieved by treating **14** with methanolic ammonia in a steel container at 50 °C (Scheme 2). For the synthesis of 3-deaza-3-haloguanosines, all halogenations were carried out with N-acetylated derivative **19** to give **20**, **21**, and **22** in good yields. Removal of the acetyl groups can be done by treatment with methanolic ammonia at room temperature to give **23** and **24**; however, the 3-deaza-3-iodoguanosine derivative could not be obtained due to the undesirable reduction of the iodo substituent under the deprotection of the acetyl group (Scheme 3).[15] All of the halogenated 3-deazapurine ribonucleosides were converted to free nucleosides **6**−**8**, **15**−**17**, **25**, and **26** by treatment with methanolic ammonia or tetrabutylammonium fluoride (TBAF).

Scheme 1[a]



[a] Reagents: (a) (1) aqueous Me_2NH in EtOH 80 °C, then aqueous AcOH in EtOH, (2) Ac_2O, pyridine; (b) *N*-halosuccinimide, CH_2Cl_2 or DMF; (c) NH_3/MeOH.

Synthesis of 3-Deaza-3-fluoropurine Ribonucleosides. Since the need for organofluorine compounds has increased not only for biological and pharmacological application but also as organic materials, many fluorinating agents have been developed.[16] We first examined the direct fluorination of **2** with electrophilic fluorinating reagents; however, all attempts with *N*-fluoropyridinium

(9) (a) Aoyagi, M.; Minakawa, N.; Matsuda, A. *Tetrahedron Lett.* **1993**, *34*, 103−106. (b) Yamagata, Y.; Kato, M.; Fujii, S.; Aoyagi, M.; Minakawa, N.; Matsuda, A. *Nucleosides Nucleotides* **1994**, *13*, 1327−1335.

(10) Coincident with our report, Acevedo et al. reported the synthesis of 2′-deoxy-3-alkyl(aryl)-3-deazaguanosines. They indicated that a bulky substituent such as a 1-naphthylethyl group forces the sugar puckering into an unusual C3′-endo conformation, although the nucleoside prefers the anti conformation; see: Acevedo, O. L.; Andrews, R. S.; Cook, P. D. *Nucleosides Nucleotides* **1993**, *12*, 403−416.

(11) Minakawa, N.; Kojima, N.; Matsuda, A. *Heterocycles* **1996**, *42*, 149−154.

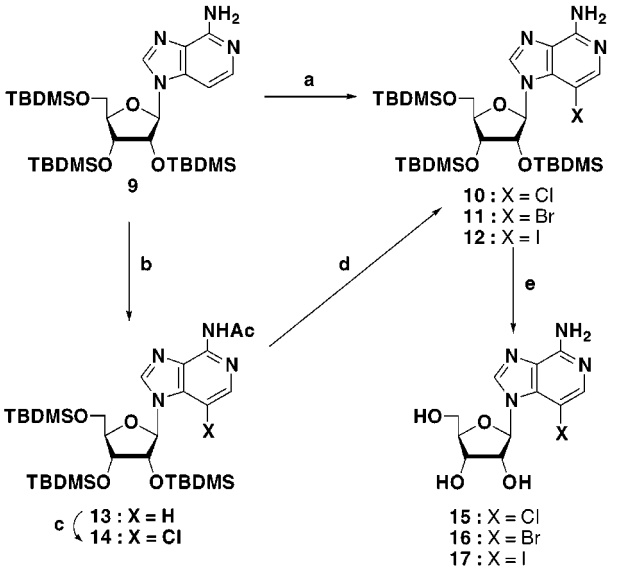
(12) Minakawa, N.; Takeda, T.; Sasaki, T.; Matsuda, A.; Ueda, T. *J. Med. Chem.* **1991**, *34*, 778−786.

(13) Minakawa, N.; Matsuda, A. *Tetrahedron* **1993**, *49*, 557−570.

(14) Unlike the reaction with **2**, the reaction mixture immediately turned dark brown and the reaction gave a complex mixture. Although purification and identification were unsuccessful, the byproducts appeared to be polychlorinated 3-deazaadenosine derivatives.

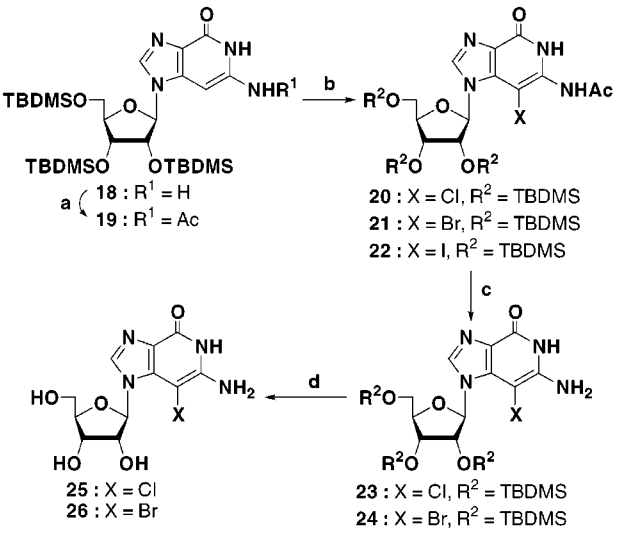
(15) Although direct iodination of **18** with NIS in CH_2Cl_2 at −20 °C gave the desired 3-deaza-3-iodoguanosine derivative, the product was unstable and gave a complex mixture including **18** under usual storage conditions.

Scheme 2[a]



[a] Reagents: (a) *N*-halosuccinimide, CH_2Cl_2 or DMF; (b) Ac_2O, Et_3N, DMAP, CH_3CN, then NH_3/MeOH; (c) *N*-chlorosuccinimide, CH_2Cl_2; (d) NH_3/MeOH, 50 °C; (e) TBAF, THF.

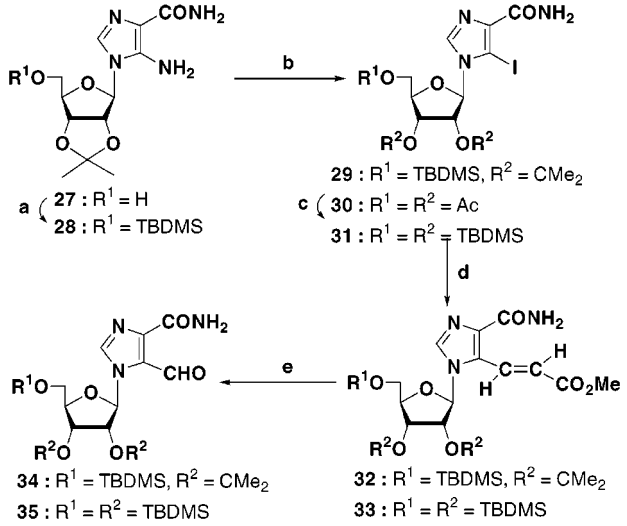
Scheme 3[a]



[a] Reagents: (a) Ac_2O, pyridine, then NH_3/MeOH; (b) *N*-halosuccinimide, CH_2Cl_2, or DMF; (c) NH_3/MeOH; (d) TBAF, THF.

salts[17] or F_2 gas gave poor results with regard to recovery or decomposition of the starting material. Therefore, we planned to synthesize the desired compounds by preparing substrates with fluorinated substituents at the 5-position of imidazole nucleosides, followed by ring closure. 5-Formylimidazole-4-carboxamide derivatives **34** and **35** were thought to be appropriate substrates for the synthesis of the target compounds. The key intermediates were synthesized as shown in Scheme 4.

Scheme 4[a]



[a] Reagents: (a) TBDMSCl, imidazole, DMF; (b) isoamyl nitrite, CH_2I_2, 100 °C; (c) (1) NH_3/MeOH, (2) TBDMSCl, imidazole, DMF; (d) methyl acrylate, Et_3N, $(PhCN)_2PdCl_2$, CH_3CN, 100 °C (e) (1) O_3, MeOH, −78 °C, then Me_2S, or (2) OsO_4, *N*-methylmorpholine *N*-oxide, acetone−H_2O, then $NaIO_4$.

After silylation of a sugar hydroxyl group at the 5′-position of **27**, **28** was diazotized with isoamyl nitrite in the presence of diiodomethane at 100 °C to give **29** in 69% yield. Although palladium-catalyzed formylation of **29** would be conceivably possible,[18] treatment of **29** with tributyltin hydride and carbon monoxide in the presence of $Pd(PPh_3)_4$ resulted in recovery of the starting material along with only a trace amount of 5-formyl derivative **34**. Therefore, **34** was synthesized by ozonolysis of 5(*E*)-(2-carbomethoxyvinyl) derivative **32**.[11] Treatment of **29** with methyl acrylate and Et_3N in the presence of bis(benzonitrile)palladium dichloride in CH_3CN gave **32** in 80% yield. When **32** was ozonized in MeOH, followed by reduction of the resulting ozonide with dimethyl sulfide, 5-formyl derivative **34** was obtained in 98% yield. In a similar manner, **31** obtained from **30**[12] in two steps was converted into 5(*E*)-(2-carbomethoxyvinyl) derivative **33**. Osmylation of **33**, followed by in situ periodate oxidation, gave a good result, compared with the ozonolysis of **33**, to give the desired 5-formyl derivative **35** in 85% yield.

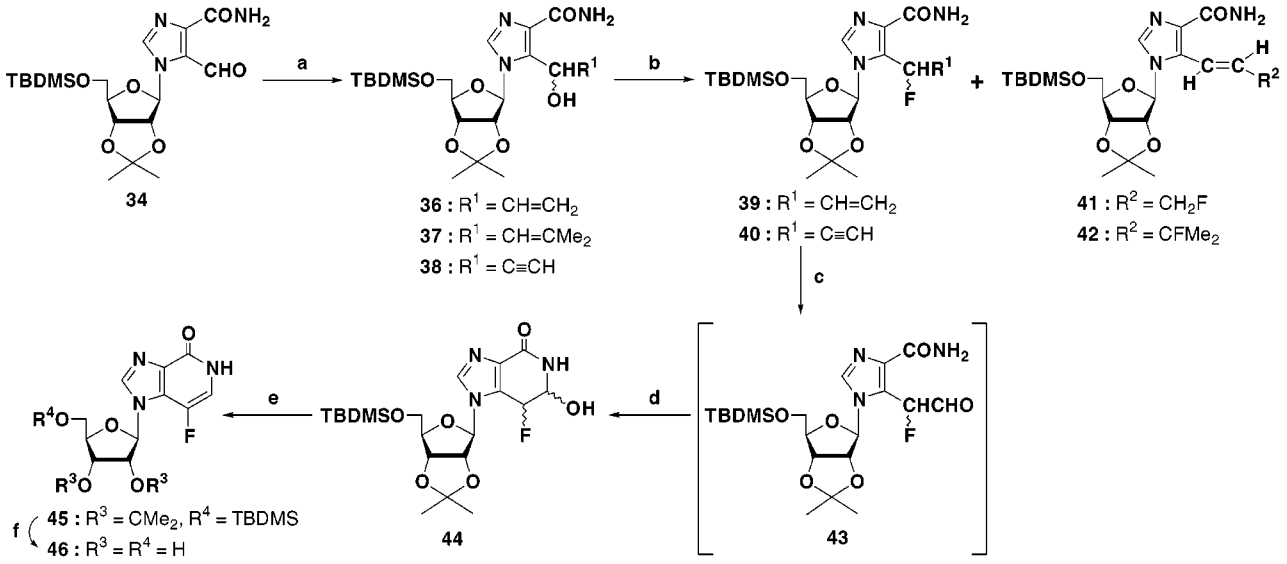
Initially, we examined the synthesis of 3-deaza-3-fluoroinosine (**46**) (Scheme 5). The addition reaction of **34** with vinylmagnesium bromide in THF gave 5-(1-hydroxy-2-propenyl) derivative **36** in 93% yield. If the resulting hydroxyl group can be replaced by a fluorine, followed by conversion of the vinyl group into a formyl group, the desired ring closure between the 5-carboxamide and the formyl groups to give a 3-deaza-3-fluorohypoxanthine skeleton would be possible. When **36** was treated with diethylaminosulfur trifluoride (DAST) in CH_2Cl_2 at −15 °C, the desired 5-(1-fluoro-2-propenyl) derivative **39** was obtained as a mixture of diastereomers (about 3:2) in 37% yield along with 5(*E*)-(3-fluoro-1-propenyl) derivative **41** in 31% yield. Formation of **41** may occur via an S_N2' reaction and/or generation of an allylic cation during this reaction. The separated **39** was then treated with potassium permanganate in aqueous

(16) For review articles, see: (a) Purrington, S. T.; Kagan, B. S.; Patrick, T. B. *Chem. Rev.* **1986**, *86*, 997−1018. (b) Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505−515. (c) Rozen, S. *Chem. Rev.* **1996**, *96*, 1717−1736. (d) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737−1755.

(17) Commercially available *N*-fluoro-3,5-dichloropyridinium triflate, *N*-fluoropyridinium tetrafluoroborate, and *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate were examined for direct fluorination.

(18) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 452−461.

Scheme 5[a]



[a] Reagents: (a) vinylmagnesium bromide (or 1-bromo-2-methylpropene, *t*-BuLi, or trimethylsilylacetylene, *n*-BuLi), THF; (b) DAST, CH_2Cl_2; (c) (1) $KMnO_4$, 18-crown-6, THF, then $NaIO_4$, or (2) H_2, Lindlar, EtOH, then conditions (1); (d) aqueous $NaHCO_3$, $CHCl_3$, 80 °C; (e) Ac_2O, DMAP, pyridine, rt to 100 °C; (f) aqueous TFA.

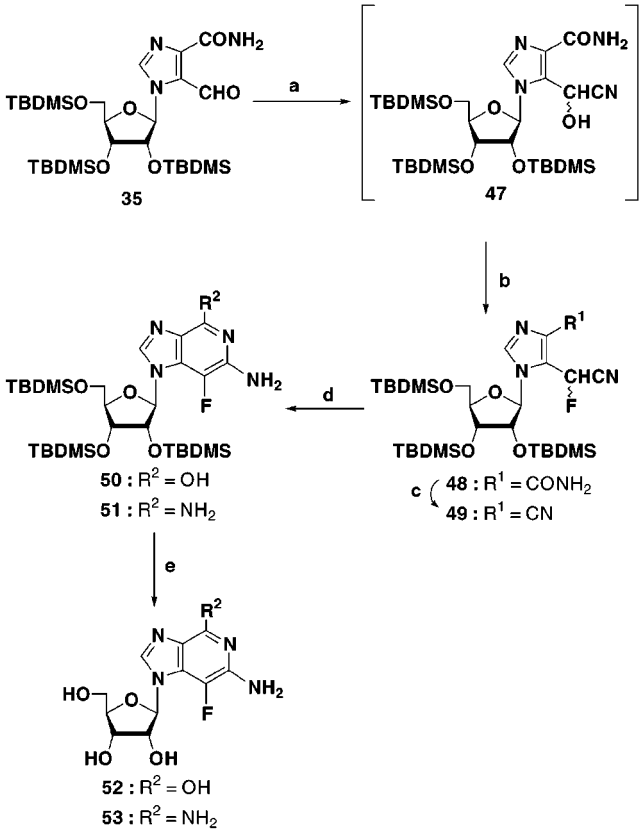
THF in the presence of 18-crown-6, followed by sodium periodate to give two new spots on TLC analysis. The relative proportion of the more polar spot increased upon lengthening the reaction time, and subsequent treatment of the reaction mixture with aqueous sodium bicarbonate gave the more polar spot predominantly. The structure of the more polar spot was confirmed to be **44**, but not **45**, on the basis of its MS spectrum, in which a molecular ion peak was detected at *m*/*z* 458 as MH^+, and its UV spectrum (λ_{max}, 246 nm), together with the ^1H NMR spectrum, in which two dissociable protons were observed at 8.36, 8.26 (in a ratio of 2:1 due to the NH), and 6.87 ppm (as a multiplet due to the OH). During the oxidation reaction of **39**, the less polar spot corresponding to **43** was detected by TLC analysis upon staining with 3,5-dinitrophenylhydrazine. The intramolecular addition of the carbamoyl group at the 4-position should be fast. Surprisingly, the imidazo[4,5-*c*]-6,7-dihydropyridin-4(5*H*)-one derivative **44** was found to be quite stable; treatment of **44** with aqueous AcOH under heating did not give the dehydrated product **45**. Therefore, the hydroxyl group of **44** was acetylated using Ac_2O and DMAP in pyridine, and subsequent heating gave the desired **45** in 92% yield. Deblocking of the protecting groups at the sugar moiety in **45** was achieved with 75% trifluoroacetic acid (TFA) to furnish 3-deaza-3-fluoroinosine (**46**) in quantitative yield.

As expected, **34** was an important intermediate for the synthesis of **46**. However, fluorination of **36** with DAST did not give a satisfying yield of **39**. If the byproduct **41** was formed via an S_N2' mechanism, bulky substituents at the terminus of the olefin would prevent undesired fluorination. To examine this possibility, a carbanion derived from 1-bromo-2-methylpropene was added to the formyl group of **34**. The resulting **37** was then treated with DAST under the same conditions, but exclusively gave the undesired 5(*E*)-(3-fluoro-3-methyl-1-butenyl) derivative **42** in 80% yield (data not shown). On the basis of these experiments, the fluorination of the allylic alcohol by DAST should occur via the allylic cation, which was further stabilized by the terminal dimethyl group of **37** to give **42** predominantly. To improve the yield of **46**, we next tried using a propargyl alcohol system. Reaction of **34** with lithium (trimethylsilyl)acetylide in THF at −78 °C, followed by treatment with methanolic ammonia for 3 h at room temperature, gave a mixture of diastereomers of **38**, which was separable using a silica gel column. Treatment of the mixture of diastereomers of **38** with DAST in CH_2Cl_2 at −15 °C exclusively gave the desired 5-(1-fluoropropynyl) derivative **40** as a mixture of diastereomers in 89% yield. Since the reaction of one of the diastereomers **38** under the same conditions again gave the mixture of diastereomers **40** (data not shown), the fluorination reaction should proceed via a cationic intermediate. A partial catalytic reduction of the acetylenic moiety was performed using Lindlar catalyst to give **39** in 70% yield. After the hydrogenolysis, **44** was obtained in 70% yield from **40** without isolation of **39**.

The synthesis of 3-deaza-3-fluoroguanosine (**52**) can be achieved by a strategy similar to that used for the synthesis of **46**. As shown in Scheme 6, if the hydroxyl group of the cyanohydrin **47** can be converted into its corresponding fluoride, ring closure from the carbamoyl group at the 4-position would proceed smoothly. Since the glycosyl linkage of 3-deazaguanosine derivatives is expected to be unstable relative to that of 3-deazainosine derivatives under acidic conditions,[19] we used tris-TBDMS derivative **35** instead of **34** as a starting material. Compound **35** was vigorously stirred with NaCN in a mixture of EtOAc and aqueous 1 M sodium bicarbonate solution, and the resulting cyanohydrin **47**, without purification due to the possibility of decomposition during isolation, was then treated with DAST in CH_2Cl_2 at −15 °C to give the desired 5-cyanofluoromethyl derivative **48** as a mixture of diastereomers in 73% yield. The ring closure of **48** to 3-deaza-3-fluoroguanine derivative **50** was achieved under heating at 60 °C in a mixture of EtOH and aqueous 5% K_2CO_3 solution in 86% yield.

(19) Minakawa, N.; Kojima, N.; Matsuda, A. Unpublished work.

Scheme 6[a]

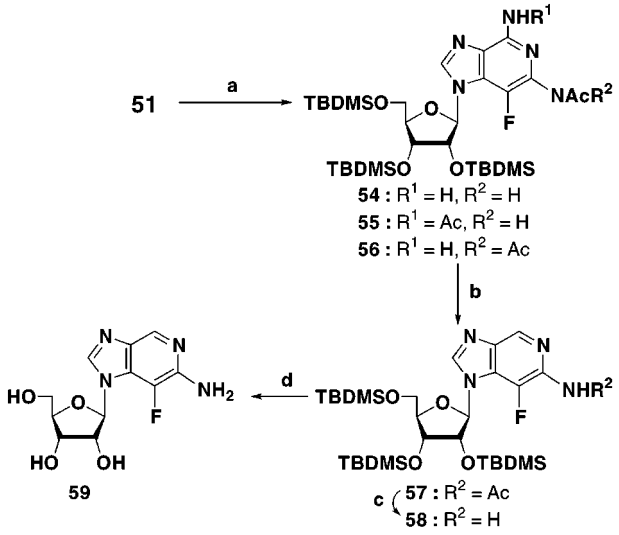


[a] Reagents: (a) NaCN, aqueous $NaHCO_3$−AcOEt; (b) DAST, CH_2Cl_2; (c) $POCl_3$, Et_3N, CH_2Cl_2; (d) (1) aqueous Na_2CO_3−EtOH, 60 °C, or (2) NH_3/EtOH, 120 °C; (e) (1) TBAF, THF, or (2) NH_4F, MeOH.

Deprotection of **50** with TBAF in THF furnished 3-deaza-3-fluoroguanosine (**52**) in 70% yield as crystals. On the other hand, the carbamoyl group in **48** was dehydrated to a cyano group using $POCl_3$ to give **49**, which was heated in methanolic ammonia at 120 °C in a steel container to afford diamino derivative **51** in 79% yield. Deprotection of **51** using TBAF proceeded smoothly, but separation of the resulting **53** and the reagent used was difficult. Therefore, **51** was deprotected by ammonium fluoride in MeOH to give **53** in 74% yield.

For the synthesis of 3-deaza-3-fluoroadenosine derivatives, conversion of the corresponding deazainosines as a starting material is the usual approach. However, deazapurines are more electron-rich than the corresponding purines. Therefore, 6-chloro-3-deazapurine derivatives were transformed to their 3-deazaadenosine derivatives via treatment with hydrazine instead of ammonia.[20] Although the fluorine group at the 3-position has an electron-withdrawing character, treatment of 6-chloro-3-deaza-3-fluoropurine derivative[21] with ammonia did not give the desired 3-deazaadenine derivative. Even treatment with hydrazine gave a complex mixture (data not shown). Therefore, we decided to convert the 2,6-diamino-3-deaza-3-fluoropurine derivative **51** into the 3-deaza-3-fluoroadenine derivative via selective reductive deamination. Acetylation of **51** with Ac_2O in the presence of DMAP in pyridine at room temperature gave a mixture of mono- and diacetylated derivatives of **51** that was successively treated with methanolic ammonia for a short period of time at room temperature to give the monoacetylated derivative **54** in 81% yield from **51**. To identify which amino group was acetylated, the reductive deamination of **54** was performed with isoamyl nitrite in THF[22] to give **57** in 59% yield, which was then deblocked with NaOMe in MeOH, followed by TBAF to furnish **59** in 60% yield, but not the desired 3-deaza-3-fluoroadenosine (**64**) (Scheme 7). The UV spectrum of **59** in H_2O showed two absorption maxima at 260 nm (ϵ = 6500) and 292 nm (ϵ = 3200), which were significantly different from those of other 3-deaza-3-haloadenosines (see the Experimental Section). Moreover, the ^1H NMR spectrum of **59** supported its structure; i.e., the coupling constant between H-6 and the fluorine was 1.5 Hz and was rather small relative to that of 3-deaza-3-fluoroinosine (**46**) ($J_{H-2,\,F}$ = 6.1 Hz). On the other hand, treatment of **51** with AcCl in pyridine gave the diacetamide derivative **55** in 92% yield. Upon treatment of **55** with methanolic ammonia at room temperature, none of the acetyl group was removed. However, when **55** was heated at 80 °C with methanolic ammonia in a steel container, **54** was obtained in 90% yield. Thus, the structure of the diacetylated compound obtained when **51** was treated with acetic anhydride should be **56**. From these results, it was revealed that selective acylation of the amino group at 2-position could be done by treatment of **51** with an acylating reagent, followed by methanolic ammonia. Although the acetyl group at the 6-position is less labile than that of the 2-position, the acetyl group is stable against methanolic ammonia at room temperature. Thus, if an acyl-protecting group, which is deprotected by methanolic ammonia at room temperature, was chosen as that of the 2-position, selective protection of the amino group at the 6-position could be done. We first selected a trifluoroacetyl group to be introduced to the amino group at the 2-position. Treatment of **51** with trifluoroacetic

Scheme 7[a]



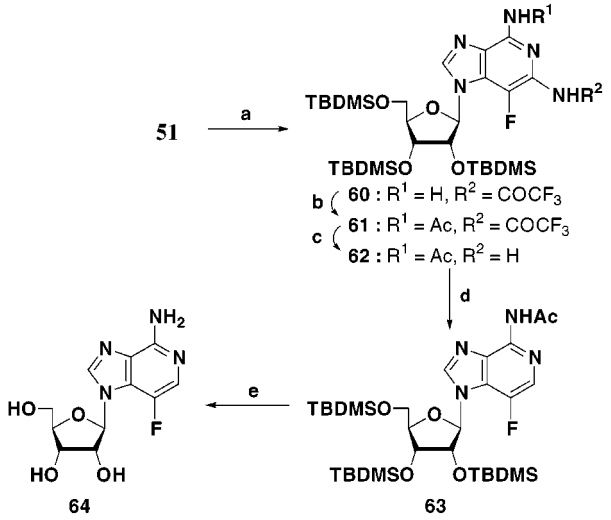
[a] Reagents: (a) (1) Ac_2O, DMAP, pyridine, then NH_3/MeOH, or (2) AcCl, pyridine, then NH_3/MeOH; (b) isoamyl nitrite, THF, 60 °C; (c) NaOMe, MeOH; (d) TBAF, THF.

(20) Rousseau, R. J.; Townsend, L. B.; Robins, R. K. *Biochemistry* **1966**, *5*, 756−760.

(21) Triacetylated 6-chloro-3-deaza-3-fluoropurine derivative was obtained by treatment of triacetylated 3-deaza-3-fluoroinosine with $POCl_3$ and DMF in 94% yield.

(22) Nair, V.; Chamberlain, S. D. *Synthesis* **1984**, 401−403.

Scheme 8[a]



[a] Reagents: (a) trifluoroacetic anhydride, Et_3N, CH_2Cl_2, then NH_3/MeOH; (b) AcCl, pyridine; (c) NH_3/MeOH; (d) isoamyl nitrite, THF, 60 °C; (e) NH_3/MeOH, 120 °C, then TBAF, THF.

anhydride in the presence of Et_3N in CH_2Cl_2 followed by treatment with methanolic ammonia afforded N^2-trifluoroacetamide **60** in 91% yield. Subsequent acetylation of **60** with AcCl in pyridine gave N^6-acetamido-N^2-trifluoroacetamide derivative **61**, which was treated again with methanolic ammonia for 24 h at room temperature without purification to give the desired 2-amino-N^6-acetamide derivative **62** in 80% yield from **51**. The reductive deamination of **62** gave **63** in 55% yield, which was deprotected first with methanolic ammonia at 80 °C and then with TBAF to give 3-deaza-3-fluoroadenosine (**64**) in 57% yield from **63** (Scheme 8). The UV spectrum of **64** showed an absorption maximum at 267 nm (ϵ = 8000), which is close to those of **6**−**8**, but different from that of **59**.

Acid−Base Properties of 3-Deaza-3-halopurine Ribonucleosides. The pK_a values of 3-deazapurine ribonucleosides are appreciably different than those of natural purine nucleosides,[23] and thus, this should be affected by nucleoside−enzyme interactions. As mentioned above, we envisioned introducing an electron-withdrawing halogen atom as a bulky substituent at the 3-position not only to fix the conformation around the glycosyl bond but also to minimize differences in the pK_a values between 3-deazapurine derivatives and natural purine ribonucleosides. We first measured the pK_a values of the halogenated nucleosides, relative to those of 3-deaza and natural purine ribonucleosides.[24] The results are listed in Table 1. The pK_a value of N^1H of inosine was 9.1, while that of 3-deazainosine (3-zI) was calculated to be 13.1. The effects of the nitrogen atom at the 3-position of the purine ring influenced these differences. Introduction of halogen atoms at the 3-position of 3-zI increased the acidity of the N^1H by about 2 pK_a units. Excluding fluorine, a higher electronegativity of the halogen atom was associated with a higher acidity of the N^1H. Although fluorine is a very electronegative atom, the fluorine atom also acts as an electron-donating substituent due to participation of its antibonding 2p orbital when it binds to unsaturated carbon.[25] This would explain why the pK_a value of **46** was not proportional to the electronegativity of its halogen atoms, due to both its −I and +M effects. In contrast, the pK_a value of 3-deaza-3-methylinosine (3-Me-3-zI) was 13.7, which is much larger than that of 3-zI. The same tendency was observed for 3-deazaadenosine (3-zA) and 3-deazaguanosine (3-zG) derivatives, and the pK_a values of 3-deaza-3-halopurine ribonucleosides were close to those of natural purine ribonucleosides.

Table 1. pK_a Values of Purine and 3-Deazapurine Analogues

compd	pK_{a1}[a]	pK_{a2}[b]
inosine	9.1	
3-zI	13.1	
46 (X = F)	11.2	
6 (X = Cl)	11.1	
7 (X = Br)	11.3	
8 (X = I)	11.7	
3-Me-3zI	13.7	
adenosine	3.6	
3-zA	7.0	
64 (X = F)	5.2	
15 (X = Cl)	5.1	
16 (X = Br)	5.2	
17 (X = I)	5.2	
guanosine	1.9	9.2
3-zG	2.7	12.3
52 (X = F)	ND	10.4
25 (X = Cl)	2.0	10.5
26 (X = Br)	2.1	10.5

[a] Values represent pK_a values of the N^1 position for inosine and adenosine derivatives and of the N^7 position for guanosine derivatives. [b] Values represent pK_a values of the N^1 position. [c] Not determined.

Conformational Studies Using NMR and NOE Experiments. Analyses with ^{1}H NMR, ^{13}C NMR, and NOE spectroscopy have been used to study the dynamic equilibrium of syn/anti around the glycosyl bond and sugar pucker modes.[26,27] Conformational studies of 3-deaza-3-halopurine ribonucleosides were performed using NMR and NOE experiments. In these investigations, an unexpected phenomenon was observed in ^{1}H NMR spectra. The ^{1}H NMR chemical shifts of the synthetic nucleosides are listed together with those of natural inosine, adenosine, and guanosine in Table 2. As can be seen, large

(23) Seela, F.; Rosemeyer, H.; Fischer, S. *Helv. Chim. Acta* **1990**, *73*, 1602−1611.

(24) The pK_a values of all nucleosides were measured by a slight modification of the method reported by Shugar and Fox. A 0.2 M NaCl solution was used for all pH ranges instead of buffers; see: Shugar, D.; Fox, J. J. *Biochim. Biophys. Acta* **1952**, *9*, 199−218.

(25) It is known that the donor ability by resonance (+M effect) of the halogens follows the series F > Cl > Br > I. For example, pK_a values of substituted phenols are 9.95 (phenol), 9.28 (*m*-F), 9.02 (*m*-Cl), 9.11 (*m*-Br), and 9.17 (*m*-I), respectively. This trend is explained in terms of electron-donating effect of fluorine; see: Modena, G.; Scorrano, G. In *The Chemistry of The Carbon−halogen Bond, Part 1*; Patai, S., Ed.; John Wiley & Sons Ltd.: New York, 1973; Chapter 6, pp 301−406.

(26) For examples of conformational studies on the syn/anti equilibrium, see: (a) Davis, J. P.; Hart, P. A. *Tetrahedron* **1972**, *28*, 2883−2891. (b) Stolarski, R.; Dudycz, L.; Shugar, D. *Eur. J. Biochem.* **1980**, *108*, 111−121. (c) Stolarski, R.; Hagberg, C.; Shugar, D. *Eur. J. Biochem.* **1984**, *138*, 187−192. (d) Davies, D. B.; Rajani, P.; Sadikot, H. *J. Chem. Soc., Perkin Trans. 2* **1985**, 279−285. (e) Rosemeyer, H.; Toth, G.; Golankiewicz, B.; Kazimierczuk, Z.; Bourgeois, W.; Kretschmer, U.; Muth, H. P.; Seela, F. *J. Org. Chem.* **1990**, *55*, 5784−5790. (f) Cho, B. P.; Evans, F. E. *Biochem. Biophys. Res. Commun.* **1991**, *180*, 273−278.

(27) For examples of conformational studies of the ribose conformer, see: (a) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1973**, *95*, 2333−2344. (b) Davies, D. B.; Danyluk, S. S. *Biochemistry* **1974**, *13*, 4417−4434. (c) Yokoyama, S.; Yamaizumi, Z.; Nishimura, S.; Miyazawa, T. *Nucleic Acids Res.* **1979**, *6*, 2611−2626.

Table 2. ^{1}H NMR Spectral Data[a,b]

compd	NH	H-8	H-2	NH_2[c]	H-1′($J_{1',2'}$)[d]	H-2′	H-3′($J_{3',4'}$)[d]	H-4′	H-5′
inosine	12.36	8.31	8.05		5.84 (5.9)	4.46	4.10 (3.9)	3.92	3.62, 3.52
3-zI	11.18	8.22	7.16		5.71 (6.6)	4.23	4.06 (3.3)	3.94	3.62, 3.56
46 (X = F)	11.19	8.47	7.41		5.89 (5.7)	4.33	4.09 (3.4)	3.95	3.67, 3.57
6 (X = Cl)	11.58	8.51	7.36		6.23 (4.9)	4.33	4.08 (4.4)	3.93	3.68, 3.57
7 (X = Br)	11.60	8.50	7.41		6.47 (5.0)	4.38	4.08 (3.8)	3.93	3.65, 3.54
8 (X = I)	11.49	8.44	7.44		6.61 (5.5)	4.44	4.10 (3.3)	3.92	3.59, 3.55
3-Me-3zI	11.04	8.37	6.91		6.00 (5.4)	4.30	4.09 (3.4)	3.94	3.67, 3.57
adenosine		8.32	8.11	7.32	5.85 (6.6)	4.59	4.12 (3.3)	3.94	3.64, 3.56
3-zA		8.29	7.66	6.15	5.75 (6.2)	4.31	4.09 (3.3)	3.95	3.66, 3.59
64 (X = F)		8.47	7.67	6.17	5.92 (5.7)	4.35	4.09 (3.4)	3.94	3.65, 3.57
15 (X = Cl)		8.53	7.65	6.43	6.35 (5.1)	4.37	4.11 (4.4)	3.93	3.66, 3.56
16 (X = Br)		8.54	7.73	6.46	6.48 (5.5)	4.40	4.10 (4.4)	3.92	3.64, 3.54
17 (X = I)		8.49	7.88	6.40	6.62 (5.5)	4.46	4.10 (4.4)	3.92	3.60, 3.55
guanosine	10.59	7.91		6.42	5.67 (5.9)	4.37	4.05 (3.3)	3.84	3.58, 3.48
3-zG	10.29	7.66		5.56	5.46 (6.1)	4.21	4.01 (3.9)	3.87	3.61, 3.51
52 (X = F)	10.47	8.04		5.50	5.77 (5.5)	4.26	4.04 (3.9)	3.89	3.60, 3.55
25 (X = Cl)	10.67	8.13		5.76	6.28 (4.9)	4.27	4.06 (4.4)	3.88	3.63, 3.53
26 (X = Br)	10.72	8.13		5.71	6.43 (4.9)	4.30	4.06 (4.4)	3.88	3.61, 3.55

[a] Chemical shifts in DMSO-d_6. Assignment of ^{1}H signals was based on two-dimensional NMR experiments. [b] Full spectral data of synthetic nucleosides are provided in the Supporting Information. [c] Values represent 6-NH_2 for adenosine derivatives and 2-NH_2 for guanosine derivatives. [d] Coupling constants (in parentheses).

Table 3. ^{13}C NMR Spectral Data[a,b]

compd	C2	C3	C4	C5	C6	C8	C1′	C2′	C3′	C4′	C5′
inosine	145.8		148.1	124.4	156.5	138.7	87.4	74.0	70.2	85.6	61.2
3-zI	129.5	93.3	138.3	131.8	157.9	139.2	88.7	74.5	70.1	85.4	61.1
46 (X = F)	115.1	137.5	129.3	132.3	156.3	139.5	89.4	75.2	69.8	85.5	60.8
6 (X = Cl)	128.6	98.4	134.3	132.6	156.8	139.6	88.4	75.3	69.4	85.0	60.4
7 (X = Br)	131.1	83.0	135.2	133.0	156.9	139.7	87.6	75.0	69.4	85.0	60.5
8 (X = I)	136.6	49.4	137.2	133.3	157.1	139.8	86.1	74.4	69.7	85.1	60.8
adenosine	152.3		149.0	119.3	156.1	139.8	87.9	73.4	70.6	85.8	61.6
3-zA	137.7	97.5	139.4	126.8	152.0	140.2	88.7	73.9	70.1	85.6	61.2
64 (X = F)	126.0	140.8	126.6	128.5	149.4	140.2	89.4	74.8	69.9	85.4	61.0
15 (X = Cl)	140.1	101.8	133.7	127.9	151.6	140.1	88.4	75.0	69.6	85.0	60.7
16 (X = Br)	142.7	87.8	134.7	128.2	152.0	140.2	87.6	74.8	69.6	84.9	60.7
17 (X = I)	148.8	56.4	137.1	128.5	152.5	140.3	86.1	74.2	69.8	84.9	60.9
guanosine	153.6		151.2	116.7	156.7	135.5	86.3	73.6	70.3	85.1	61.4
3-zG	142.4	70.5	147.6	123.0	156.4	136.6	88.1	73.8	70.1	85.2	61.2
52 (X = F)	135.4	121.4	132.0	122.3	154.2	137.0	89.0	74.7	69.9	85.2	61.0
25 (X = Cl)	143.9	75.5	137.6	124.1	155.2	137.0	88.0	74.9	69.5	84.7	60.6
26 (X = Br)	144.6	61.5	138.5	124.5	155.4	137.2	87.4	74.7	69.5	84.7	60.7

[a] Chemical shifts in DMSO-d_6. Assignment of ^{13}C signals was based on DEPT and HSQC experiments. [b] Full spectral data including coupling constants of **46**, **64**, and **52** are provided in the Supporting Information.

differences in H-1′ chemical shifts were observed between 3-deazapurine ribonucleosides and 3-deaza-3-halopurine ribonucleosides, especially the 3-chloro, bromo, and iodo derivatives. For example, the H-1′ chemical shift of 3-deazainosine was characterized at 5.71 ppm, whereas those of **6**, **7**, and **8** exhibited large downfield shifts (0.6−0.9 ppm). The downfield shift was much less (0.18 ppm) in **46**. Although small downfield shifts (0.1−0.2 ppm) were observed in H-2's, other sugar protons exhibited almost the same chemical shifts as 3-zI. Furthermore, the same tendency was observed in 3-deazaadenosine and 3-deazaguanosine derivatives. Such anomalous downfield shifts of proton signals were observed in steric compression molecules.[28] As one interpretation of this phenomenon, intramolecular van der Waals effects, which cause magnetic deshielding, with other proximate atoms including hydrogen and halogen atoms can be considered.[29] Furthermore, it is known that van der Waals effects between a hydrogen atom and halogens such as chlorine and bromine atoms show a larger magnetic deshielding than those between two hydrogen atoms.[29b] The above description is in good agreement with our ^{1}H NMR spectral data, since the downfield shifts in 3-Me-3zI, for which the same effects is expected between the H-1′ and one of the hydrogen atoms of methyl group, was smaller (0.29 ppm) than those of 3-deaza-3-halopurine derivatives such as **6**−**8**. Although 3-deaza-3-halopurine ribonucleosides are considered to be rather flexible molecules for sugar pucker modes, which may also attribute to change the proton chemical shifts, van der Waals effects would be one of the explanations of the anomalous proton deshielding. In the ^{13}C NMR spectra (Table 3), small upfield shifts of C-1′ due to van der Waals effects were observed except for 3-deaza-3-fluoro derivatives.[29a,30] The

(28) For examples, see: (a) Slomp, G.; McGarvey, B. R. *J. Am. Chem. Soc.* **1959**, *81*, 2200−2201. (b) Nagata, W.; Terasawa, T.; Tori, K. *J. Am. Chem. Soc.* **1964**, *86*, 3746−3749. (c) Arnold, D. R.; Trecker, D. J.; Whipple, E. B. *J. Am. Chem. Soc.* **1965**, *87*, 2596−2602. (d) Winstein, S.; Carter, P.; Anet, F. A. L.; Bourn, A. J. R. *J. Am. Chem. Soc.* **1965**, *87*, 5247−5249. (e) Cheney, B. V. *J. Am. Chem. Soc.* **1968**, *90*, 5386-5390.

(29) For examples, see: (a) Schaefer, T.; Reynolds, W. F.; Yonemono, T. *Can. J. Chem.* **1963**, *41*, 2969−2976. (b) Yonemoto, T. *Can. J. Chem.* **1966**, *44*, 223−231. (c) De Coen, J. L.; Elefante, G.; Liquori, A. M.; Damiani, A. *Nature* **1967**, *216*, 910−913. (d) Castellano, S.; Sun, C.; Kostelnik, R. *Tetrahedron Lett.* **1967**, *51*, 5205−5209. (e) Bartle, K. D.; Smith, J. A. S. *Spectrochim. Acta* **1967**, *23A*, 1689−1714. (f) Rummens, F. H. A. *NMR: Basic Princ. Prog.* **1975**, **10**, 118pp. (g) Bohr, J. E.; Hunt, K. L. C. *J. Chem. Phys.* **1987**, *86*, 5441−5448.

(30) Cheney, B. V.; Grant, D. M. *J. Am. Chem. Soc.* **1968**, *90*, 5386-5390.

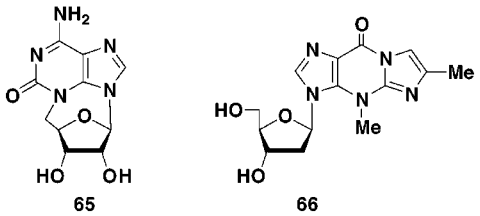


Figure 1. Structures of conformationally fixed nucleosides.

large differences in chemical shifts, especially at C-3, between 3-deazapurine ribonucleosides and 3-deaza-3-halopurine ribonucleosides were consistent with those between benzene and monohalogenated benzenes.[31] Thus, downfield shifts in proportion to electronegativity were observed in the 3-fluoro and 3-chloro derivatives. In contrast, upfield shifts were observed due to heavy-atom effects, which are greater than inductive effects, in the 3-bromo and 3-iodo derivatives.

The ribose conformation of the 3-deaza-3-halopurine ribonucleosides is easily predicted from the coupling constants of the ribose ($J_{1',2'}$ and $J_{3',4'}$) listed in Table 2.[27] As is well-known, the sugar pucker modes of natural purine ribonucleosides prefer a C2′-endo conformer.[3] As can be seen from the coupling constants, the C2′-endo conformers of inosine and guanosine in DMSO-d_6 were calculated to have a population of 60%, while that of adenosine was slightly higher (66%). Although the coupling constants ($J_{1',2'}$ and $J_{3',4'}$) of the 3-deaza-3-halopurine ribonucleosides show some scatter, all of the nucleosides were found to exist preferentially as the C2′-endo in solution, like natural purine ribonucleosides.

The syn/anti conformation around the glycosyl bond was examined using NOE experiments. NOE spectroscopy has been found to give a direct approach to qualitative and semiquantitative information about the syn/anti conformation. Thus, one can presume if irradiation of H-8 in purine ribonucleosides exhibits a strong NOE at H-1′ and small NOEs at H-2′ and H-3′, then the syn conformer should be preferred. On the other hand, if irradiation of H-8 exhibits a strong NOE at H-2′ and a smaller NOE at H-1′, the anti conformer should dominate. Rosemeyer et al.[26e] reported a semiquantitative estimation of the syn/anti conformer populations of nucleosides using NOE spectroscopy. In their method, N^3,5′-anhydroisoguanosine (**65**) and 2′-deoxywyosine (**66**) were used as syn- and anti-fixed nucleosides, respectively, and NOE values at H-1′, H-2′, and H-3′ upon irradiation of H-8 (H-2 for **66**) were used to established a calibration graph for the semiquantitative estimation of the syn and anti conformer populations of β-D-ribonucleosides. We used this method to obtain a semiquantitative estimation of the syn and anti populations of the 3-deaza-3-halopurine ribonucleosides. Initially, **65** and **66** were prepared according to previous reports (Figure 1).[26e,32] The NOE measurements were performed in the same manner as in Rosemeyer's report, and the NOE data are listed in Table 4. A maximal NOE was observed at H-1′ upon irradiation of H-8 in syn-fixed **65** (7.8%), and simultaneously, no NOE was observed at H-2′ and H-3′. On the other hand, anti-fixed **66** exhibited

(31) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. In *Spectrometric Identification of Organic Compounds*, 4th Ed.; John Wiley & Sons: New York, 1981; pp 264−266.

(32) Golankiewicz, B.; Ostrowski, T.; Folkman, W. *Nucleic Acids Res.* **1990**, *18*, 4779−4782.

Table 4. Results of NOE Experiments on 3-Deazainosine Derivatives[a,b]

	65	**66**	inosine	**3-zI**	**46**	**6**	**7**	**8**
NOE of H-1′ (%)	7.8	1.1	5.1	5.2	2.4	1.0	0.6	0.6
H-2′	0	9.4	4.7	3.3	4.8	7.8	10.1	10.8
H-3′	0	3.0	0.9	0.8	0.8	1.5	1.4	1.8
H-2′ + H-3′ (%)	0	12.4	5.6	4.1	5.6	9.3	11.5	12.6

[a] On irradiation of H-8 (H-2 for **66**). [b] Measured in DMSO-d_6 (0.05 M, 400 MHz).

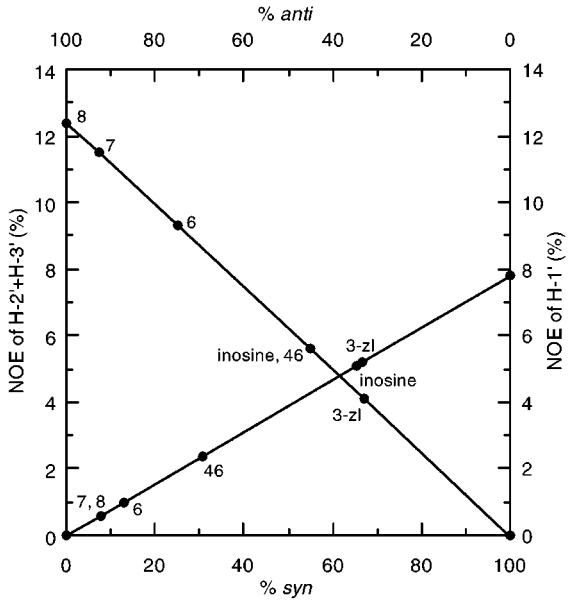


Figure 2. Calibration graph for estimating the syn and anti conformer populations of inosine and 3-deazainosine derivatives.

large NOE values at H-2′ and H-3′ (12.4%) upon irradiation of H-8, while a small NOE (1.1%) was observed at H-1′. A calibration graph was set up with these data, and the NOE data of the 3-deaza-3-halopurine ribonucleosides, including those of inosine and 3-zI, were plotted on the calibration graph (Figure 2). As shown in Figure 2, inosine and 3-zI slightly prefer the syn range (65% syn). On the other hand, the introduction of halogens at the 3-position resulted in a predominance for the anti conformer with an increasing van der Waals radius of the halogen substituents. Compound **8** exhibited the same NOE tendency as anti-fixed 2′-deoxywyosine (**66**) and was estimated to be a 100% anti substrate. The NOE values at H-2′ and H-3′ of **7** and **6** were smaller than those in the anti-fixed model, and were estimated to be 92% and 75% anti substrates, respectively. However, the NOE values of these nucleosides at H-1′ were smaller than that in the anti-fixed model, and thus, **7** and **6** are also considered to be rather fixed in the anti conformational range due to steric repulsion of the bromo and chloro substituents. 3-Deaza-3-fluoroinosine (**46**) was estimated to be 45% anti and 30% syn based on the calibration graph. One possible explanation for this discrepancy is that this compound shows free rotation around the glycosyl linkage and a predominant unusual high-syn conformation with a reduction of NOE.[26e] These NOE experiments also indicated that the sugar of 3-deazainosine derivatives prefers the C2′-endo conformation; i.e., strong NOE's were observed at H-2's and smaller ones were observed at H-3′.[33] The same tendency was

observed in 3-deazaadenosine and 3-deazaguanosine derivatives (data not shown).

In conclusion, the synthesis of 3-deaza-3-halopurine ribonucleosides was accomplished by direct halogenation of the 3-deazapurine ribonucleosides or derivatization from the 5-formylimidazole-4-carboxamide derivatives. 3-Deazapurine ribonucleosides with halogens (iodo, bromo, and chloro) at the 3-position should be good model compounds for studying nucleoside−enzyme interactions with fixed glycosyl torsion angles in the anti region, flexible sugar conformation, and pK_a values at the nucleobases close to those in natural ribonucleobases. On the other hand, 3-deaza-3-fluoropurine ribonucleosides should be better probes for such studies in models with free rotation around the glycosyl bond than 3-deazapurine ribonucleosides. The use of these analogues in enzyme reactions should be the force of further study.

Experimental Section

General Methods. Physical data were measured as follows: Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 270, 400, or 500 MHz and 67.5, 100, or 125 MHz instruments in $CDCl_3$ or DMSO-d_6 as the solvent with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were detected by addition of D_2O. TLC was done on Merck Kieselgel F254 precoated plates. Silica gel used for column chromatography was YMC gel 60A (70−230 mesh).

1-(2,3,5-Tri-*O*-acetyl-*β*-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (2). An aqueous MeN_2H solution (50%, 15 mL) was added to a suspension of **1**[12] (777 mg, 2.91 mmol) in EtOH (30 mL), and the mixture was heated at 80 °C in a steel container. After 5 h, the reaction mixture was concentrated in vacuo, and the residue was dissolved in EtOH−50% aqueous AcOH (10 mL−10 mL), and the mixture was stirred overnight at room temperature. The solvent was removed in vacuo and then coevaporated several times with EtOH and benzene to give crude 3-deazainosine. Acetic anhydride (1.1 mL, 11.6 mmol) was added to a suspension of 3-deazainosine in pyridine (30 mL), and the reaction mixture was stirred at room temperature overnight. Five milliliters of EtOH was added to the mixture to quench the reaction. The mixture was concentrated in vacuo, and the residue was dissolved in $CHCl_3$, which was washed with saturated aqueous $NaHCO_3$, followed by saturated brine. The separated organic layer was dried (Na_2SO_4) and concentrated in vacuo and then coevaporated several times with toluene. The residue was purified by a silica gel column (3.2 × 9 cm), eluted with 0−12% EtOH in $CHCl_3$, to give **2** (1.02 g, 89% from **1**, crystallized from EtOH): mp 200−201 °C; MS *m*/*z* 393 (M^+); ^{1}H NMR ($CDCl_3$) 12.69 (br s, 1 H, NH), 8.04 (s, 1 H), 7.36 (br d, 1 H, J = 7.1 Hz), 6.65 (d, 1 H, J = 7.1 Hz), 5.98 (d, 1 H, J = 5.0 Hz), 5.49 (dd, 1 H, J = 5.0, 5.5 Hz), 5.41 (dd, 1 H, J = 5.5, 4.4 Hz), 4.49 (m, 1 H), 4.42 (br s, 2 H), 2.17, 2.16, 2.11 (each s, each 3 H). Anal. Calcd for $C_{17}H_{19}N_3O_8$: C, 51.91; H, 4.87; N, 10.68. Found: C, 51.74; H, 4.77; N, 10.85.

7-Chloro-1-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (3). A mixture of **2** (393 mg, 1.0 mmol) and *N*-chlorosuccinimide (NCS, 200 mg, 1.5 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature. After 15 h, NCS (266 mg, 2.0 mmol) was further added to the mixture and the mixture was stirred for an additional 24 h. After addition of cyclohexene (0.2 mL) to decompose an excess NCS, the mixture was concentrated in vacuo, and the residue was purified by a silica gel column (2.7 × 13 cm), eluted with 0−6% EtOH in $CHCl_3$, to give **3** (302 mg, 71%) as a bright yellow foam: MS *m*/*z* 427, 429 (M^+); ^{1}H NMR ($CDCl_3$) 13.06 (br s, 1 H), 8.27 (s, 1 H), 7.46 (s, 1 H), 6.75 (d, 1 H, J = 4.4 Hz), 5.58 (dd, 1 H, J = 3.9, 5.0 Hz), 5.43 (dd, 1 H, J = 5.0, 5.5 Hz), 4.42 (m, 3 H), 2.20, 2.14, 2.12 (each s, each 3 H). Used immediately in the next stage.

7-Bromo-1-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (4). In a manner similar to that above, the reaction of **2** (393 mg, 1 mmol) with *N*-bromosuccinimide (NBS) in dry CH_2Cl_2 gave **4** (366 mg, 78%) as a bright purple glass: MS *m*/*z* 471, 473 (M^+); ^{1}H NMR ($CDCl_3$) 13.19 (br s, 1 H), 8.26 (s, 1 H), 7.51 (s, 1 H), 6.89 (d, 1 H, J = 4.4 Hz), 5.59 (dd, 1 H, J = 4.4, 5.0 Hz), 5.42 (dd, 1 H, J = 5.0, 5.5 Hz), 4.47 (ddd, 1 H, J = 5.5, 2.7, 2.2 Hz), 4.42 (s, 2 H), 2.19 2.13, 2.11 (each s, each 3 H). Used immediately in the next stage.

7-Iodo-1-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (5). In a manner similar to that above, the reaction of **2** (393 mg, 1 mmol) with *N*-iodosuccinimide (NIS) in dry DMF under shading gave **5** (391 mg, 75%) as a yellow foam: FAB-MS *m*/*z* 520 (MH^+); ^{1}H NMR ($CDCl_3$) 13.01 (br s, 1 H), 8.25 (s, 1 H), 7.66 (s, 1 H), 7.05 (d, 1 H, J = 5.0 Hz), 5.62 (t, 1 H, J = 5.0 Hz), 5.44 (dd, 1 H, J = 5.0, 5.5 Hz), 4.49 (ddd, 1 H, J = 5.5, 2.7, 2.2 Hz), 4.41 (br s, 2 H), 2.20 2.14, 2.13 (each s, each 3 H). Used immediately in the next stage.

7-Chloro-1-*β*-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one (3-Chloro-3-deazainosine, 6). Compound **3** (300 mg, 0.70 mmol) was dissolved in methanolic ammonia (saturated at 0 °C, 10 mL), and the mixture was kept overnight at room temperature. The solvent was removed in vacuo, and the residue was purified by a silica gel column (2.7 × 6 cm), eluted with 5−30% EtOH in $CHCl_3$, to give **6** (115 mg, 55%, crystallized from MeOH): mp 171−173 °C dec; FAB-MS *m*/*z* 302, 304 (MH^+); UV λ_{max} (H_2O) 261 nm (ϵ 9700); UV λ_{max} (0.5 N HCl) 274 nm (ϵ 8300); UV λ_{max} (0.5 N NaOH) 269 nm (ϵ 10 200). Anal. Calcd for $C_{11}H_{12}ClN_3O_5 \cdot {}^1/_3$MeOH: C, 43.58; H, 4.30; N, 13.46. Found: C, 43.21; H, 4.19; N, 13.24.

7-Bromo-1-*β*-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one (3-Bromo-3-deazainosine, 7). In the same manner as described for **6**, the reaction of **4** (294 mg, 0.62 mmol) with methanolic ammonia (10 mL) gave **7** (150 mg, 70%, crystallized from MeOH): mp 150−152 °C dec; FAB-MS *m*/*z* 346, 348 (MH^+); UV λ_{max} (H_2O) 264 nm (ϵ 9800); UV λ_{max} (0.5 N HCl) 276 nm (ϵ 8500); UV λ_{max} (0.5 N NaOH) 269 nm (ϵ 10 200). Anal. Calcd for $C_{11}H_{12}BrN_3O_5 \cdot {}^3/_4$MeOH: C, 38.12; H, 4.08; N, 11.35. Found: C, 37.97; H, 4.16; N, 11.25.

7-Iodo-1-*β*-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one (3-deaza-3-iodoinosine, 8). In the same manner as for **6**, the reaction of **5** (391 mg, 0.66 mmol) with methanolic ammonia (15 mL) gave **8** (239 mg, 92%, crystallized from MeOH−H_2O): mp 189−191 °C dec; FAB-MS *m*/*z* 394 (MH^+); UV λ_{max} (H_2O) 263 nm (ϵ 10 600); UV λ_{max} (0.5 N HCl) 280 nm (ϵ 8400); UV λ_{max} (0.5 N NaOH) 269 nm (ϵ 11 100). Anal. Calcd for $C_{11}H_{12}IN_3O_5 \cdot {}^3/_5$MeOH: C, 33.79; H, 3.52; N, 10.19. Found: C, 33.65; H, 3.56; N, 9.95.

4-Amino-7-bromo-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)imidazo[4,5-*c*]pyridine (11). Compound **9** (122 mg, 0.20 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and cooled at −15 °C. To the mixture was added the suspension of NBS (53 mg, 0.30 mmol) in dry CH_2Cl_2 (2 mL), and the resulting mixture was stirred for 30 min. After addition of cyclohexene (20 μL), the mixture was concentrated in vacuo, and the residue was dissolved in AcOEt, which was washed with H_2O, followed by saturated brine. The separated organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by a silica gel column (1.7 × 9 cm), eluted with 25−50% AcOEt in hexane, to give **11** (102 mg, 74%) as a yellow solid: FAB-MS *m*/*z* 687, 689 (MH^+); ^{1}H NMR ($CDCl_3$) 8.26 (s, 1 H), 7.90 (s, 1 H), 6.94 (d, 1 H, J = 7.1 Hz), 5.16 (br s, 2 H), 4.36 (dd, 1 H, J = 7.1, 4.4 Hz), 4.18 (d, 1 H, J = 4.4 Hz), 4.10 (dd, 1 H, J = 2.7, 2.2 Hz), 3.89 (dd, 1 H, J = 2.7, 11.5 Hz), 3.79 (dd, 1 H, J = 2.2, 11.5 Hz), 0.98, 0.95, 0.73 (each s, each 9 H), 0.18, 0.17, 0.12, 0.11, −0.13, −0.44 (each s, each 3 H). Used immediately in the next stage.

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4-Amino-7-iodo-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridine (12). A mixture of **9** (608 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol) in dry DMF (10 mL) was stirred for 11 h at room temperature under shading. After addition of cyclohexene (0.1 mL), the mixture was concentrated in vacuo, and the residue was dissolved in AcOEt, which was washed with H_2O, followed by saturated brine. The separated organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by a silica gel column (3.2 × 12 cm), eluted with 25−50% AcOEt in hexane, to give **12** (524 mg, 71%) as a yellow solid: MS *m*/*z* 734 (M^+); ^{1}H NMR ($CDCl_3$) 8.23 (s, 1 H), 8.10 (s, 1 H), 7.10 (d, 1 H, *J* = 7.7 Hz), 5.14 (br s, 2 H), 4.42 (dd, 1 H, *J* = 7.7, 4.4 Hz), 4.17 (d, 1 H, *J* = 4.4 Hz), 4.10 (dd, 1 H, *J* = 2.8, 2.2 Hz), 3.88 (dd, 1 H, *J* = 2.8, 11.5 Hz), 3.78 (dd, 1 H, *J* = 2.2, 11.5 Hz), 0.98, 0.97, 0.72 (each s, each 9 H), 0.17, 0.16, 0.13, 0.11, −0.13, −0.43 (each s, each 3 H). Used immediately in the next stage.

4-Amino-7-bromo-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridine (3-Bromo-3-deazaadenosine, 16). A THF solution of TBAF (1 M, 3.1 mL, 3.1 mmol) was added to a solution of **11** (540 mg, 0.79 mmol) in dry THF (10 mL) at 0 °C. The mixture was stirred for 1 h at room temperature and concentrated in vacuo. The residue was purified by a silica gel column (3.2 × 9 cm), eluted with 5−30% EtOH in $CHCl_3$, to give **12** (250 mg, 92%, crystallized from EtOH−H_2O): mp 224−227 °C dec; FAB-MS *m*/*z* 345, 347 (MH^+); UV λ_{max} (H_2O) 272 nm (ε 11 700); UV λ_{max} (0.5 N HCl) 270 nm (ε 11 900); UV λ_{max} (0.5 N NaOH) 272 nm (ε 12 900). Anal. Calcd for $C_{11}H_{13}BrN_4O_4$: C, 38.28; H, 3.80; N, 16.23. Found: C, 38.31; H, 3.76; N, 16.17.

4-Amino-7-iodo-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridine (3-Deaza-3-iodoadenosine, 17). In the same manner as for **16**, the reaction of **12** (524 mg, 0.71 mmol) with TBAF (1 M THF solution, 2.9 mL, 2.9 mmol) gave **17** (228 mg, 82%, crystallized from MeOH−H_2O): mp 213-215 °C dec; FAB-MS *m*/*z* 393 (MH^+); UV λ_{max} (H_2O) 273 nm (ε 12 600); UV λ_{max} (0.5 N HCl) 271 nm (ε 12 100); UV λ_{max} (0.5 N NaOH) 273 nm (ε 13 200). Anal. Calcd for $C_{11}H_{13}IN_4O_4$: C, 33.69; H, 3.34; N, 14.29. Found: C, 33.97; H, 3.31; N, 14.24.

4-Acetamido-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridine (13). A mixture of **9** (500 mg, 0.82 mmol), Et_3N (0.45 mL, 3.3 mmol), DMAP (10 mg), and Ac_2O (0.3 mL, 3.3 mmol) in dry CH_3CN (10 mL) was stirred for 20 h at room temperature, and EtOH (2 mL) was added to the mixture to decompose an excess of Ac_2O. The mixture was concentrated in vacuo, the residue (mono- and diacetylated compounds) was dissolved in methanolic ammonia (saturated at 0 °C, 10 mL), and the mixture was kept for 20 min at room temperature. The solvent was removed in vacuo, and the residue was purified by a silica gel column (3.2 × 8 cm), eluted with 0−6% EtOH in $CHCl_3$, to give **13** (501 mg, 94%) as a bright yellow foam: MS *m*/*z* 650 (M^+); ^{1}H NMR ($CDCl_3$) 8.44 (br s, 1 H), 8.15 (d, 1 H, *J* = 6.0 Hz), 8.10 (s, 1 H), 7.42 (d, 1 H, *J* = 6.0 Hz), 5.83 (d, 1 H, *J* = 7.7 Hz), 4.38 (dd, 1 H, *J* = 7.7, 5.0 Hz), 4.20 (d, 1 H, *J* = 5.0 Hz), 4.15 (t, 1 H, *J* = 2.2 Hz), 3.96 (dd, 1 H, *J* = 2.2, 11.5 Hz), 3.84 (dd, 1 H, *J* = 2.2, 11.5 Hz), 2.52 (br s, 3 H), 0.99, 0.95, 0.73 (each s, each 9 H), 0.20, 0.17, 0.13, 0.11, −0.14, −0.63 (each s, each 3 H). Used immediately in the next stage.

4-Acetamido-7-chloro-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridine (14). A mixture of **13** (314 mg, 0.48 mmol) and NCS (321 mg, 2.4 mmol) in dry CH_2Cl_2 (15 mL) was stirred at room temperature. After 27 h, NCS (321 mg, 2.4 mmol) was further added to the mixture, which was stirred for an additional 18 h. After addition of cyclohexene (0.5 mL), the mixture was concentrated in vacuo. Diethyl ether (10 mL) was added to the residue, and an insoluble material was removed by filtration. The filtrate was concentrated in vacuo, and the residue was dissolved in AcOEt, which was washed with H_2O, followed by saturated brine. The separated organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by a silica gel column (2.7 × 13 cm), eluted with 25−50% AcOEt in hexane, to give **14** (248 mg, 75%) as a white solid: FAB-MS *m*/*z* 685, 687 (MH^+); ^{1}H NMR ($CDCl_3$) 8.55 (br s, 1 H), 8.43 (s, 1 H), 8.11 (s, 1 H), 6.75 (d, 1 H, *J* = 7.1 Hz), 4.34 (dd, 1 H, *J* = 7.1, 4.4 Hz), 4.19 (br d, 1 H), 4.12 (br s, 1 H), 3.93 (dd, 1 H, *J* = 2.8, 11.5 Hz), 3.80 (dd, 1 H, *J* = 1.7, 11.5 Hz), 2.52 (s, 3 H), 0.99, 0.95, 0.73 (each s, each 9 H), 0.18, 0.17, 0.13, 0.11, −0.11, −0.49 (each s, each 3 H). Used immediately in the next stage.

4-Amino-7-chloro-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridine (3-Chloro-3-deazaadenosine, 15). A solution of **14** (430 mg, 0.63 mmol) in methanolic ammonia (saturated at 0 °C, 25 mL) was heated for 70 h at 50 °C in a steel container. The solvent was removed in vacuo, and the residue was purified by a short silica gel column (3.2 × 5 cm) to remove acetamide, eluted with 33−50% AcOEt in hexane. The eluates were concentrated to dryness in vacuo to give **10**. A THF solution of TBAF (1 M, 2.3 mL, 2.3 mmol) was added to a solution of **10** in dry THF (10 mL) at 0 °C. The mixture was stirred for 1 h at room temperature and concentrated in vacuo. The residue was purified by a silica gel column (2.7 × 11 cm), eluted with 5−30% EtOH in $CHCl_3$, to give **15** (128 mg, 68%, crystallized from EtOH−H_2O): mp 225−228 °C dec; FAB-MS *m*/*z* 301, 303 (MH^+); UV λ_{max} (H_2O) 270 nm (ε 11 400); UV λ_{max} (0.5 N HCl) 269 nm (ε 12 400); UV λ_{max} (0.5 N NaOH) 270 nm (ε 11 900). Anal. Calcd for $C_{11}H_{13}ClN_4O_4 \cdot H_2O$: C, 41.45; H, 4.74; N, 17.58. Found: C, 41.58; H, 4.73; N, 17.32.

6-Acetamido-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (19). A solution of **18**[13] (842 mg, 1.35 mmol) in dry pyridine (10 mL) containing Ac_2O (0.64 mL, 6.75 mmol) was stirred overnight at room temperature. To the mixture was added methanolic ammonia (saturated at 0 °C, 10 mL), and the whole was kept for 5 min at room temperature. The solvent was removed in vacuo, and the residue was dissolved in $CHCl_3$, which was washed by H_2O, followed by saturated brine. The separated organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by a silica gel column (3.2 × 12 cm), eluted with 0−8% EtOH in $CHCl_3$, to give **19** (811 mg, 90%) as a pale yellow foam: MS *m*/*z* 666 (M^+); ^{1}H NMR ($CDCl_3$) 11.73 (br s, 1 H), 10.63 (br s, 1 H), 8.14 (s, 1 H), 7.58 (s, 1 H), 5.77 (d, 1 H, *J* = 5.5 Hz), 4.27 (m, 2 H), 4.14 (br s, 1 H), 3.99−3.80 (m, 2 H), 2.48 (s, 3 H), 0.96, 0.95, 0.94 (each s, each 9 H), 0.15, 0.14, −0.05, −0.28 (each s, each 3 H), 0.11 (s, 6 H). Used immediately in the next stage.

6-Acetamido-7-chloro-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (20). In a manner similar to that for **3**, the reaction of **19** (700 mg, 1.05 mmol) with NCS (280 mg, 2.1 mmol) in dry CH_2Cl_2 (20 mL) to give **20** (654 mg, 89%) as a pale yellow foam: FAB-MS *m*/*z* 701, 703 (MH^+); ^{1}H NMR ($CDCl_3$) 12.00 (br s, 1 H), 8.21 (s, 1 H), 8.04 (br s, 1 H), 6.61 (d, 1 H, *J* = 7.1 Hz), 4.32 (dd, 1 H, *J* = 7.1, 4.4 Hz), 4.16 (dd, 1 H, *J* = 4.4, 3.8 Hz), 4.09 (ddd, 1 H, *J* = 3.8, 2.7, 2.2 Hz), 3.89 (dd, 1 H, *J* = 2.7, 11.5 Hz), 3.78 (dd, 1 H, *J* = 2.2, 11.5 Hz), 2.29 (s, 3 H), 0.96, 0.93, 0.75 (each s, each 9 H), 0.16, 0.14, 0.11, 0.10, −0.09, −0.39 (each s, each 3 H). Used immediately in the next stage.

6-Acetamido-7-bromo-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (21). In a manner similar to that for **4**, the reaction of **19** (623 mg, 0.94 mmol) with NBS (183 mg, 1.03 mmol) in dry CH_2Cl_2 at −20 °C gave **21** (548 mg, 79%) as a pale brown foam: FAB-MS *m*/*z* 745, 747 (MH^+); ^{1}H NMR ($CDCl_3$) 12.11 (br s, 1 H), 8.20 (s, 1 H), 8.00 (br s, 1 H), 6.81 (d, 1 H, *J* = 7.1 Hz), 4.36 (dd, 1 H, *J* = 7.1, 4.4 Hz), 4.15 (dd, 1 H, *J* = 4.4, 3.8 Hz), 4.08 (br s, 1 H), 3.87 (dd, 1 H, *J* = 2.8, 11.5 Hz), 3.77 (dd, 1 H, *J* = 1.7, 11.5 Hz), 2.30 (s, 3 H), 0.96, 0.94, 0.74 (each s, each 9 H), 0.16, 0.14, 0.12, 0.11, −0.10, −0.39 (each s, each 3 H). Used immediately in the next stage.

6-Acetamido-7-iodo-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (22). In the same manner as for **5**, the reaction of **19** (646 mg, 0.97 mmol) with NIS (327 mg, 1.46 mmol) gave **22** (548 mg, 79%) as a yellow foam: FAB-MS *m*/*z* 793 (MH^+); ^{1}H NMR ($CDCl_3$) 12.28 (br s, 1 H), 8.18 (s, 1 H), 8.13 (br s, 1 H), 7.04 (d, 1 H, *J* = 7.7 Hz), 4.42 (dd, 1 H, *J* = 7.7, 4.4 Hz), 4.15 (d, 1 H, *J* = 4.4 Hz), 4.09 (br s, 1 H), 3.85 (dd, 1 H, *J* = 2.7, 11.5 Hz), 3.76 (dd,

1 H, J = 2.2, 11.5 Hz), 2.30 (s, 3 H), 0.95 (s, 18 H), 0.73 (s, 9 H), 0.15, 0.14, 0.13, 0.11, −0.11, −0.37 (each s, each 3 H). Used immediately in the next stage.

6-Amino-7-chloro-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (23). A solution of **20** (646 mg, 0.92 mmol) in methanolic ammonia (saturated at 0 °C, 25 mL) was kept for 2 days at room temperature. The solvent was removed in vacuo, and the residue was purified by a silica gel column (3.2 × 12 cm), eluted with 0−8% EtOH in $CHCl_3$, to give **23** (464 mg, 76%) as a white solid: FAB-MS m/z 659 (MH^+); ^{1}H NMR ($CDCl_3$) 13.03 (br s, 1 H), 8.02 (s, 1 H), 6.68 (d, 1 H, J = 7.1 Hz), 5.36 (br s, 2 H), 4.30 (dd, 1 H, J = 7.1, 4.4 Hz), 4.16 (d, 1 H, J = 4.4 Hz), 4.07 (br s, 1 H), 3.88 (dd, 1 H, J = 2.7, 11.5 Hz), 3.78 (dd, 1 H, J = 2.2, 11.5 Hz), 0.96, 0.94, 0.77 (each s, each 9 H), 0.16, 0.14, 0.12, 0.10, −0.09, −0.36 (each s, each 3 H). Used immediately in the next stage.

6-Amino-7-bromo-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (24). In the same manner as above, the reaction of **21** (548 mg, 0.74 mmol) with methanolic ammonia (saturated at 0 °C, 25 mL) gave **24** (424 mg, 82%) as a brown foam: FAB-MS m/z 703, 705 (MH^+); ^{1}H NMR ($CDCl_3$) 13.13 (br s, 1 H), 8.01 (s, 1 H), 6.88 (d, 1 H, J = 7.1 Hz), 5.41 (br s, 2 H), 4.33 (dd, 1 H, J = 7.1, 4.4 Hz), 4.16 (d, 1 H, J = 4.4 Hz), 4.07 (br s, 1 H), 3.86 (dd, 1 H, J = 2.8, 11.5 Hz), 3.77 (br d, 1 H, J = 11.5 Hz), 0.96, 0.95, 0.78 (each s, each 9 H), 0.15, 0.14, 0.12, 0.10, −0.10, −0.35 (each s, each 3 H). Used immediately in the next stage.

6-Amino-7-chloro-1-*β*-D-ribofuranosylimidazo[4,5-*c*]-pyridin-4(5*H*)-one (3-Chloro-3-deazaguanosine, 25). A THF solution of TBAF (1 M, 2.7 mL, 2.7 mmol) was added to a solution of **23** (450 mg, 0.68 mmol) in dry THF (10 mL) at 0 °C. The mixture was stirred for 40 min at room temperature and neutralized with AcOH. The solvent was removed in vacuo, and a mixture of H_2O−EtOH (10 mL−10 mL) was added to the resulting white solid. The suspension was heated in a water bath and then cooled to room temperature. The precipitate was collected and washed with EtOH to give **25** (182 mg, 84%) as a white powder: FAB-MS m/z 317 (MH^+); UV λ_{max} (H_2O) 275 nm (ϵ 10 000), 310 nm (ϵ 8400); λ_{max} (0.5 N HCl) 293 nm (ϵ 10 500), 320 (sh) nm (ϵ 7400); λ_{max} (0.5 N NaOH) 287 nm (ϵ 11 500). Anal. Calcd for $C_{11}H_{13}ClN_4O_5 \cdot {}^1/_2$EtOH: C, 42.42; H, 4.75; N, 16.49. Found: C, 42.11; H, 4.42; N, 16.66.

6-Amino-7-bromo-1-*β*-D-ribofuranosylimidazo[4,5-*c*]-pyridin-4(5*H*)-one (3-Bromo-3-deazaguanosine, 26). In the same manner as for **25**, the reaction of **24** (424 mg, 0.60 mmol) with TBAF (1 M THF solution, 2.4 mL, 2.4 mmol) gave **26** (136 mg, 63%) as a pale blue powder: FAB-MS m/z 361, 363 (MH^+); UV λ_{max} (H_2O) 275 nm (ϵ 9900), 311 nm (ϵ 8400); λ_{max} (0.5 N HCl) 294 nm (ϵ 10 100), 317 (sh) nm (ϵ 7400); λ_{max} (0.5 N NaOH) 285 nm (ϵ 11 200). Anal. Calcd for $C_{11}H_{13}BrN_4O_5$: C, 36.58; H, 3.63; N, 15.51. Found: C, 36.58; H, 3.72; N, 15.13.

5-Amino-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)imidazole-4-carboxamide (28). A mixture of **27** (9.0 g, 30 mmol), imidazole (4.9 g, 72 mmol), and *tert*-butyldimethylsilyl chloride (5.43 g, 36 mmol) in DMF (120 mL) was stirred for 3.5 h at room temperature. The reaction was quenched by addition of EtOH, and the mixture was concentrated in vacuo. The residue was partitioned between AcOEt and H_2O, and the organic layer was washed with H_2O, followed by saturated brine. The separated organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by a silica gel column (6.0 × 8 cm), eluted with hexane/AcOEt (1:1−0:1) to give **28** (12.5 g, quant as a white foam): MS m/z 412 (M^+); ^{1}H NMR ($CDCl_3$) 6.99 (s, 1 H), 6.46 (br s, 1 H), 5.56 (d, 1 H, J = 3.3 Hz), 5.44 (br s, 2 H), 5.13 (br s, 1 H), 4.91 (m, 2 H), 4.16 (m, 1 H), 3.93 (dd, 1 H, J = 2.0, 11.9 Hz), 3.82 (dd, 1 H, J = 1.9, 11.9 Hz), 1.56, 1.34 (each s, each 3 H), 0.88 (s, 9 H), 0.09, 0.07 (each s, each 3 H). Anal. Calcd for $C_{18}H_{32}N_4O_5Si$: C, 52.40; H, 7.82; N, 13.58. Found: C, 52.12; H, 7.81; N, 13.25.

5-Iodo-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)imidazole-4-carboxamide (29). A solution of isoamyl nitrite (5 mL) in CH_2I_2 (50 mL) was heated at 100 °C, and a solution of **28** (3.51 g, 8.5 mmol) in $CHCl_3$ (5 mL) was added dropwise to the preheated solution. After being stirred for 15 min at 100 °C, the reaction mixture was absorbed onto a silica gel column (5.0 × 20 cm), which was eluted with 0−4% EtOH in $CHCl_3$ to give **29** (3.07 g, 69%, crystallized from hexane−AcOEt): mp 159−160 °C; MS m/z 523 (M^+); ^{1}H NMR ($CDCl_3$) 8.01 (s, 1 H), 7.00 (br s, 1 H), 5.93 (d, 1 H, J = 3.3 Hz), 5.36 (br s, 1 H), 4.82 (dd, 1 H, J = 3.3, 5.9 Hz), 4.71 (dd, 1 H, J = 5.9, 2.6 Hz), 4.35 (m, 1 H), 3.91 (dd, 1 H, J = 1.9, 11.2 Hz), 3.80 (dd, 1 H, J = 2.6, 11.2 Hz), 1.62, 1.36 (each s, each 3 H), 0.88 (s, 9 H), 0.08 (s, 6 H). Anal. Calcd for $C_{18}H_{30}IN_3O_5Si$: C, 41.30; H, 5.78; N, 8.02. Found: C, 41.56; H, 5.57; N, 7.80.

5-Iodo-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)imidazole-4-carboxamide (31). A solution of **30**[12] (24.42 g, 49.3 mmol) in methanolic ammonia (saturated at 0 °C, 150 mL) was kept overnight at room temperature. The solvent was removed in vacuo, and EtOH was added to the residue. The suspension was heated in a water bath and then cooled to room temperature. The precipitate was collected and washed with EtOH. The resulting yellow solid was silylated in the same manner as for **28** to give **31** (22.32 g, 64% as a yellow foam): MS m/z 711 (M^+); ^{1}H NMR ($CDCl_3$) 8.10 (s, 1 H), 6.99 (br s, 1 H), 5.79 (d, 1 H, J = 5.9 Hz), 5.31 (br s, 1 H), 4.29 (dd, 1 H, J = 5.9, 3.6 Hz), 4.26 (m, 1 H), 4.18 (m, 1 H), 3.88 (dd, 1 H, J = 2.6, 11.2 Hz), 3.75 (dd, 1 H, J = 2.0, 11.2 Hz), 0.94, 0.91, 0.83 (each s, each 9 H), 0.12, 0.09, 0.08, −0.02, −0.05, −0.20 (each s, each 3 H). Anal. Calcd for $C_{27}H_{54}IN_3O_5Si_3$: C, 45.55; H, 7.65; N, 5.90. Found: C, 45.80; H, 7.46; N, 5.82.

5(*E*)-(2-Carbomethoxyvinyl)-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)imidazole-4-carboxamide (32). A mixture of **29** (1.57 g, 3.0 mmol), bis(benzonitrile)palladium dichloride (86 mg, 0.23 mmol), methyl acrylate (0.54 mL, 6.0 mmol), and Et_3N (0.63 mL, 4.5 mmol) in dry CH_3CN (10 mL) in a sealed glass tube was heated for 14 h at 100 °C. The reaction mixture was filtered through a Celite pad and washed with EtOH. The combined filtrate and washings were concentrated in vacuo, and the residue was purified by a silica gel column (3.6 × 15 cm), eluted with hexane/AcOEt (2:1−1:2), to give **32** (1.15 g, 80% as a yellow foam): EI-MS m/z 481 (M^+); ^{1}H NMR ($CDCl_3$) 8.16, 6.93 (each d, each 1 H, J = 16.0 Hz), 7.93 (s, 1 H), 7.12, 5.40 (each br s, each 1 H), 5.93 (d, 1 H, J = 3.2 Hz), 4.79 (m, 2 H), 4.40 (m. 1 H), 3.87 (m, 2 H), 3.80 (s, 3 H), 1.64, 1.38 (each s, each 3 H), 0.89 (s, 9 H), 0.10, 0.01 (each s, each 3 H). Used immediately in the next stage.

5(*E*)-(2-Carbomethoxyvinyl)-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)imidazole-4-carboxamide (33). In the same manner as described for **32**, **31** (2.13 g, 3.0 mmol) was treated with methyl acrylate to give **33** (1.78 g, 89% as a yellow foam): EI-MS m/z 669 (M^+); ^{1}H NMR ($CDCl_3$) 8.12, 6.95 (each d, each 1 H, J = 16.4 Hz), 7.95 (s, 1 H), 7.12, 5.37 (each br s, each 1 H), 5.89 (d, 1 H, J = 7.1 Hz), 4.31 (dd, 1 H, J = 7.1, 4.4 Hz), 4.19 (dd, 1 H, J = 4.4, 1.2 Hz), 4.06 (ddd, 1 H, J = 1.2, 3.1, 2.4 Hz), 3.86 (dd, 1 H, J = 3.1, 11.4 Hz), 3.77 (dd, 1 H, J = 2.4, 11.4 Hz), 3.78 (s, 3 H), 0.96, 0.94, 0.80 (each s, each 9 H), 0.14 (s, 6 H), 0.12, 0.11, −0.04, −0.24 (each s, each 3 H). Used immediately in the next stage.

5-Formyl-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)imidazole-4-carboxamide (34). Ozonized oxygen was bubbled through a solution of **32** (4.53 g, 9.35 mmol) in MeOH (100 mL) at −78 °C. After 15 min, N_2 gas was bubbled through the solution to remove excess ozonized oxygen. Dimethyl sulfide (3.4 mL, 46.7 mmol) was added to the solution at −78 °C, and then the reaction mixture was allowed to warm to room temperature. The solvent was removed in vacuo, and the residue was purified by a silica gel column (6.0 × 10 cm), eluted with hexane/AcOEt (3:1−1:2), to give **34** (3.91 g, 98%, crystallized from hexane−AcOEt): mp 138−139 °C; EI-MS m/z 425 (M^+); ^{1}H NMR ($CDCl_3$) 10.65 (s, 1 H), 8.21 (s, 1 H), 7.20, 5.58 (each br s, each 1 H), 6.57 (d, 1 H, J = 1.7 Hz), 4.81 (dd, 1 H, J = 1.7 Hz), 4.61 (m, 1 H), 4.38 (m. 1 H), 3.91 (m, 2 H), 1.63, 1.37 (each s, each 3 H), 0.90 (s,

9 H), 0.12, 0.12 (each s, each 3 H). Anal. Calcd for $C_{19}H_{31}N_3O_6Si$: C, 53.63; H, 7.34; N, 9.87. Found: C, 53.60; H, 7.46; N, 9.93.

5-Formyl-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carboxamide (35). A solution of osmium tetraoxide in *t*-BuOH (0.02 M, 26.0 mL, 0.52 mmol) was added dropwise to a solution of **33** (6.95 g, 10.4 mmol) in acetone−H_2O (9:1, 100 mL) containing *N*-methylmorpholine *N*-oxide (2.43 g, 20.7 mmol), and the whole was stirred for 4 days at room temperature. An aqueous solution of sodium periodate (9.10 g, 41.5 mmol in 25 mL of H_2O) was added to the mixture, which was stirred for an additional 23 h and then filtered. The filtrate was reduced to a half volume in vacuo, diluted with 1 M aqueous sodium thiosulfate (200 mL), and extracted with AcOEt (3 × 70 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by a silica gel column (5.0 × 12 cm), eluted with hexane/AcOEt (10:1−3:1), to give **35** (5.39 g, 85% as a white foam): EI-MS *m*/*z* 613 (M^+); ^{1}H NMR ($CDCl_3$) 10.63 (s, 1 H), 8.54 (s, 1 H), 7.25, 5.56 (each br s, each 1 H), 6.31 (d, 1 H, *J* = 2.3 Hz), 4.22 (m, 1 H), 4.16 (m, 1 H), 4.11 (m, 1 H), 4.09 (dd, 1 H, *J* = 2.2, 12.1 Hz), 3.83 (dd, 1 H, *J* = 1.5, 11.8 Hz), 0.98, 0.91, 0.90 (each s, each 9 H), 0.18, 0.16, 0.11, 0.08, 0.06, −0.03 (each s, each 1H). Anal. Calcd for $C_{28}H_{55}N_3O_6Si_3$: C, 54.77; H, 9.03; N, 6.84. Found: C, 54.59; H, 8.89; N, 6.66.

5-(1-Hydroxy-2-propenyl)-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamide (36). A THF solution of vinylmagnesium bromide (1 M, 27.5 mL, 27.5 mmol) was added dropwise over 30 min to a solution of **34** (3.9 g, 9.2 mmol) in dry THF (100 mL) at −40 °C. After the mixture was stirred for 3.5 h at the same temperature, the reaction was quenched by addition of 1 M aqueous NH_4Cl (55 mL) and then allowed to warm at room temperature. The mixture was extracted with AcOEt (100 mL), and the organic layer was washed with H_2O, followed by brine. The layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by a silica gel column (4.8 × 12 cm), eluted with hexane/AcOEt (2:1−1:3), to give **36** (3.85 g, 93%, crystallized from hexane−AcOEt): mp 160−161 °C and 165−166 °C; EI-MS *m*/*z* 453 (M^+); ^{1}H NMR ($CDCl_3$) 7.74 (s, 1 H), 7.37 (d, 4/9 H, *J* = 11.0 Hz), 7.02 (d, 5/9 H, *J* = 11.0 Hz), 7.24, 5.54 (each br s, each 1 H), 6.17−6.00 (m, 1 H), 5.82 (d, 5/9 H, *J* = 3.3 Hz), 5.74 (d, 4/9 H, *J* = 3.3 Hz), 5.41−5.24 (m, 1 H), 5.22−5.12 (m, 2 H), 4.82 (dd, 4/9 H, *J* = 6.0, 3.3 Hz), 4.80 (dd, 5/9 H, *J* = 6.0, 2.2 Hz), 4.75 (dd, 4/9 H, *J* = 3.3, 6.0 Hz), 4.64 (dd, 5/9 H, *J* = 3.3, 6.0 Hz), 4.42 (ddd, 5/9 H, *J* = 2.2, 2.7, 2.8 Hz), 4.42 (ddd, 4/9 H, *J* = 2.2, 2.7, 2.8 Hz), 3.92 (dd, 5/9 H, *J* = 2.7, 11.5 Hz), 3.90 (dd, 4/9 H, *J* = 2.7, 11.5 Hz), 3.80 (dd, 5/9 H, *J* = 2.7, 11.5 Hz), 3.80 (dd, 4/9 H, *J* = 2.7, 11.5 Hz), 1.59, 1.35 (each s, each 15/9 H), 1.59, 1.36 (each s, each 12/9 H), 0.87 (s, 36/9 H), 0.86 (s, 45/9 H), 0.08−0.07 (s × 4, 6 H). Anal. Calcd for $C_{21}H_{35}N_3O_6Si$: C, 55.61; H, 7.78; N, 9.26. Found: C, 55.36; H, 7.72; N, 9.22.

5-(1-Fluoro-2-propenyl)-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamide (39) and 5(*E*)-(3-fluoro-1-propenyl)-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamide (41). A solution of **36** (820 mg, 1.81 mmol) in dry CH_2Cl_2 was added dropwise over 40 min to a solution of DAST (0.5 mL, 3.6 mmol) in dry CH_2Cl_2 at −15 °C, and the whole was stirred for 1 h at that temperature. To this mixture was added 1 M aqueous $NaHCO_3$ (5 mL), and the whole was stirred for 20 min and then allowed to warm at room temperature. The mixture was diluted with AcOEt (100 mL), and the organic layer was washed with H_2O, followed by brine. The layer was dried (Na_2SO_4) and concentrated in vacuo, and the residue was purified by a silica gel column (3.0 × 12 cm), eluted with hexane/AcOEt (2:1−2:3), to give **39** (307 mg, 37% as a pale yellow foam) and **41** (255 mg, 31% as a yellow foam).

Physical data for compound **39**: EI-MS *m*/*z* 455 (M^+); UV λ_{max} (MeOH) 240 nm; ^{1}H NMR ($CDCl_3$) 8.00 (s, 3/5 H), 7.93 (s, 2/5 H), 7.37−7.16 (m, 1 H, *J* = 40.0 Hz), 7.10, 5.50 (each br s, each 1 H), 6.23−6.15 (m, 1 H), 6.12 (d, 2/5 H, *J* = 2.2 Hz), 6.08 (d, 3/5 H, *J* = 2.2 Hz), 5.51−5.32 (m, 1 H), 4.88−4.80 (m, 1 H), 4.71−4.61 (m, 1 H), 4.30 (dt, 2/5 H), 4.24 (dt, 3/5 H), 3.98 (dd, 3/5 H, *J* = 2.2, 11.5 Hz), 3.95 (dd, 2/5 H, *J* = 2.2, 11.5 Hz), 3.84 (dd, 3/5 H, *J* = 2.2, 11.5 Hz), 3.83 (dd, 2/5 H, *J* = 2.2, 11.5 Hz), 1.58, 1.35 (each s, each 3 H), 0.94 (s, 9 H), 0.14, 0.13 (each s, each 3 H).

Physical data for compound **41**: EI-MS *m*/*z* 455 (M^+); UV λ_{max} (MeOH) 271 nm; ^{1}H NMR ($CDCl_3$) 7.87 (s, 1 H), 7.16 (ddd, 1 H, *J* = 16.5, 1.7, 4.4 Hz), 7.15, 5.31 (each br s, each 1 H), 6.74 (ddt, 1 H, *J* = 16.5, 14.3, 5.5 Hz), 5.91 (d, 1 H, *J* = 3.8 Hz), 5.08 (ddd, 1 H, *J* = 1.7, 5.5, 47.3 Hz), 4.86 (dd, 1 H, *J* = 3.8, 6.0 Hz), 4.75 (dd, 1 H, *J* = 6.0, 3.3 Hz), 4.37 (dt, 1 H, *J* = 3.3, 2.7 Hz), 3.92 (dd, 1 H, *J* = 2.7, 11.5 Hz), 3.82 (dd, 1 H, *J* = 2.7, 11.5 Hz), 1.62, 1.38 (each s, each 3 H), 0.91 (s, 9 H), 0.11, 0.10 (each s, each 3 H).

7-Fluoro-6-hydroxy-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-6,7-dihydroimidazo[4,5-*c*]pyridin-4(5*H*)-one (44). Method A. An aqueous solution of $KMnO_4$ (440 mg, 2.78 mmol, dissolved in 20 mL of H_2O) was added dropwise over 1 h to a solution of **39** (840 mg, 1.85 mmol) and 18-crown-6 (75 mg, 0.28 mmol) in dry THF (30 mL) at 0 °C. After being stirred for 1 h, the reaction mixture was filtered through a Celite pad, which was washed with EtOH. The combined filtrate and washings were concentrated to dryness in vacuo, and the residue was partitioned between $CHCl_3$ and H_2O. The aqueous layer was extracted with $CHCl_3$ three times. The combined organic layers were concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (30 mL). To the solution was added an aqueous solution of $NaIO_4$ (1.19 g, 5.55 mmol, dissolved in 10 mL of H_2O), and the mixture was stirred for 17 h at room temperature. The mixture was diluted with $CHCl_3$ (40 mL), and the organic layer was washed with H_2O. The solvent was concentrated to half of its original volume, and 5% aqueous Na_2CO_3 (20 mL) was added to the solution, which was then heated for 1 h at 80 °C. The reaction mixture was diluted with $CHCl_3$, and the separated organic layer was washed with H_2O, followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo, and the residue was purified by a silica gel column (3.5 × 8 cm), eluted with 0−6% EtOH in $CHCl_3$, to give **44** (624 mg, 74% as a white foam): FAB-MS *m*/*z* 458 (MH^+); UV λ_{max} (MeOH) 246 nm; ^{1}H NMR ($CDCl_3$) 8.38 (br d, 2/3 H, *J* = 2.9 Hz), 8.26 (br d, 1/3 H, *J* = 3.0 Hz), 7.94 (d, 1/3 H), 7.88 (d, 2/3 H), 6.87 (m, 1 H), 5.87 (d, 1/3 H, *J* = 2.7 Hz), 5.84 (d, 2/3 H, *J* = 3.5 Hz), 5.80 (d, 2/3 H, *J* = 50.7 Hz), 5.66 (d, 1/3 H, *J* = 50.2 Hz), 5.51 (d, 2/3 H, *J* = 1.2 Hz), 5.48 (d, 1/3 H, *J* = 1.1 Hz), 4.89−4.78 (m, 2 H), 4.51 (m, 1/3 H,), 4.37 (m, 2/3 H), 3.93−3.80 (m, 2 H), 1.61 and 1.37 (each s, each 6/3 H), 1.60, 1.38 (each s, each 3/3 H), 0.88 (s, 18/3 H), 0.82 (s, 9/3 H), 0.12, 0.03 (each s, each 3/3 H), 0.08, 0.07 (each s, each 6/3 H). Anal. Calcd for $C_{20}H_{32}FN_3O_6Si\cdot{}^1/_4EtOH$: C, 52.49; H, 7.20; N, 8.96. Found: C, 52.51; H, 7.16; N, 8.84.

Method B. A suspension of **40** (450 mg, 1.0 mmol) and Lindlar catalyst (60 mg) in EtOH (30 mL) was shaken under hydrogen (50 psi) on a Parr hydrogenation apparatus for 16 h at room temperature. The reaction mixture was filtered through a Celite pad, which was washed with EtOH. The filtrate and washings were concentrated in vacuo to give **39**. Compound **39** was successively converted as above to give **44** (320 mg, 70% from **40**).

7-Fluoro-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (45). A mixture of **44** (430 mg, 0.94 mmol), Ac_2O (0.13 mL, 1.4 mmol), and DMAP (6 mg, 0.05 mmol) in dry pyridine (20 mL) was stirred for 1 h at room temperature. The reaction was quenched by addition of EtOH (1 mL), and then the mixture was heated for 30 min at 100 °C. The solvent was removed in vacuo, and the residue was dissolved in $CHCl_3$, which was washed with H_2O, followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo, and the residue was purified by a silica gel column (3.0 × 9 cm), eluted with 0−6% EtOH in $CHCl_3$, to give **45** (380 mg, 92% as a white foam): FAB-MS *m*/*z* 440 (MH^+); UV λ_{max} (MeOH) 259 nm; λ_{max} (H^+) 260 nm; λ_{max} (OH^-) 268 nm; ^{1}H NMR ($CDCl_3$) 12.93 (br s, 1 H), 8.23 (s, 1 H), 7.29 (d, 1 H, *J* = 5.2 Hz), 6.20 (d, 1 H, *J*

= 3.0 Hz), 4.87 (dd, 1 H, *J* = 6.0, 2.6 Hz), 4.81 (dd, 1 H, *J* = 3.0, 6.0 Hz), 4.42 (dt, 1 H, *J* = 2.6, 3.0 Hz), 3.96 (dd, 1 H, *J* = 2.6, 11.4 Hz), 3.86 (dd, 1 H, *J* = 3.0, 11.4 Hz), 1.63, 1.38 (each s, each 3 H), 0.91 (s, 9 H), 0.12, 0.11 (each s, each 3 H). Anal. Calcd for $C_{20}H_{30}FN_3O_5Si$: C, 54.65; H, 6.88; N, 9.56. Found: C, 54.49; H, 6.78; N, 9.38.

5-(1-Hydroxypropynyl)-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)imidazole-4-carboxamide (38). A hexane solution of BuLi (1.66 M, 15.0 mL, 24.8 mmol) was added at a rate that the temperature did not exceed −65 °C to a solution of (trimethylsilyl)acetylene (3.6 mL, 25.4 mmol) in dry THF (40 mL). After the mixture was stirred for 30 min, a solution of **34** (2.7 g, 6.35 mmol) in dry THF (20 mL) was added dropwise over 1 h, and the whole was stirred for an additional 1.5 h at −78 °C. The reaction was quenched by addition of 1 M aqueous NH_4Cl (40 mL) and then allowed to warm at room temperature. The mixture was extracted with AcOEt (150 mL), and the organic layer was washed with H_2O, followed by brine. The layer was dried (Na_2SO_4) and concentrated in vacuo. To the residue was added methanolic ammonia (saturated at 0 °C, 100 mL), and the mixture was kept for 3 h at room temperature. The solvent was removed in vacuo, and the residue was purified by a silica gel column (4.6 × 10 cm), eluted with hexane/AcOEt (3:1−2:3), to give **38** (2.57 g, 90% as a white foam): EI-MS *m*/*z* 451 (M^+); ^{1}H NMR ($CDCl_3$) 7.79 (d, 4/7 H, *J* = 10.4 Hz), 7.71 (s, 4/7 H), 7.71 (s, 3/7 H), 7.28 (d, 3/7 H, *J* = 10.7 Hz), 7.20, 5.62 (each br s, each 1 H), 5.90 (s, 3/7 H), 5.85 (d, 4/7 H, *J* = 3.3 Hz), 5.76 (dd, 4/7 H, *J* = 10.4, 2.2 Hz), 5.72 (dd, 3/7 H, *J* = 10.7, 2.2 Hz), 4.84−4.82 (m, 10/7 H), 4.74 (dd, 4/7 H, *J* = 3.3, 6.0 Hz), 4.47 (m, 3/7 H), 4.42 (m, 4/7 H), 3.93 (dd, 4/7 H, *J* = 2.8, 11.5 Hz), 3.91 (dd, 3/7 H, *J* = 2.4, 11.5 Hz), 3.82 (dd, 4/7 H, *J* = 2.2, 11.5 Hz), 3.80 (dd, 3/7 H, *J* = 2.8, 11.5 Hz), 2.54 (d, 4/7 H, *J* = 2.2 Hz), 2.52 (d, 3/7 H, *J* = 2.2 Hz), 1.61, 1.36 (each s, each 12/7 H), 1.61, 1.38 (each s, each 9/7 H), 0.88 (s, 36/7 H), 0.84 (s, 27/7 H), 0.09, 0.08 (each s, each 12/7 H), 0.07, 0.04 (each s, each 9/7 H). Used immediately in the next stage.

5-(1-Fluoropropynyl)-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)imidazole-4-carboxamide (40). A solution of **38** (2.56 g, 2.84 mmol) in dry CH_2Cl_2 was added dropwise over 1 h to a solution of DAST (1.50 mL, 11.4 mmol) in dry CH_2Cl_2 at −15 °C. The mixture was allowed to warm at room temperature and stirred for 30 min. To this mixture was added aqueous $NaHCO_3$ (1 M, 40 mL), and the whole was stirred for 20 min. The mixture was extracted with $CHCl_3$ (100 mL), and the organic layer was washed with H_2O, followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo, and the residue was purified by a silica gel column (4.0 × 10 cm), eluted with hexane/AcOEt (3:1−1:1), to give **40** (2.3 g, 89%, crystallized from hexane−AcOEt): mp 134−135 °C and 151−152 °C; FAB-MS *m*/*z* 454 (MH^+); ^{1}H NMR ($CDCl_3$) 8.07 (d, 3/5 H, *J* = 0.9 Hz), 8.03 (d, 2/5 H, *J* = 1.3 Hz), 7.53 (dd, 3/5 H, *J* = 44.2, 2.3 Hz), 7.50 (dd, 2/5 H, *J* = 44.2, 2.3 Hz), 7.12, 5.48 (each br s, each 1 H), 6.45 (d, 3/5 H, *J* = 2.8 Hz), 6.36 (d, 2/5 H, *J* = 2.6 Hz), 4.94 (dd, 2/5 H, *J* = 5.9, 3.8 Hz), 4.89−4.86 (m, 5/5 H), 4.66 (dd, 3/5 H, *J* = 2.8, 5.7 Hz), 4.34 (m, 3/5 H), 4.29 (m, 2/5 H), 4.02 (dd, 3/5 H, *J* = 2.1, 11.6 Hz), 3.97 (dd, 2/5 H, *J* = 2.2, 11.6 Hz), 3.87 (dd, 3/5 H, *J* = 2.5, 11.6 Hz), 3.86 (dd, 2/5 H, *J* = 2.3, 11.6 Hz), 2.91 (d, 2/5 H, *J* = 2.3 Hz), 2.90 (d, 3/5 H, *J* = 2.3 Hz), 1.61, 1.36 (each s, each 9/5 H), 1.60, 1.36 (each s, each 6/5 H), 0.95 (s, 27/5 H), 0.94 (s, 18/5 H), 0.14, 0.12 (each s, each 3 H). Anal. Calcd for $C_{21}H_{32}FN_3O_5Si$: C, 55.61; H, 7.11; N, 9.26. Found: C, 55.71; H, 7.13; N, 9.24.

7-Fluoro-1-*β*-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one (3-Deaza-3-fluoroinosine, 46). An aqueous TFA solution (75%, 10 mL) containing **45** (290 mg, 0.66 mmol) was stirred for 1 h at room temperature. The solvent was removed in vacuo and coevaporated with EtOH three times. The residue was purified by a silica gel column (2.2 × 6 cm), eluted with 0−30% EtOH in $CHCl_3$, to give **46** (196 mg, quant crystallized from MeOH−H_2O): mp >300 °C; FAB-MS *m*/*z* 286 (MH^+); UV λ_{max} (H_2O) 260 nm (ϵ 9000); λ_{max} (0.5 N HCl) 274 nm (ϵ 8800); λ_{max} (0.5 N NaOH) 267 nm (ϵ 9000). Anal. Calcd for $C_{11}H_{12}FN_3O_5 \cdot {}^3/_5MeOH$: C, 45.76; H, 4.77; N, 13.80. Found: C, 45.47; H, 4.65; N, 14.00.

5-Cyanofluoromethyl-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)imidazole-4-carboxamide (48). Sodium cyanide (2.82 g, 57.6 mmol) was added to a solution of **35** (3.53 g, 5.86 mmol) in a mixture of AcOEt (150 mL) and 1 M aqueous $NaHCO_3$ (150 mL), and the whole was vigorously stirred for 20 h at room temperature. The separated organic layer was washed with H_2O, followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give crude **47**. A solution of **47** in dry CH_2Cl_2 was added dropwise over 1 h to a solution of DAST (1.52 mL, 11.5 mmol) in dry CH_2Cl_2 at −15 °C. The mixture was allowed to warm at room temperature and stirred for 30 min. To this mixture was added aqueous $NaHCO_3$ (1 M, 40 mL), and the mixture was stirred for 20 min. The mixture was extracted with $CHCl_3$ (60 mL), and the organic layer was washed with H_2O, followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo, and the residue was purified by a silica gel column (4.0 × 10 cm), eluted with hexane/AcOEt (9:1−3:1), to give **48** (2.69 g, 73% as a pale yellow foam): FAB-MS *m*/*z* 643 (MH^+); UV λ_{max} (MeOH) 233 nm; ^{1}H NMR ($CDCl_3$) 8.20 (d, 3/5 H, *J* = 1.8 Hz), 7.95 (d, 2/5 H, *J* = 1.7 Hz), 7.74 (d, 2/5 H, *J* = 42.9 Hz), 7.69 (d, 3/5 H, *J* = 43.3 Hz), 7.13, 5.56 (each br s, each 1 H) 5.96 (d, 3/5 H, *J* = 5.2 Hz), 5.91 (d, 2/5 H, *J* = 6.6 Hz), 4.42 (dd, 1 H, *J* = 6.6, 4.3 Hz), 4.30 (dd, 1 H, *J* = 5.2, 4.1 Hz), 4.26−4.22 (m, 1 H), 4.14−4.11 (m, 1 H), 4.10−3.78 (m, 2 H), 0.98, 0.93, 0.84 (each s, each 27/5 H), 0.96, 0.94, 0.83 (each s, each 18/5 H), 0.17, 0.17, 0.14, 0.14, 0.13, 0.12, 0.11, 0.10, −0.02, −0.03, −0.15, −0.16 (each s, total 18 H). Anal. Calcd for $C_{29}H_{55}FN_4O_5Si_3$: C, 54.17; H, 8.62; N, 8.71. Found: C, 54.15; H, 8.59; N, 8.38.

6-Amino-7-fluoro-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (50). A solution of **48** (2.20 g, 3.43 mmol) in a mixture of EtOH (50 mL) and 5% aqueous Na_2CO_3 (50 mL) was heated for 30 min at 60 °C. The solvent was removed, and the residue was partitioned between $CHCl_3$ and H_2O. The aqueous layer was extracted with $CHCl_3$ three times. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by a silica gel column (4.0 × 12 cm), eluted with 0−10% EtOH in $CHCl_3$, to give **50** (1.89 g, 86% as a yellow foam): FAB-MS *m*/*z* 643 (MH^+); UV λ_{max} (MeOH) 273 nm; ^{1}H NMR ($CDCl_3$) 11.15 (br s, 1 H), 8.00 (s, 1 H), 6.01 (d, 1 H, *J* = 6.6 Hz), 4.86 (br s, 2 H), 4.27 (dd, 1 H, *J* = 6.6, 4.7 Hz), 4.19 (dd, 1 H, *J* = 4.7, 1.6 Hz), 4.09 (ddd, 1 H, *J* = 1.6, 2.8, 2.1 Hz), 3.91 (dd, 1 H, *J* = 2.8, 11.5 Hz), 3.78 (dd, 1 H, *J* = 2.1, 11.5 Hz), 0.96, 0.93, 0.80 (each s, each 9 H), 0.16, 0.15, 0.11, 0.10, −0.06, −0.34 (each s, each 3 H). Anal. Calcd for $C_{29}H_{55}FN_4O_5Si_3$: C, 54.17; H, 8.62; N, 8.71. Found: C, 54.09; H, 8.65; N, 8.59.

6-Amino-7-fluoro-1-*β*-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one (3-Deaza-3-fluoroguanosine, 52). A THF solution of TBAF (1 M, 11.0 mL, 11.0 mmol) was added to a solution of **50** (1.77 g, 2.76 mmol) in THF (40 mL) at 0 °C. The mixture was stirred for 1 h at room temperature and neutralized with AcOH. The solvent was removed in vacuo, and the residue was dissolved in H_2O (100 mL), which was washed with $CHCl_3$ three times. The aqueous layer was concentrated in vacuo, and the residue was coevaporated with EtOH three times. The resulting solid was crystallized from MeOH to give **52** (575 mg, 70%): mp >300 °C; FAB-MS *m*/*z* 301 (MH^+); UV λ_{max} (H_2O) 274 nm (ϵ 8300), 309 nm (ϵ 7100); λ_{max} (0.5 N NaOH) 288 nm (ϵ 9500). Anal. Calcd for $C_{11}H_{13}FN_4O_5 \cdot {}^1/_4H_2O$: C, 43.35; H, 4.47; N, 18.38. Found: C, 43.63; H, 4.32; N, 18.08.

5-Cyanofluoromethyl-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)imidazole-4-carbonitrile (49). Phosphorus oxychloride (1.0 mL, 10.7 mmol) was added dropwise to a mixture of **48** (2.3 g, 3.58 mmol) and Et_3N (5.0 mL, 35.8 mmol) in dry CH_2Cl_2 at 0 °C, and the whole was stirred for 1 h at that temperature. The reaction mixture was poured into ice-cold saturated aqueous $NaHCO_3$ (80 mL) and extracted with $CHCl_3$. The organic layer was washed with H_2O, followed by brine. The organic layer was dried (Na_2SO_4) and concen-

trated in vacuo, and the residue was purified by a silica gel column (3.5 × 10 cm), eluted with hexane/AcOEt (20:1−6:1), to give **49** (2.01 g, 90% as a pale yellow oil): FAB-MS *m*/*z* 625 (MH^+); UV λ_{max} (MeOH) 266 nm; ^{1}H NMR ($CDCl_3$) 7.95 (s, 1 H), 6.81 (d, 3/5 H, J = 44.5 Hz), 6.63 (d, 2/5 H, J = 44.5 Hz), 5.75 (d, 3/5 H, J = 6.6 Hz), 5.73 (d, 2/5 H, J = 7.2 Hz), 4.23−4.08 (m, 3H), 3.97 (dd, 3/5 H, J = 2.5, 11.9 Hz), 3.89 (dd, 2/5 H, J = 2.7, 11.5 Hz), 3.86−3.79 (m, 1 H), 0.97, 0.96, 0.94, 0.94, 0.82, 0.82 (each s, total 27 H), 0.18, 0.18, 0.17, 0.17, 0.12, 0.11, 0.11, 0.10, −0.02, −0.04, −0.25, −0.32 (each s, total 18 H). Used immediately in the next stage.

4,6-Diamino-7-fluoro-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)imidazo[4,5-*c*]pyridine (51). A solution of **49** (1.93 g, 3.10 mmol) in ethanolic ammonia (saturated at 0 °C, 50 mL) was heated for 20 h at 120 °C in a steel container. The reaction mixture was concentrated in vacuo, and the residue was purified by a silica gel column (3.5 × 8 cm), eluted with 0−4% EtOH in $CHCl_3$, to give **51** (1.58 g, 79% as a yellow foam): FAB-MS *m*/*z* 642 (MH^+); UV λ_{max} (MeOH) 283 nm; ^{1}H NMR ($CDCl_3$) 7.95 (s, 1 H), 6.02 (d, 1 H, J = 6.6 Hz), 4.81, 4.12 (each br s, each 2 H), 4.29 (dd, 1 H, J = 6.6, 4.9 Hz), 4.19 (dd, 1 H, J = 4.9, 4.4 Hz), 4.09 (ddd, 1 H, J = 4.4, 3.5, 2.5 Hz), 3.90 (dd, 1 H, J = 3.5, 11.2 Hz), 3.78 (dd, 1 H, J = 2.5, 11.2 Hz), 0.96, 0.94, 0.78 (each s, each 9 H), 0.15, 0.14, 0.11, 0.10, −0.07, −0.37 (each s, each 3 H). Anal. Calcd for $C_{29}H_{56}FN_5O_4Si_3$: C, 54.25; H, 8.79; N, 10.91. Found: C, 54.19; H, 8.50; N, 10.61.

4,6-Diamino-7-fluoro-1-*β*-D-ribofuranosylimidazo[4,5-*c*]pyridine (53). A mixture of **51** (90 mg, 0.14 mmol) and NH_4F (103 mg, 2.8 mmol) in MeOH (5 mL) was heated overnight under reflux. The solvent was removed in vacuo, and the residue was purified by a silica gel column (3.0 × 4 cm), eluted with 10−30% MeOH in $CHCl_3$, to give **53** (31 mg, 74%, crystallized from EtOH−H_2O): mp 215−216 °C; FAB-MS *m*/*z* 300 (MH^+); UV λ_{max} (H_2O) 282 nm (ϵ 9300); λ_{max} (0.5 N HCl) 276 nm (ϵ 9300), 324 nm (ϵ 8600); λ_{max} (0.5 N NaOH) 280 nm (ϵ 9900); ^{1}H NMR (DMSO-d_6) 8.04 (s, 1 H), 5.81 (d, 1 H, J = 6.0 Hz), 5.75, 5.19 (each br s, each 2 H), 5.45 (d, 1 H, J = 6.0 Hz), 5.18 (d, 1 H, J = 5.0 Hz), 5.02 (dd, 1 H, J = 5.5, 4.9 Hz), 4.29 (dt, 1 H, J = 6.0, 5.5 Hz), 4.05 (ddd, 1 H, J = 5.5, 5.0, 3.8 Hz), 3.89 (ddd, 1 H, J = 3.8, 4.1, 4.4 Hz), 3.61 (ddd, 1 H, J = 4.1, 12.1, 5.5 Hz), 3.55 (ddd, 1 H, J = 4.4, 12.1, 4.9 Hz). ^{13}C NMR (DMSO-d_6) 146.5, 141.8 (J = 11.0 Hz), 138.0 (J = 188.0 Hz), 128.8 (J = 8.0 Hz), 126.3, 124.5, 89.2, 85.3, 74.6, 70.2, 61.4. Anal. Calcd for $C_{11}H_{14}FN_5O_4$: C, 44.15; H, 4.72; N, 23.40. Found: C, 44.10; H, 4.67; N, 23.14.

6-Acetamido-4-amino-7-fluoro-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)imidazo[4,5-*c*]pyridine (54). A mixture of **51** (1.08 g, 1.68 mmol), Ac_2O (0.79 mL, 8.4 mmol), and DMAP (42 mg, 0.34 mmol) in dry pyridine (40 mL) was stirred for 20 h at room temperature. The reaction was quenched by addition of EtOH (5 mL), and the solvent was removed in vacuo. The residue was dissolved in $CHCl_3$, which was washed with H_2O, followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo, and methanolic ammonia (saturated at 0 °C, 40 mL) was added to the residue. After being kept for 20 min at room temperature, the solvent was removed in vacuo, and the residue was coevaporated several times with toluene. The residue was purified by a silica gel column (3.5 × 10 cm), eluted with 0−8% EtOH in $CHCl_3$, to give **54** (929 mg, 81% as a pale yellow foam): FAB-MS *m*/*z* 684 (MH^+); UV λ_{max} (MeOH) 279 nm; ^{1}H NMR ($CDCl_3$) 8.23 (s, 1 H), 7.42 (br s, 1 H), 6.10 (d, 1 H, J = 6.0 Hz), 5.08 (br s, 2 H), 4.32 (dd, 1 H, J = 6.0, 4.7 Hz), 4.21 (dd, 1 H, J = 4.7, 4.4 Hz), 4.11 (ddd, 1 H, J = 4.4, 3.0, 2.2 Hz), 3.94 (dd, 1 H, J = 3.0, 11.5 Hz), 3.80 (dd, 1 H, J = 2.2, 11.5 Hz), 2.24 (s, 3 H), 0.98, 0.94, 0.77 (each s, each 9 H), 0.17, 0.16, 0.11, 0.10, −0.06, −0.37 (each s, each 3 H). Anal. Calcd for $C_{31}H_{58}FN_5O_5Si_3$: C, 54.43; H, 8.55; N, 10.24. Found: C, 54.51; H, 8.36; N, 10.06.

6-Acetamido-7-fluoro-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)imidazo[4,5-*c*]pyridine (57). A THF solution (50 mL) of **54** (920 mg, 1.35 mmol) was heated at 60 °C, and isoamyl nitrite (2.73 mL, 20.3 mmol) was added to the mixture. After being stirred for 4 h at that temperature, more isoamyl nitrite (2.73 mL, 20.3 mmol) was added, and the whole was stirred for an additional 4 h. The reaction mixture was concentrated in vacuo, and the residue was purified by a silica gel column (3.0 × 8 cm), eluted with 0−8% EtOH in $CHCl_3$, to give **57** (529 mg, 59% as a yellow foam): FAB-MS *m*/*z* 669 (MH^+); UV λ_{max} (MeOH) 259 nm; λ_{max} (H^+) 270 nm; ^{1}H NMR ($CDCl_3$) 8.68 (d, 1 H, J = 1.1 Hz), 8.48 (s, 1 H), 7.78 (br s, 1 H), 6.17 (d, 1 H, J = 6.0 Hz), 4.33 (dd, 1 H, J = 6.0, 4.7 Hz), 4.22 (dd, 1 H, J = 4.7, 4.2 Hz), 4.14 (ddd, 1 H, J = 4.2, 2.7, 2.2 Hz), 3.97 (dd, 1 H, J = 2.7, 11.5 Hz), 3.82 (dd, 1 H, J = 2.2, 11.5 Hz), 2.30 (s, 3 H), 0.98, 0.94, 0.75 (each s, each 9 H), 0.18, 0.17, 0.11, 0.11, −0.06, −0.37 (each s, each 3 H). Anal. Calcd for $C_{31}H_{57}FN_4O_5Si_3$: C, 55.65; H, 8.59; N, 8.37. Found: C, 55.55; H, 8.43; N, 8.27.

6-Amino-7-fluoro-1-*β*-D-ribofuranosylimidazo[4,5-*c*]pyridine (59). A MeOH solution of NaOMe (1 M, 2.8 mL, 2.8 mmol) was added to a solution of **57** (370 mg, 0.55 mmol) in dry MeOH (20 mL). After being stirred for 24 h at room temperature, more 1 M MaOMe (2.8 mL, 2.8 mmol) was added, and the mixture was stirred for an additional 48 h at that temperature. The reaction mixture was neutralized with 1 M aqueous HCl, and the solution was concentrated in vacuo. The residue was partitioned between $CHCl_3$ and H_2O, and the aqueous layer was extracted three times with $CHCl_3$. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give crude **58**. A THF solution of TBAF (1 M, 1.75 mL, 1.75 mmol) was added to a solution of **58** in THF (15 mL) at 0 °C, and the mixture was stirred for 90 min at room temperature. The reaction mixture was concentrated in vacuo, and the residue was purified on a silica gel column (2.5 × 10 cm), eluted with 0−25% EtOH in $CHCl_3$, to give **59** (94 mg, 60%, crystallized from MeOH−H_2O): mp 228−231 °C dec; FAB-MS *m*/*z* 285 (MH^+); UV λ_{max} (H_2O) 260 nm (ϵ 6500), 292 nm (ϵ 3200); λ_{max} (0.5 N HCl) 265 nm (ϵ 5900), 271 nm (ϵ 5900), 319 nm (ϵ 4700); λ_{max} (0.5 N NaOH) 260 nm (ϵ 6800), 293 nm (ϵ 3700); ^{1}H NMR (DMSO-d_6) 8.36 (s, 1 H), 8.23 (d, 1 H, J = 1.5 Hz), 5.88 (d, 1 H, J = 5.8 Hz), 5.80 (br s, 2 H), 5.50 (d, 1 H, J = 6.1 Hz), 5.21 (d, 1 H, J = 4.8 Hz), 5.06 (t, 1 H, J = 5.3 Hz), 4.34 (ddd, 1 H, J = 5.7, 6.1, 5.8 Hz), 4.08 (ddd, 1 H, J = 4.9, 4.8, 3.8 Hz), 3.93 (dt, 1 H, J = 3.8, 4.1 Hz), 3.63 (ddd, 1 H, J = 4.1, 11.9, 5.3 Hz), 3.55 (ddd, 1 H, J = 4.1, 11.9, 5.3 Hz). ^{13}C NMR (DMSO-d_6) 144.2 (J = 9.2 Hz), 142.0, 136.7, 134.7 (J = 5.5 Hz), 130.8 (J = 250.0 Hz), 127.5 (J = 5.6 Hz), 89.3 (J = 3.6 Hz), 85.4, 74.5, 70.0, 61.2. Anal. Calcd for $C_{11}H_{13}FN_4O_4$: C, 46.48; H, 4.61; N, 19.71. Found: C, 46.38; H, 4.78; N, 19.39.

4-Amino-7-fluoro-6-trifluoroacetamido-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)imidazo[4,5-*c*]pyridine (60). Trifluoroacetic anhydride (0.44 mL, 3.10 mmol) was added to a solution of **51** (1.35 g, 2.10 mmol) in dry CH_2Cl_2 (35 mL) containing Et_3N (0.43 mL, 3.10 mmol) in an ice bath. After being stirred for 1.5 h at 0 °C, the reaction was quenched by addition of EtOH (5 mL). The solvent was removed in vacuo, and the residue was dissolved in AcOEt (70 mL), which was washed successively with H_2O, saturated aqueous $NaHCO_3$, and saturated brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Methanolic ammonia (saturated at 0 °C, 30 mL) was added to the residue, and the mixture was kept for 45 min at room temperature. The solvent was concentrated in vacuo, and the residue was purified on a silica gel column (3.5 × 6 cm), eluted with hexane/AcOEt (3:1−3:2), to give **60** (1.50 g, 97% as a white foam): FAB-MS *m*/*z* 738 (MH^+); UV λ_{max} (MeOH) 275 nm; λ_{max} (H^+) 271 nm; ^{1}H NMR ($CDCl_3$) 8.28 (s, 1 H), 8.09 (br s, 1 H), 6.09 (d, 1 H, J = 5.5 Hz), 5.12 (br s, 2 H), 4.33 (dd, 1 H, J = 5.5, 4.4 Hz), 4.21 (t, 1 H, J = 4.4 Hz), 4.12 (ddd, 1 H, J = 4.4, 2.5, 2.2 Hz), 3.94 (dd, 1 H, J = 2.5, 11.0 Hz), 3.80 (dd, 1 H, J = 2.2, 11.0 Hz), 0.97, 0.94, 0.77 (each s, each 9 H), 0.17, 0.15, 0.11, 0.11, −0.06, −0.37 (each s, each 3 H). Anal. Calcd for $C_{31}H_{55}F_4N_5O_5Si_3$: C, 50.45; H, 7.51; N, 9.49. Found: C, 50.39; H, 7.29; N, 9.36.

4-Acetamido-6-amino-7-fluoro-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)imidazo[4,5-*c*]pyridine (62). Acetyl chloride (0.17 mL, 2.39 mmol) was added to a solution of **60** (1.60 g, 2.17 mmol) in dry pyridine (40 mL), and the whole was stirred for 50 min at room temperature.

The reaction was quenched by addition of EtOH (5 mL), and the solvent was removed in vacuo. The residue was dissolved in AcOEt (70 mL), which was washed with H_2O, followed by saturated brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo, and the residue was coevaporated with toluene. Methanolic ammonia (saturated at 0 °C, 40 mL) was added to the residue, and the mixture was kept for 24 h at room temperature. The solvent was concentrated in vacuo, and the residue was purified by a silica gel column (3.5 × 10 cm), eluted with hexane/AcOEt (2:1−1:4), to give **62** (1.19 g, 80%, crystallized from AcOEt−hexane): mp 174−175 °C; FAB-MS *m*/*z* 684 (MH^+); UV λ_{max} (MeOH) 272, 313 nm; λ_{max} (H^+) 276, 283, 338 nm; ^{1}H NMR ($CDCl_3$) 8.19 (br s, 1 H), 8.07 (s, 1 H), 6.04 (d, 1 H, J = 6.6 Hz), 4.38 (br s, 2 H), 4.29 (dd, 1 H, J = 6.6, 5.5 Hz), 4.21 (dd, 1 H, J = 5.5, 4.4 Hz), 4.11 (ddd, 1 H, J = 4.4, 3.3, 2.2 Hz), 3.91 (dd, 1 H, J = 3.3, 12.1 Hz), 3.79 (dd, 1 H, J = 2.2, 12.1 Hz), 2.46 (br s, 3 H), 0.97, 0.94, 0.77 (each s, each 9 H), 0.16, 0.15, 0.11, 0.11, −0.07, −0.40 (each s, each 3 H). Anal. Calcd for $C_{31}H_{58}FN_5O_5Si_3$: C, 54.43; H, 8.55; N, 10.24. Found: C, 54.15; H, 8.52; N, 10.29.

4-Acetamido-7-fluoro-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)imidazo[4,5-*c*]pyridine (63). In the same manner as described for **57**, **62** was treated with isoamyl nitrite in dry THF giving **63** (748 mg, 55% as a yellow foam): FAB-MS *m*/*z* 669 (MH^+); UV λ_{max} (MeOH) 266 nm; λ_{max} (H^+) 289 nm; ^{1}H NMR ($CDCl_3$) 8.37 (s, 1 H), 8.37 (br s, 1 H), 8.05 (d, 1 H, J = 2.2 Hz), 6.13 (d, 1 H, J = 5.5 Hz), 4.32 (t, 1 H, J = 5.5 Hz), 4.22 (dd, 1 H, J = 5.5, 4.4 Hz), 4.14 (ddd, 1 H, J = 4.4, 3.3, 2.2 Hz), 3.95 (dd, 1 H, J = 3.3, 11.0 Hz), 3.81 (dd, 1 H, J = 2.2, 11.0 Hz), 2.49 (s, 3 H), 0.98, 0.94, 0.76 (each s, each 9 H), 0.18, 0.17, 0.12, 0.11, −0.07, −0.45 (each s, each 3 H). Anal. Calcd for $C_{31}H_{57}FN_4O_5Si_3$: C, 55.65; H, 8.59; N, 8.37. Found: C, 55.39; H, 8.48; N, 8.26.

4-Amino-7-fluoro-1-*β*-D-ribofuranosylimidazo[4,5-*c*]pyridine (3-Deaza-3-fluoroadenosine, 64). A solution of **63** (400 mg, 0.60 mmol) in methanolic ammonia (saturated at 0 °C, 35 mL) was heated for 20 h at 120 °C in a steel container. The reaction mixture was concentrated to dryness in vacuo to give a crude deacetylated product. A THF solution of TBAF (1 M, 2.0 mL, 2.0 mmol) was added to a solution of the deacetylated product in THF (15 mL) at 0 °C, and the mixture was stirred for 90 min at room temperature. The solvent was removed in vacuo, and the residue was purified by a silica gel column (2.5 × 10 cm), eluted with 0−25% EtOH in $CHCl_3$, to give **64** (97 mg, 57%, crystallized from MeOH−H_2O): mp 217−220 °C dec; FAB-MS *m*/*z* 285 (MH^+); UV λ_{max} (MeOH) 267 nm (ϵ 8000); λ_{max} (0.5 N HCl) 265 nm (ϵ 8600); λ_{max} (0.5 N NaOH) 267 nm (ϵ 8500). Anal. Calcd for $C_{11}H_{13}FN_4O_4 \cdot {}^2/_5MeOH$: C, 46.09; H, 4.95; N, 18.86. Found: C, 45.74; H, 4.67; N, 18.84.

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Supporting Information Available: Complete ^{1}H NMR spectral information for compounds **6**−**8**, **15**−**17**, **25**, **26**, **46**, **52**, and **64**. Complete ^{13}C NMR spectral information for compounds **46**, **52**, and **64**. This material is available free of charge via the Internet at http://pubs.acs.org.

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