*Tetrahedron* Vol. 49, No. 3, pp. 557-570, 1993
Printed in Great Britain

0040-4020/93 $5.00+.00


# Nucleosides and Nucleotides. 116. Convenient Syntheses of 3-Deazaadenosine, 3-Deazaguanosine, and 3-Deazainosine via Ring Closure of 5-Ethynyl-1-β-D-ribofuranosylimidazole-4-carboxamide or -carbonitrile[1]

**Noriaki Minakawa and Akira Matsuda***

*Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan*

(*Received in Japan* 28 *September* 1992)

*Key Words*: nucleoside; 3-deazapurine nucleoside; 3-deazaadenosine; 3-deazaguanosine; 3-deazainosine; acetylene; antiviral agent

***Abstract:*** An easy chemical synthesis of 3-deazapurine nucleosides, 3-deazainosine [1-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one (**8**)], 3-deazaguanosine [6-amino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one (**23**)], and 3-deazaadenosine [4-amino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridine (**29**)] is described. The approach consists of ring closure between substituents at 4- and 5-positions of the imidazole ring. Treatment of 5-ethynyl-1-β-D-ribofuranosylimidazole-4-carboxamide (**2**), which was readily obtained from AICA-riboside (**1**), with aqueous dimethylamine, followed by aqueous acetic acid gave **8** in 64% yield. 5-(2-Hydroxyiminoethyl)-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**19**) was synthesized from **3** by treatment of aqueous dimethylamine, followed by hydroxylamine hydrochloride. Dehydration of **19** was achieved by phenyl isocyanate to give 5-cyanomethyl derivative **21**, from which 3-deazaguanosine (**23**) was easily obtained. 3-Deazaadenosine (**29**) was synthesized from 5-ethynyl-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (**25**).

## INTRODUCTION

A number of antibiotics of the deazapurine series have been isolated and synthesized. Among them, 3-deazapurine nucleosides, especially 3-deazaadenosine [4-amino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridine (**29**)] and -guanosine [6-amino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one (**23**)], are of special interest because of their biological properties. 3-Deazaadenosine inhibits biochemical methylations by acting as either an inhibitor or a substrate of *S*-adenosylhomocystein hydrolase.[2] It has antiviral[3] and antimalarial activities.[4] It was also reported that the nucleoside inhibits the reverse transcriptase of HIV-1.[5] Furthermore, it has been in Phase 2 clinical trials for patients with rheumatoid arthritis.[6] 3-Deazaguanosine has been demonstrated to have potent antiviral activity *in vitro* against a variety of DNA and RNA viruses[7] as well as *in vivo* activity against L1210 leukemia and adenocarcinoma 755 in mice.[8] 2'-Deoxy analogues of 3-deazapurine nucleoside were also used as valuable probes for study of protein-nucleic acid interactions.[9] In spite of these interesting biological and pharmacological properties, only a few methods of synthesis of these compounds have been reported. 3-Deazaadenosine was originally synthesized by Robins *et al.*[10] Then Mizuno and his coworkers synthesized it *via* a similar route along with 3-deazainosine [1-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one (**8**)], starting from 6-chloroimidazo[4,5-*c*]pyridine.[11] A slight modification was introduced by May and Townsend with 4,6-dichloroimidazo[4,5-*c*]pyridine as a starting

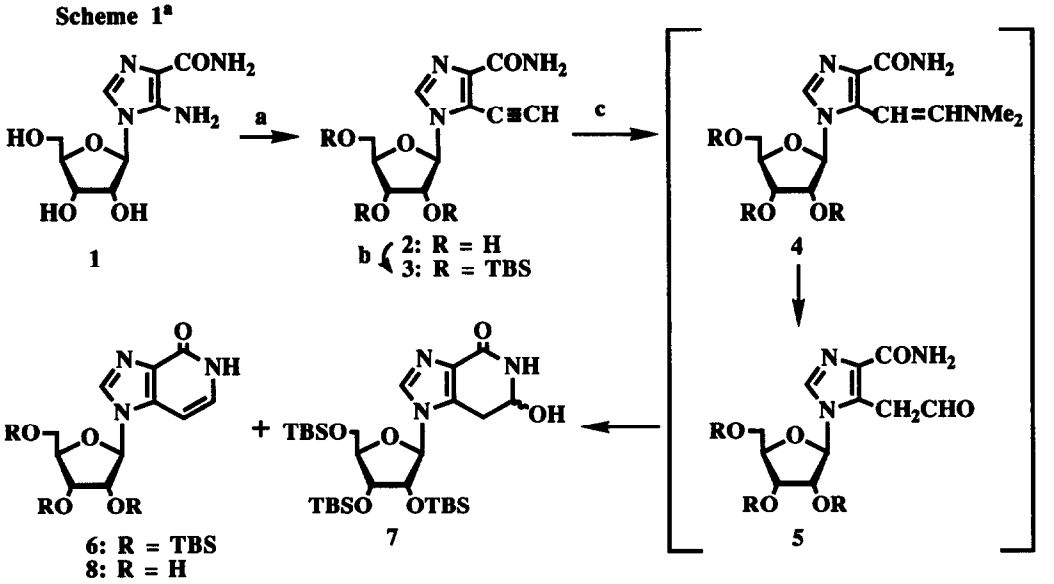
material,[12] and Montgomery *et al.* optimized their conditions.[13] However, all of these involved classical condensation methods with appropriate imidazo[4,5-*c*]pyridines and sugars, which suffer from regio- and stereochemical disadvantages. 3-Deazaguanosine was also synthesized by Robins and his coworkers by the condensation method.[14] This method takes many tedious steps for synthesis of the imidazo[4,5-*c*]pyridine ring. Tanaka *et al.* reported the first synthesis of 3-deazaguanosine from a naturally occurring nucleoside, uridine.[15] It dose not require the troublesome separation of regio- and stereoisomers, but it is insufficient in overall yield. Therefore, it seems worthwhile to develop a new synthetic route not only for 3-deazaadenosine and -inosine but also 3-deazaguanosine from readily available nucleosides which will be free from these disadvantages. To achieve our purpose, the straightforward synthetic route is to synthesize 4-carboxamidoimidazole nucleosides having formylmethyl and cyanomethyl groups at the 5-position, followed by ring closure of these nucleosides to obtain the target nucleosides. We have already reported introduction of alkynyl groups into the 5-position of such imidazole nucleosides, which were easily obtained from 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICA-riboside, **1**), by a palladium-catalyzed cross-coupling reaction.[16] Modification of terminal alkynes has already been demonstrated as the Willgerodt-Kindler reaction.[17] We found that these 5-alkynyl derivatives were important precursors for our purpose. In this paper, we describe a new convenient method for synthesizing 3-deazapurine nucleosides from 5-ethynyl-1-β-D-ribofuranosylimidazole-4-carboxamide (**2**) and -4-carbonitrile (**24**).[16] Further, we found this procedure could be used for some internal alkyne derivatives to afford 2-alkyl-3-deazainosines.

## RESULTS AND DISCUSSION

**Synthesis of 3-deazainosine (8) and its 2-substituted derivatives.** Compared with 3-deazaadenosine and -guanosine, 3-deazainosine has not enough been investigated for its biological and pharmacological properties. There is only one report on a synthesis by Mizuno *et al.*[11] Initially, we tried to synthesize 3-deazainosine (**8**).

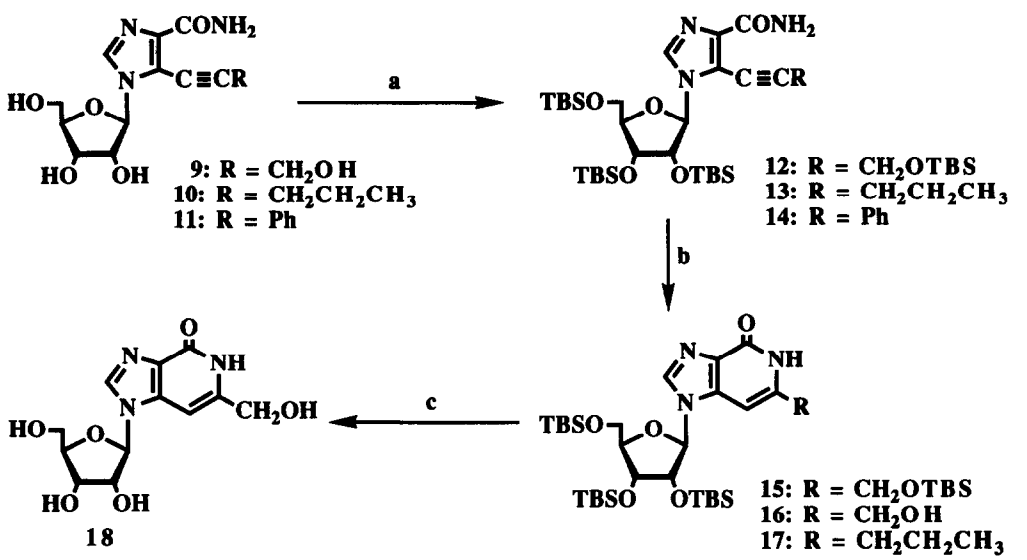
To ease the detection of products, **2** was silylated with *tert*-butyldimethylsilyl chloride (TBSCl) in *N*,*N*-dimethylformamide (DMF) in the presence of imidazole to give 5-ethynyl-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**3**) in 92% yield. When **3** was treated with aqueous dimethylamine in EtOH at 80 °C in a sealed tube, the desired 1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (**6**) along with an epimeric mixture of 6-hydroxy-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-6,7-dihydroimidazo[4,5-*c*]pyridin-4(5*H*)-ones (**7**) were obtained in 82% yield (about a 1 : 2 ratio). These were separable each other by a silica gel column but the ratio varied each reaction due to instability of **7**. The formation of **7** suggested that an intermediate **5** was formed by hydrolysis of **4** and then spontaneous cyclization took place during workup. Actually, on TLC analyses of the reaction mixture, the starting material **3** was completely consumed and a new spot, which corresponded to **4**, with an *Rf* value slightly lower than the starting material [*Rf* = 0.5 for **4** (R = TBS) and 0.55 for **3** with EtOH:$CHCl_3$ = 1:15], was detected as a major component, but the spots correspond to **6** and **7** were hardly detected.[18] However during purification including silica gel column chromatography, the spot due to **4** disappeared and only **6** and **7** were obtained. These results suggested that the intermediate **4** was easily acid-hydrolyzed to form **5**, which spontaneously cyclized to provide **7**. The structure of **7** was confirmed by its FAB-mass and $^1H$ NMR spectra. However, **7** was unstable towards acid to form the desired aromatized 3-deazainosine derivative **6**. During measurements of its $^1H$ NMR, it was observed that **7** was gradually

**Scheme 1**[a]




[a]a) ref. 16; b) TBSCl, imidazole in DMF, room temperature; c) 50% aqueous $Me_2NH$ in EtOH, 80 °C, then 50% aqueous AcOH in EtOH, room temperature.

**Scheme 2**[a]

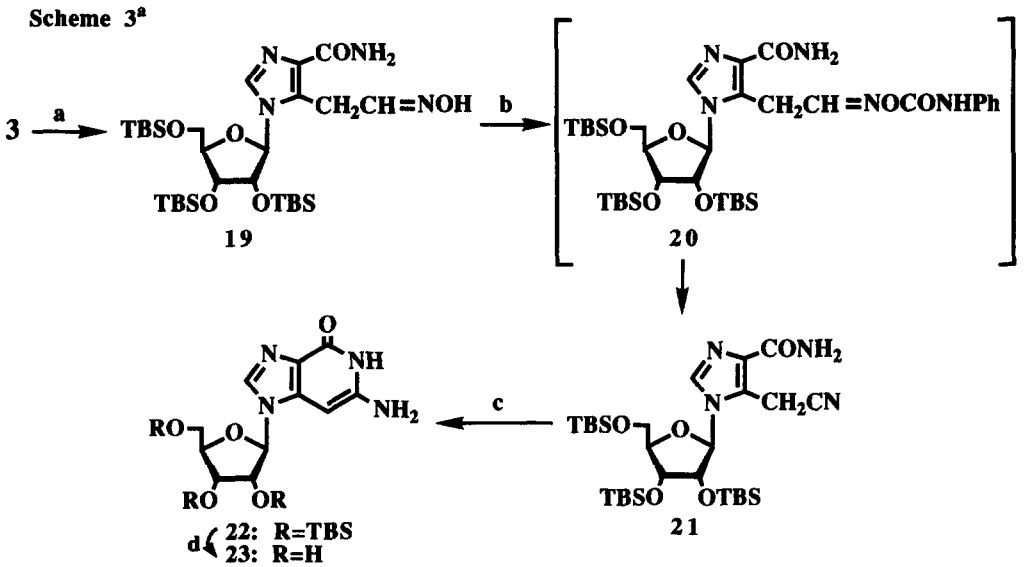



[a]a) TBSCl, imidazole in DMF, room temperature; b) 50% aqueous $Me_2NH$ in EtOH, 50 °C; c) 1 M TBAF in THF.

dehydrated to **6** in the $CDCl_3$ contains $D_2O$ probably due to contaminating acid. Thus, treatment of **7** with 50% aqueous acetic acid in THF gave **6** in 87% yield. Compound **6** was then deprotected with tetrabutylammonium fluoride (TBAF) to afford 3-deazainosine (**8**) quantitatively. The structure of **8** was confirmed by its $^1H$ NMR spectrum (DMSO-$d_6$), in which two aromatic proton signals appeared at 7.14 and 6.69 ppm as a broad triplet and a doublet, respectively. The signal at 7.14 ppm assigned as H-6 was changed to a doublet upon addition of $D_2O$. UV spectrum and melting point of **8** were identical with those reported by Mizuno *et al.*[11] 3-Deazainosine (**8**) was more conveniently prepared from **2** by treatment with aqueous dimethylamine, followed by 50% aqueous acetic acid–EtOH (1: 1) in 64% yield after crystallization.

We next examined this ring closure with internal alkyne derivatives. Three internal alkyne derivatives **9**–**11**[15] were chosen. Silylation of these compounds was done in the same manner as for **3** and gave **12**–**14**. Treatment of **12** with aqueous dimethylamine in EtOH at 80 °C in a sealed tube gave the desired ring closure products, 6-(*tert*-butyldimethylsiloxymethyl)-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-imidazo[4,5-*c*]pyridin-4(5*H*)-one (**15**) and its desilylated derivative **16**, in 31% and 45% yields, respectively. On the other hand, **13** and **14** did not react with aqueous dimethylamine under the same conditions. Either prolongation of the reaction time or rise of temperature caused the decomposition of **13** and **14**. Compound **17** was obtained in only 14% yield from **13**, when treated at 120 °C for 21 h. A mixture of **15** and **16** was deprotected by TBAF to give 6-hydroxymethyl-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one (**18**) in 87% yield. Compound **18** showed a quite similar UV spectrum pattern to that of **8**; the former was slightly shifted to longer wavelengths. Its mass and $^1H$ NMR spectra also supported the structure **18** (see experimental section).

**Scheme 3**[a]




[a]a) 50% aqueous $Me_2NH$ in EtOH, 50 °C, then $NH_2OH$•HCl, AcOH, room temperature; b) PhNCO in benzene, room temperature; c) 5% aqueous $Na_2CO_3$–EtOH, 100 °C; d) 1 M TBAF in THF.

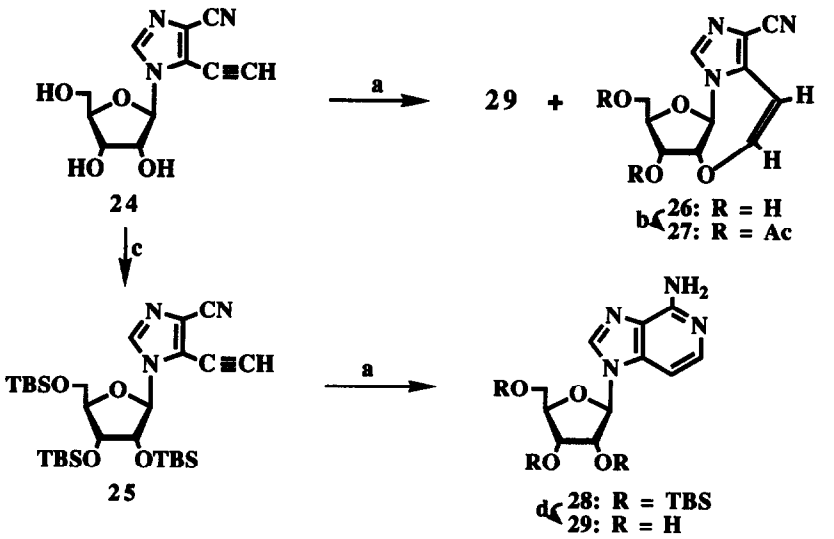
**Synthesis of 3-deazaguanosine (23).** 3-Deazaguanosine (**23**) has been synthesized by two groups. In these methods, 5-cyanomethylimidazole-4-carboxamide riboside is a key intermediate. It could be easily prepared if the formylmethyl group of **5** reacts with hydroxylamine in preference to ring closure.

After the hydroamination of **3** was done at 50 °C with aqueous dimethylamine for several hours, hydroxylamine hydrochloride and acetic acid were added to the reaction mixture. In this reaction, the desired 5-(2-hydroxyiminoethyl)-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**19**) was obtained in 91% yield without formation of **6** or **7**. After several attempts, we found phenyl isocyanate to be good for dehydration. Treatment of **19** with phenyl isocyanate in benzene gave intermediate **20**, which was subsequently heated in pyridine at 50 °C to give 5-cyanomethyl-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**21**) in 66% yield. Compound **21** has an adsorption at 2250 $cm^{-1}$ in its IR spectrum. The $^1H$ NMR spectrum showed, in addition to all the expected signals, the cyanomethylene proton signals at 4.68 and 4.27 ppm as doublets. The ring closure of **21** was done with 5% aqueous sodium carbonate–EtOH under reflux conditions to furnish the desired 6-amino-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (**22**) in 82% yield.[14] For practical synthesis of **22**, it was not necessary to isolate **21**. Compound **22** was then deprotected with TBAF to give 3-deazaguanosine (**23**) in 78% yield.

**Synthesis of 3-deazaadenosine (29).** For the synthesis of 3-deazaadenosine (**29**), it could be prepared if ammonia react with 5-ethynyl-1-β-D-ribofuranosylimidazole-4-carbonitrile (**24**). We first treated **24**, which was readily accessible from AICA-riboside (**1**)[16], with methanolic ammonia at 120 °C in a sealed tube. Silica gel column chromatography of the reaction mixture afforded two nucleosidic products. The $^1H$ NMR spectrum of the more polar nucleoside **29**, isolated as crystals in 17% yield, had two aromatic proton signals at 6.91 and 7.66 ppm as doublets ($J$ = 5.9 Hz) due to H-7 and H-6, respectively, along with an amino proton signal at 6.15 ppm as a broad singlet. This was assigned as the desired 3-deazaadenosine (**29**). A less polar nucleoside **26**, also isolated in 31% yield as crystals, showed a molecular ion peak at *m/z* 249 in its mass spectrum. The $^1H$ NMR spectrum in DMSO-$d_6$ showed also two vinylic proton signals at 5.66 and 6.79 ppm as doublets ($J$ = 7.7 Hz) and a primary and a secondary alcohol signals at 4.96 (doublet of doublet) and 5.84 (doublet) ppm, respectively. In the IR spectrum, an evident absorption at 2220 $cm^{-1}$ indicated the existence of a cyano group. Furthermore, **26** was converted to its diacetate **27** by treatment with acetic anhydride in pyridine. In the $^1H$ NMR spectrum of **27**, 3' and 5'-proton signals appeared at 5.53 and 4.19 ppm, respectively, which were appreciably shifted to downfield in the range 0.7–1.2 ppm compare with those of **26** due to the acetylation of hydroxy groups (see experimental section).[19] Therefore, the structure of this nucleoside was confirmed as 5,2'-*O*-cycloetheno-1-β-D-ribofuranosylimidazole-4-carbonitrile (**26**). In this reaction, the 4-cyano group is relatively unreactive toward ammonia and the reaction between the 2'-OH and the 5-substituent to form **26** is preferentially occurred in unprotected form.

Thus, hydroxy groups of the sugar moiety in **24** should be protected and 2,3,5-tri-*O*-TBS derivative **25** was prepared in 83% yield. When **25** was treated with methanolic ammonia as above, 4-amino-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridine (**28**) was obtained in 76% yield. Compound **28** was then deprotected to the free nucleoside, 3-deazaadenosine (**29**). As previously described by Mizuno *et al.*, there have been remarkable discrepancies among reported $^1H$ NMR spectra of 3-deazaadenosine.[20] This is due to partial hydrochloride formation since the classical synthesis of **29** has used

**Scheme 4**[a]




[a]a) $NH_3$ / MeOH, 120 °C; b) $Ac_2O$ in pyridine, room temperature; c) TBSCl, imidazole in DMF, room temperature; d) 1 M TBAF in THF

the corresponding 4-chloroimidazo[4,5-*c*]pyridine nucleoside, which was treated with hydrazine followed by Raney nickel. However, in our method, **29** was obtained as a free base form which is free from this perplexing problem.

In conclusion, 3-deazapurine nucleosides such as 3-deazainosine, 3-deazaguanosine, and 3-deazaadenosine have been generally synthesized from AICA-riboside without formation of undesirable by-products. Additionally, we synthesized 2-substituted-3-deazainosine by using this method. This simple method has generality for the synthesis of a wide variety of 3-deazapurine derivatives.

## EXPERMENTAL SECTION

**General Methods.** Physical data were measured as follows: Melting points were measured on a Yanagimoto Mp-3 micro melting point apparatus and are uncorrected. $^1$H-NMR spectra were recorded on JEOL JNM FX-100 or JEOL GX-270 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 $D_2O$. UV spectra were recorded with a Shimadzu UV-260 or UV-2100S spectrophotometer. Mass spectra were recorded on a JEOL JMS DX-303 or JEOL JMS HX-110 spectrometer. TLC was done on Merck Kieselgel F254 precoated plates. Silica gel used for column chromatography was YMC gel 60A (70-230 mesh).

**5-Ethynyl-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carboxamide (3).** A mixture of **2**[16b] (670 mg, 2.51 mmol), *tert*-butyldimethylsilyl chloride (1.51 g, 10.0

mmol), and imidazole (1.37 g, 20 mmol) in dry DMF (15 ml) was stirred for 46 h at room temperature, and then the reaction was quenched by addition of EtOH (5 ml). The mixture was concentrated to dryness *in vacuo* and the residue was dissolved in AcOEt. The solution was washed successively with $H_2O$ and saturated aqueous NaCl. The separated organic layer was dried ($Na_2SO_4$) and concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (3.2 x 10 cm), eluted with 25–50% AcOEt in hexane, to give **3** (1.40 g, 92% as a yellow foam): MS *m/z* 610 ($M^+$+1); $^1$H NMR ($CDCl_3$) 7.93 (s, 1 H, H-2), 6.92 (br s, 1 H, $NH_a$), 5.84 (d, 1 H, H-1', $J_{1',2'}$ = 5.1 Hz), 5.47 (br s, 1 H, $NH_b$), 4.28 (dd, 1 H, H-2', $J_{2',1'}$ = 5.1, $J_{2',3'}$ = 4.4 Hz), 4.21 (dd, 1 H, H-3', $J_{3',2'}$ = 4.4, $J_{3',4'}$ = 3.7 Hz), 4.09 (ddd, 1 H, H-4', $J_{4',3'}$ = 3.7, $J_{4',5'a}$ = 2.9, $J_{4',5'b}$ = 1.8 Hz), 3.93 (dd, 1 H, H-5'a, $J_{5'a,4'}$ = 2.9, $J_{5'a,5'b}$ = 11.4 Hz), 3.78 (dd, 1 H, H-5'b, $J_{5'b,4'}$ = 1.8, $J_{5'b,5'a}$ = 11.4 Hz), 3.76 (s, 1 H, acetylene proton), 0.96, 0.92, 0.85 (each s, each 9 H, *tert*-butyl), 0.09 (s, 6 H, methyl x 2), 0.14, 0.13, -0.01, -0.15 (each s, each 3 H, methyl).

**1-(2,3,5-Tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (6) and (6*R*)- and (6*S*)-hydroxy-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-6,7-dihydroimidazo[4,5-*c*]pyridin-4(5*H*)-one (7).** Aqueous dimethylamine (50%, 5 ml) was added to a solution of **3** (266 mg, 0.41 mmol) in EtOH (10 ml) and the mixture was heated at 80 °C for 4.5 h in a sealed tube. After the starting material was completely consumed, the reaction mixture was concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (2.7 x 8 cm), eluted with 0–8% EtOH in $CHCl_3$, to give **6** (67 mg, 27%) as yellow crystals and **7** (141 mg, 55% as a light brown oil). Compound **6** was recrystallized from hexane–AcOEt as white crystals.

Physical data for **6**: mp 251–252 °C; MS *m/z* 609 ($M^+$); $^1$H NMR (DMSO-$d_6$) 11.23 (d, 1 H, NH, $J$ = 6.6 Hz), 8.19 (s, 1 H, H-2), 7.06 (dd, 1 H, H-6, $J$ = 6.6, $J$ = 7.1 Hz), 6.71 (d, 1 H, H-3, $J$ = 7.1 Hz), 5.75 (d, 1 H, H-1', $J_{1',2'}$ = 7.7 Hz), 4.36 (dd, 1 H, H-2', $J_{2',1'}$ = 7.7, $J_{2',3'}$ = 4.9 Hz), 4.15 (d, 1 H, H-3', $J_{3',4'}$ = 4.9 Hz), 3.89 (br s, 1 H, H-4'), 3.91–3.78 (m, 2 H, H-5'a, b), 0.91 (s, 18 H, *tert*-butyl x 2), 0.70 (s, 9 H, *tert*-butyl), 0.12, 0.11, 0.10, 0.09, -0.16, -0.57 (each s, each 3 H, methyl). Anal. Calcd for $C_{29}H_{55}N_3O_5Si_3$: C, 57.10; H, 9.09; N, 6.89. Found: C, 56.83; H, 8.85; N, 6.80.

Physical data for **7**: FAB-MS *m/z* 627 ($M^+$+1); $^1$H NMR ($CDCl_3$) 7.99 (br s, 1 H, NH), 7.80, 7.79 (each s, 1 H, H-2), 5.80 (br s, 1 H, OH), 5.49 (d, 1 H, H-1', $J_{1',2'}$ = 7.0 Hz), 5.41 (br s, 1 H, H-6), 4.26–4.13 (m, 2 H, H-2', 3'), 4.06 (br s, 1 H, H-4'), 3.91–3.75 (m, 2 H, H-5'a, b), 3.16 (br s, 2 H, H-7), 0.96–0.75 (m, 27 H, *tert*-butyl x 3), 0.16—0.30 (m, 18 H, methyl x 6).

**Conversion of 7 into 6.** A solution of **7** (64 mg, 0.10 mmol) in THF (3 ml)–50% aqueous acetic acid (1 ml) was stirred for 1.5 h at room temrerature. The mixture was concentrated to dryness *in vacuo* and the residue was coevaporated three times with EtOH. The residue was purified by a silica gel column (1.5 x 5 cm), eluted with 0–6% EtOH in $CHCl_3$, to give **6** (54 mg, 87% as white crystals).

**1-β-D-Ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one (8).** Aqueous dimethylamine (50%, 15 ml) was added to a suspension of **2** (400 mg, 1.50 mmol) in EtOH (40 ml) and the mixture was heated at 80 °C for 5.5 h in a sealed tube. After the starting material was completely consumed, the reaction mixture was concentrated to dryness *in vacuo* and the residue was dissolved in a mixture of EtOH (15 ml)–50% aqueous acetic acid (15 ml), and the mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and then coevaporated several times with EtOH. The resulting solid was crystallized from EtOH–$H_2O$ to give **8** (257 mg, 64% as a pale yellow crystal): mp 218–219 °C (lit.[11] mp 218–219 °C); FAB-MS *m/z* 268 ($M^+$+1); UV $\lambda_{max}$ ($H_2O$) 257 nm (ε 10300); UV $\lambda_{max}$ (0.5 N HCl) 269 nm (ε 9800); UV $\lambda_{max}$

(0.5 N NaOH) 264 nm (ε 10600); $^1$H NMR (DMSO-$d_6$) 11.18 (br s, 1 H, NH), 8.22 (s, 1 H, H-2), 7.14 (br t, 1 H, H-6), 6.69 (d, 1 H, H-7, $J_{7,6}$ = 7.1 Hz), 5.71 (d, 1 H, H-1', $J_{1',2'}$ = 6.6 Hz), 5.47 (d, 1 H, 2'-OH, $J_{2'\text{-OH},2'}$ = 6.6 Hz), 5.19 (d, 1 H, 3'-OH, $J_{3'\text{-OH},3'}$ = 4.9 Hz), 5.08 (dd, 1 H, 5'-OH, $J_{5'\text{-OH},5'a}$ = 4.9 Hz, $J_{5'\text{-OH},5'b}$ = 5.5 Hz), 4.23 (dt, 1 H, H-2', $J_{2',1'} = J_{2',2'\text{-OH}}$ = 6.6, $J_{2',3'}$ = 6.0 Hz), 4.06 (ddd, 1 H, H-3', $J_{3',2'}$ = 6.0, $J_{3',3'\text{-OH}}$ = 4.9, $J_{3',4'}$ = 3.3 Hz), 3.94 (m, 1 H, H-4'), 3.60 (m, 2H, H-5'a,b); Anal. Calcd for $C_{11}H_{13}N_3O_5 \cdot 1/4H_2O$: C, 48.62; H, 5.00; N, 15.46. Found: C, 48.81; H, 4.89; N, 15.40 (dried over $P_2O_5$ *in vacuo* at 40 °C overnight).

**5-(3-*tert*-Butyldimethylsiloxy-1-propyn-1-yl)-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carboxamide (12).** A mixture of **9**[16b] (157 mg, 0.53 mmol), *tert*-butyldimethylsilyl chloride (398 mg, 2.65 mmol), and imidazole (360 mg, 5.30 mmol) in dry DMF (5 ml) was stirred for 3 days at room temperature, and then the mixture was quenched by addition of EtOH (1 ml). The mixture was concentrated to dryness *in vacuo* and the residue was dissolved in AcOEt. The solution was washed successively with $H_2O$ and saturated aqueous NaCl. The separated organic layer was dried ($Na_2SO_4$) and concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (3.0 x 10 cm), eluted with 25–50% AcOEt in hexane, to give **12** (288 mg, 72% as a coloress oil): MS *m/z* 754 ($M^+$+1) $^1$H NMR ($CDCl_3$) 7.89 (s, 1 H, H-2), 6.89 (br s, 1 H, $NH_a$), 5.82 (d, 1 H, H-1', $J_{1',2'}$ = 5.5 Hz), 5.35 (br s, 1 H, $NH_b$), 4.63, 4.56 (each d, each 1 H, $CH_2$, $J$ = 16.5 Hz), 4.27 (dd, 1 H, H-2', $J_{2',1'}$ = 5.5, $J_{2',3'}$ = 4.4 Hz), 4.21 (dd, 1 H, H-3', $J_{3',2'}$ = 4.4, $J_{3',4'}$ = 4.0 Hz), 4.07 (ddd, 1 H, H-4', $J_{4',3'}$ = 4.0, $J_{4',5'a}$ = 2.9, $J_{4',5'b}$ = 2.2 Hz), 3.90 (dd, 1 H, H-5'a, $J_{5'a,4'}$ = 2.9, $J_{5'a,5'b}$ = 11.7 Hz), 3.77 (dd, 1 H, H-5'b, $J_{5'b,4'}$ = 2.2, $J_{5'b,5'a}$ = 11.7 Hz), 0.95, 0.92, 0.90, 0.84 (each s, each 9 H, *tert*-butyl), 0.16 (s, 6H, methyl x 2), 0.14, 0.13, 0.10, 0.09, -0.01, -0.03 (each s, each 3 H, methyl).

**5-(1-Pentyn-1-yl)-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-imidazole-4-carboxamide (13).** A mixture of **10**[16b] (200 mg, 0.65 mmol), *tert*-butyldimethylsilyl chloride (390 mg, 2.60 mmol), and imidazole (354 mg, 5.20 mmol) in dry DMF (7 ml) was stirred for 3 days at room temperature, and then the reaction was quenched by addition of EtOH (1 ml). The mixture was concentrated to dryness *in vacuo* and the residue was dissolved in AcOEt. The solution was washed successively with $H_2O$ and saturated aqueous NaCl. The separated organic layer was dried ($Na_2SO_4$) and concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (2.7 x 7 cm), eluted with 25–50% AcOEt in hexane, to give **13** (323 mg, 77% as a white form): MS *m/z* 652 ($M^+$+1); $^1$H NMR ($CDCl_3$) 7.82 (s, 1 H, H-2), 6.88 (br s, 1 H, $NH_a$), 5.86 (d, 1 H, H-1', $J_{1',2'}$ = 6.2 Hz), 5.35 (br s, 1 H, $NH_b$), 4.28 (dd, 1 H, H-2', $J_{2',1'}$ = 6.2, $J_{2',3'}$ = 4.4 Hz), 4.18 (dd, 1 H, H-3', $J_{3',2'}$ = 4.4, $J_{3',4'}$ = 2.6 Hz), 4.06 (ddd, 1 H, H-4', $J_{4',3'}$ = 2.6, $J_{4',5'a}$ = 2.9, $J_{4',5'b}$ = 2.2 Hz), 3.88 (dd, 1 H, H-5'a, $J_{5'a,4'}$ = 2.9, $J_{5'a,5'b}$ = 11.4 Hz), 3.76 (dd, 1 H, H-5'b, $J_{5'b,4'}$ = 2.2, $J_{5'b,5'a}$ = 11.4 Hz), 2.48 (t, 2 H, $CH_2CH_2CH_3$, $J$ = 7.0 Hz), 1.66 (dt, 2 H, $CH_2CH_2CH_3$, $J$ = 7.0, 7.3 Hz), 1.07 (t, 3 H, $CH_2CH_2CH_3$, $J$ = 7.3 Hz), 0.95, 0.92, 0.84 (each s, each 9 H, *tert*-butyl), 0.14, 0.13, 0.10, 0.09, -0.01, -0.06 (each s, each 3 H, methyl).

**5-(Phenylethyn-1-yl)-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-imidazole-4-carboxamide (14).** A mixture of **11**[16b] (110 mg, 0.32 mmol), *tert*-butyldimethylsilyl chloride (192 mg, 1.28 mmol), and imidazole (174 mg, 2.56 mmol) in dry DMF (5 ml) was stirred for 3 days at room temperature, and then the reaction was quenched by addition of EtOH (1 ml). The mixture was concentrated to dryness *in vacuo* and the residue was dissolved in AcOEt. The solution was washed successively with $H_2O$ and saturated aqueous NaCl. The separated organic layer was dried ($Na_2SO_4$) and

concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (2.7 x 7 cm), eluted with 30–60% AcOEt in hexane, to give **14** (174 mg, 79% as a white form): MS *m/z* 685 ($M^+$+1) $^1H$ NMR ($CDCl_3$) 7.88 (s, 1 H, H-2), 7.57 (m, 2 H, Ph), 7.35 (m, 3 H, Ph), 6.92 (br s, 1 H, $NH_a$), 5.97 (d, 1 H, H-1', $J_{1',2'}$ = 6.2 Hz), 5.40 (br s, 1 H, $NH_b$), 4.33 (dd, 1 H, H-2', $J_{2',1'}$ = 6.2, $J_{2',3'}$ = 4.4 Hz), 4.21 (dd, 1 H, H-3', $J_{3',2'}$ = 4.4, $J_{3',4'}$ = 1.8 Hz), 4.08 (ddd, 1 H, H-4', $J_{4',3'}$ = 1.8, $J_{4',5'a}$ = 2.9, $J_{4',5'b}$ = 2.2 Hz), 3.88 (dd, 1 H, H-5'a, $J_{5'a,4'}$ = 2.9, $J_{5'a,5'b}$ = 11.4 Hz), 3.78 (dd, 1 H, H-5'b, $J_{5'b,4'}$ = 2.2, $J_{5'b,5'a}$ = 11.4 Hz), 0.95, 0.93, 0.80 (each s, each 9 H, *tert*-butyl), 0.14, 0.13, 0.12, 0.10, -0.07, -0.23 (each s, each 3 H, methyl).

**6-(*tert*-Butyldimethylsiloxymethyl)-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (15) and 6-hydroxymethyl-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (16).** Aqueous dimethylamine (50%, 1 ml) was added to a solution of **12** (160 mg, 0.21 mmol) in EtOH (5 ml) and the mixture was heated at 80 °C for 9 h in a sealed tube. After the starting material was completely consumed, the reaction mixture was concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (1.7 x 9 cm), eluted with 0–10% EtOH in $CHCl_3$, to give **15** (49 mg, 31% as a yellow oil) and **16** (61 mg, 45% as a yellow oil).

Physical data for **15**: MS *m/z* 753 ($M^+$); $^1H$ NMR ($CDCl_3$) 9.62 (br s, 1 H, NH), 8.04 (s, 1 H, H-2), 6.36 (s, 1 H, H-7), 5.70 (d, 1 H, H-1', $J_{1',2'}$ = 7.2 Hz), 4.66 (s, 2 H, $CH_2$), 4.28 (dd, 1 H, H-2', $J_{2',1'}$ = 7.2, $J_{2',3'}$ = 4.4 Hz), 4.19–4.11 (m, 2 H, H-3', 4'), 3.90 (dd, 1 H, H-5'a, $J_{5'a,4'}$ = 2.8, $J_{5'a,5'b}$ = 11.5 Hz), 3.80 (dd, 1 H, H-5'b, $J_{5'b,4'}$ = 2.2, $J_{5'b,5'a}$ = 11.5 Hz), 0.96, 0.95, 0.94, 0.75 (each s, each 9 H, *tert*-butyl), 0.16, 0.14, 0.13, 0.12, 0.11, 0.10, -0.11, -0.47 (each s, each 3 H, methyl).

Physical data for **16**: MS *m/z* 639 ($M^+$); $^1H$ NMR ($CDCl_3$) 12.30 (br s, 1 H, NH), 8.08 (s, 1 H, H-2), 6.52 (s, 1 H, H-7), 5.73 (d, 1 H, H-1', $J_{1',2'}$ = 7.2 Hz), 5.00 (br s, 1 H, OH), 4.69 (br s, 2 H, $CH_2$), 4.29 (dd, 1 H, H-2', $J_{2',1'}$ = 7.2, $J_{2',3'}$ = 4.4 Hz), 4.20–4.13 (m, 2 H, H-3', 4'), 3.91 (dd, 1 H, H-5'a, $J_{5'a,4'}$ = 2.7, $J_{5'a,5'b}$ = 11.5 Hz), 3.81 (dd, 1 H, H-5'b, $J_{5'b,4'}$ = 2.2, $J_{5'b,5'a}$ = 11.5 Hz), 0.96, 0.95, 0.77 (each s, each 9 H, *tert*-butyl), 0.16, 0.15, 0.12, 0.11, -0.10, -0.47 (each s, each 3 H, methyl).

**6-Propyl-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]-pyridin-4(5*H*)-one (17).** Aqueous dimethylamine (50%, 5 ml) was added to a solution of **13** (310 mg, 0.48 mmol) in EtOH (15 ml) and the whole was heated at 120 °C for 21 h in a sealed tube. The mixture was concentrated to dryness *in vacuo* and the residue was purified by a silica gel column (2.7 x 8 cm), eluted with 33–100% AcOEt in hexane, to give **17** (44 mg, 14% as a bright yellow oil): MS *m/z* 651 ($M^+$); $^1H$ NMR ($CDCl_3$) 10.88 (br s, 1 H, NH), 8.03 (s, 1 H, H-2), 6.26 (s, 1 H, H-7), 5.70 (d, 1 H, H-1', $J_{1',2'}$ = 7.1 Hz), 4.30 (dd, 1 H, H-2', $J_{2',1'}$ = 7.1, $J_{2',3'}$ = 4.9 Hz), 4.20 (m, 1 H, H-3'), 4.12 (br s, 1 H, H-4'), 3.92–3.79 (m, 2 H, H-5'a, b), 2.65 (t, 2 H, $CH_2CH_2CH_3$, $J$ = 7.7 Hz), 1.74 (m, 2 H, $CH_2CH_2CH_3$), 0.82 (m, 3 H, $CH_2CH_2CH_3$), 0.99, 0.95, 0.77 (each s, each 9 H, *tert*-butyl), 0.16, 0.15, 0.13, 0.12 (each s, each 3 H, methyl), -0.09 (s, 6H, methyl x 2).

**6-Hydroxymethyl-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one (18).** A THF solution of TBAF (1 M, 0.66 ml, 0.66 mmol) was added to a mixture of **15** (47 mg, 0.06 mmol) and **16** (59 mg, 0.09 mmol) in dry THF (4 ml) at 0 °C. The mixture was stirred for 30 min at room temperature and concentrated to dryness *in vacuo*. The residue was dissolved in $H_2O$ (3 ml) and put on a Amberlite XAD-4 resin column (2.7 x 29 cm), eluted with 0–60% MeOH in $H_2O$, to give **18** (40 mg, 87 % as a bright yellow

glass), which was crystallized from $H_2O$–MeOH as white crystals: mp 216–218 °C ; FAB-MS *m/z* 298 ($M^+$+1); UV $\lambda_{max}$ ($H_2O$) 260 nm (ε 10100) 278 nm (sh) (ε 7800); UV $\lambda_{max}$ (0.5 N HCl) 272 nm (ε 11700); UV $\lambda_{max}$ (0.5 N NaOH) 269 nm (ε 9400); $^1$H NMR (DMSO-$d_6$) 11.00 (br s, 1 H, NH) 8.21 (s, 1 H, H-2), 7.37 (s, 1 H, H-7), 5.70 (d, 1 H, H-1', $J_{1',2'}$ = 6.0 Hz), 5.50 (d, 1 H, 2'-OH, $J_{2'\text{-OH},2'}$ = 6.6 Hz), 5.41 (t, 1 H, $CH_2OH$, $J$ = 6.0 Hz), 5.22 (d, 1 H, 3'-OH, $J_{3'\text{-OH},3'}$ = 4.9 Hz), 5.08 (dd, 1 H, 5'-OH, $J_{5'\text{-OH},5'a}$ = 5.4, $J_{5'\text{-OH},5'b}$ = 4.9 Hz), 4.35 (d, 2 H, $CH_2OH$, $J$ = 6.0 Hz), 4.27 (ddd, 1 H, H-2', $J_{2',1'}$ = 6.0, $J_{2',2'\text{-OH}}$ = 6.6, $J_{2',3'}$ = 5.5 Hz), 4.08 (ddd, 1 H, H-3', $J_{3',2'}$ = 5.5, $J_{3',3'\text{-OH}}$ = 4.9, $J_{3',4'}$ = 3.3 Hz), 3.96 (m, 1 H, H-4'), 3.61 (m, 2 H, H-5'a, b); Anal. Calcd for $C_{12}H_{15}N_3O_6$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.50; H, 5.04; N, 13.92.

**5-(2-Hydroxyiminoethyl)-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-imidazole-4-carboxamide (19).** Aqueous dimethylamine (50%, 3 ml) was added to a solution of **3** (410 mg, 0.67 mmol) in EtOH (12 ml) and the mixture was heated at 50 °C for 8 h in a sealed tube. After the starting material was completely consumed, the reaction mixture was transferred to a round-bottom flask, and $NH_2OH$·HCl (94 mg, 1.34 mmol) and acetic acid (2 ml) were added to the solution at 0 °C. The whole was srirred for 7.5 h at room temperature and the reaction was quenched by addition of acetone (5 ml). The mixture was concentrated *in vacuo* and the residue was dissolved in AcOEt. The solution was washed successively with $H_2O$, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The separated organic layer was dried ($Na_2SO_4$) and concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (2.7 x 9 cm), eluted with 25–60% AcOEt in hexane, to give **19** (391 mg, 91%). An analytical sample was crystallized from hexane–AcOEt as white crystals: mp 193–194 °C; MS *m/z* 642 ($M^+$); $^1$H NMR ($CDCl_3$) 8.12 (br s, 0.67 H, N-$OH_a$), 7.75 (s, 1 H, H-2), 7.59 (br s, 0.33 H, N-$OH_b$), 7.50 (dd, 0.33 H, $CH_2CH_a$, $J$ = 4.8, 5.9 Hz), 7.04 (br s, 1 H, amide proton), 6.84 (dd, 0.67 H, $CH_2CH_b$, $J$ = 5.1, 5.9 Hz), 5.74 (d, 0.67 H, H-1'$_a$, $J$ = 7.3 Hz), 5.67 (d, 0.33 H, H-1'$_b$, $J$ = 7.0 Hz), 5.44 (br s, 1 H, amide proton), 4.41–3.72 (m, 7 H, $CH_2CH$, H-2', 3', 4', 5'a, b), 0.94, 0.93, 0.81 (each s, each 9 H, *tert*-butyl), 0.12 (s, 6 H, methyl x 2), 0.11, 0.09, -0.05, -0.28 (each s, each 3 H, methyl). Anal. Calcd for $C_{29}H_{58}N_4O_6Si_3$: C, 54.16; H, 9.09; N, 8.71. Found: C, 54.06; H, 9.20; N, 8.67.

**5-Cyanomethyl-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carboxamide (21).** Phenyl isocyanate (28 μl, 0.26 mmol) was added to a suspension of **19** (110 mg, 0.17 mmol) in dry benzene (10 ml) at 0 °C under argon atmosphere. The mixture was stirred for 1 h at room temperature, and the reaction was quenched by addition of ice. The mixture was diluted with AcOEt and washed with $H_2O$, followed by saturated aqueous NaCl. The separated organic layer was dried ($Na_2SO_4$) and concentrated to dryness *in vacuo*. The residue was dissolved in pyridine (10 ml) and the mixture was heated for 20 min at 50 °C. The mixture was concentrated to dryness *in vacuo* and the residue was coevaporated three times with toluene. The residue was purified by a silica gel column (1.7 x 5 cm), eluted with 0–33% AcOEt in hexane, to give **21** (70 mg, 66% as a colorless oil): MS *m/z* 567 ($M^+$–*tert*-butyl); IR 2250 cm$^{-1}$; $^1$H NMR ($CDCl_3$) 7.69 (s, 1 H, H-2), 7.00 (br s, 1 H, NHa), 5.69 (d, 1 H, H-1', $J_{1',2'}$ = 7.0 Hz), 5.38 (br s, 1 H, NHb), 4.68, 4.27 (each d, each 1 H, $CH_2CN$, $J$ = 16.9 Hz), 4.16 (m, 3 H, H-2', 3', 4'), 3.94 (dd, 1 H, H-5'a, $J_{5'a,4'}$ = 2.6, $J_{5'a,5'b}$ = 11.4 Hz), 3.79 (dd, 1 H, H-5'b, $J_{5'b,4'}$ = 2.2, $J_{5'b,5'a}$ = 11.4 Hz), 0.94 (s, 18 H, *tert*-butyl x 2), 0.81 (s, 9 H, *tert*-butyl), 0.13 (s, 6 H, methyl x 2), 0.12, 0.11, -0.04, -0.32 (each s, each 3 H, methyl).

**6-Amino-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]-pyridin-4(5*H*)-one (22). Preparation from 19.** Phenyl isocyanate (0.38 ml, 3.51 mmol) was added to a suspension of **19** (1.50 g, 2.43 mmol) in dry benzene (50 ml) at 0 °C under argon atmosphere. The mixture was stirred for 1.5 h at room temperature and the reaction was quenched by addition of ice. The mixture was diluted with AcOEt and washed with $H_2O$, followed by saturated aqueous NaCl. The separated organic layer was dried ($Na_2SO_4$) and concentrated to dryness *in vacuo*. The residue was dissolved in a mixture of EtOH (40 ml)–5% aqueous $Na_2CO_3$ (20 ml) and the mixture was heated under reflux for 1.5 h at 100 °C. The mixture was concentrated to dryness *in vacuo* and the residue was dissolved in $CHCl_3$, which was washed with $H_2O$, followed by saturated aqueous NaCl. The separated organic layer was dried ($Na_2SO_4$) and concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (3.2 x 12 cm), eluted with 0–12% EtOH in $CHCl_3$, to give **22** (818 mg, 56% as a pale blue foam): MS *m/z* 624 ($M^+$); $^1H$ NMR ($CDCl_3$) 12.85 (br s, 1 H, NH), 7.81 (s, 1 H, H-2), 5.61 (s, 1 H, H-7), 5.60(d, 1 H, H-1', $J_{1',2'}$ = 7.1 Hz), 4.72 (br s, 2 H, $NH_2$), 4.28 (dd, 1 H, H-2', $J_{2',1'}$ = 7.1 Hz, $J_{2',3'}$ = 4.9 Hz), 4.18 (dd, 1 H, H-3', $J_{3',2'}$ = 4.9, $J_{3',4'}$ = 6.1 Hz), 4.09 (ddd, 1 H, H-4', $J_{4',3'}$ = 6.1, $J_{4',5'a}$ = 2.7, $J_{4',5'b}$ = 2.2 Hz), 3.89 (dd, 1 H, H-5'a, $J_{5'a,4'}$ = 2.7, $J_{5'a,5'b}$= 11.5 Hz), 3.79 (dd, 1 H, H-5'b, $J_{5'b,4'}$ = 2.2, $J_{5'b,5'a}$ = 11.5 Hz), 0.96, 0.94, 0.79 (each s, each 9 H, *tert*-butyl), 0.15, 0.14, 0.12, 0.10, -0.09, -0.39 (each s, each 3 H, methyl).

**Preparation from 21.** A solution of **21** (392 mg, 0.63 mmol) in a mixture of EtOH (15 ml)–5% aqueous $Na_2CO_3$ (5 ml) was heated under reflux for 40 min at 100 °C. The mixture was concentrated to dryness *in vacuo* and the residue was purified by a silica gel column (2.7 x 8 cm), eluted with 0–12% EtOH in $CHCl_3$, to give **22** (319 mg, 56%) as a pale blue foam.

**6-Amino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one (23).** A THF solution of TBAF (1 M, 6.5 ml, 6.5 mmol) was added to a solution of **22** (810 mg, 1.30 mmol) in dry THF (15 ml) at 0 °C. The mixture was stirred for 1 h at room temperature, and concentrated to dryness *in vacuo*. The residue was dissolved in $H_2O$ (10 ml) and the whole was applied to an Amberlite XAD-4 resin column (5.4 x 34 cm), eluted with 0–80% MeOH in $H_2O$, to give **23** (285 mg, 78% as a bright brown solid) which was crystallized from $H_2O$ as white crystals: mp 217–220 °C (dec.) (lit.[14] mp 255–257 °C dec.); FAB-MS *m/z* 283 ($M^+$+1); UV $\lambda_{max}$ ($H_2O$) 271 nm (ε 11500), 299 nm (ε 8500); UV $\lambda_{max}$ (0.5 N HCl) 286 nm (ε 12400), 310 nm (sh) (ε 6300); UV $\lambda_{max}$ (0.5 N NaOH) 281 nm (ε 12000); $^1H$ NMR (DMSO-$d_6$) 10.29 (br s, 1 H, NH), 7.86 (s, 1 H, H-2), 5.56 (br s, 2 H, $NH_2$), 5.46 (d, 1 H, H-1', $J_{1',2'}$ = 6.1 Hz), 5.45 (s, 1 H, H-7), 5.44 (d, 1 H, 2'-OH, $J_{2'\text{-OH},2'}$ = 6.6 Hz), 5.17 (d, 1 H, 3'-OH, $J_{3'\text{-OH},3'}$ = 5.0 Hz), 5.00 (dd, 1 H, 5'-OH, $J_{5'\text{-OH},5'a}$ = 5.5, $J_{5'\text{-OH},5'b}$ = 5.0 Hz), 4.21 (ddd, 1 H, H-2', $J_{2',1}$ = 6.1, $J_{2',2'\text{-OH}}$ = 6.6, $J_{2',3'}$ = 5.0 Hz), 4.01 (dt, 1 H, H-3', $J_{3',2'} = J_{3',3'\text{-OH}}$ = 5.0, $J_{3',4'}$ = 3.9 Hz), 3.87 (ddd, 1 H, H-4', $J_{4',3'}$ = 3.9, $J_{4',5'a}$ = 3.8, $J_{4',5'b}$ = 4.4 Hz), 3.61 (ddd, 1 H, H-5'a, $J_{5'a,4}$ = 3.8, $J_{5'a,5'b}$ = 12.1, $J_{5'a,5'\text{-OH}}$ = 5.5 Hz), 3.51 (ddd, 1 H, H-5'b, $J_{5'b,4'}$ = 4.4, $J_{5'b,5'a}$ = 12.1, $J_{5'b,5'\text{-OH}}$ = 5.0 Hz). Anal. Calcd for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.85. Found: C, 46.93; H, 4.99; N, 19.58.

**5-Ethynyl-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (25).** A mixture of **24**[16b] (797 mg, 3.20 mmol), *tert*-butyldimethylsilyl chloride (1.92 g, 12.8 mmol), and imidazole (1.74 g, 25.6 mmol) in dry DMF (20 ml) was stirred for 72 h at room temperature, and then the reaction was quenched by addition of EtOH (5 ml). The mixture was concentrated to dryness *in vacuo* and the residue was dissolved in AcOEt. The solution was washed successively with $H_2O$ and

saturated aqueous NaCl. The separated organic layer was dried ($Na_2SO_4$) and concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (3.0 x 12 cm), eluted with 0–16% AcOEt in hexane, to give **25** (1.57 g, 83% as a yellow solid). An analytical sample was crystallized from hexane as colorless crystals: mp 101–103 °C; MS *m/z* 591 ($M^+$); $^1H$ NMR ($CDCl_3$) 8.01 (s, 1 H, H-2), 5.76 (d, 1 H, H-1', $J_{1',2'}$ = 5.5 Hz), 4.25 (dd, 1 H, H-2', $J_{2',1'}$ = 5.5, $J_{2',3'}$ = 4.4 Hz), 4.18 (dd, 1 H, H-3', $J_{3',2'}$ = 4.4, $J_{3',4'}$ = 2.9 Hz), 4.09 (q, 1 H, H-4', $J_{4',3'} = J_{4',5'a} = J_{4',5'b}$ = 2.9 Hz), , 3.91 (dd, 1 H, H-5'a, $J_{5'a,4'}$ = 2.9, $J_{5'a,5'b}$ = 11.7 Hz), 3.80 (s, 1 H, acetylene proton), 3.78 (dd, 1 H, H-5'b, $J_{5'b,4'}$ = 2.9, $J_{5'b,5'a}$ = 11.7 Hz) 0.95, 0.92, 0.85 (each s, each 9 H, *tert*-butyl), 0.14, 0.13, 0.10, 0.09, -0.01, -0.21 (each s, each 3 H, methyl); Anal. Calcd for $C_{29}H_{53}N_3O_4Si_3$: C, 58.83; H, 9.02; N, 7.10. Found: C, 58.74; H, 9.02; N, 7.00.

**5,2'-*O*-Cycloetheno-1-β-D-ribofuranosylimidazole-4-carbonitrile (26).** Methanolic ammonia (saturated at 0 °C, 10 ml) was added to a solution of **24** (200 mg , 0.80 mmol) in MeOH (5 ml) and the whole was heated at 120 °C for 3 h in a sealed tube. After the starting material was completely consumed, the reaction mixture was concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (2.1 x 6 cm), eluted with 4–35% EtOH in $CHCl_3$, to give **26** (61 mg, 31%) and **29** (36 mg, 17%). As an analytical sample, compound **26** was crystallized from EtOH–hexane as white crystals: mp 198–201 °C; MS *m/z* 249 ($M^+$); UV $\lambda_{max}$ ($H_2O$) 278 nm (ε 17700); UV $\lambda_{max}$ (0.5 N HCl) 276 nm (ε 17800); UV $\lambda_{max}$ (0.5 N NaOH) 281 nm (ε 17900); $^1H$ NMR (DMSO-$d_6$) 7.77 (s, 1 H, H-2), 6.79 (d, 1 H, vinyl proton, $J$ = 7.7 Hz), 5.84 (d, 1 H, 3'-OH, $J_{3'\text{-OH},3'}$ = 4.4 Hz), 5.69 (d, 1 H, H-1', $J_{1',2'}$ = 6.0 Hz), 5.66 (d, 1 H, vinyl proton, $J$ = 7.7 Hz), 4.96 (dd, 1 H, 5'-OH, $J_{5'\text{-OH},5'a}$ = 6.0, $J_{5'\text{- OH},5'b}$ = 5.0 Hz), 4.40 (dd, 1 H, H-2', $J_{2',1'}$ = 6.0, $J_{2',3'}$ = 4.9 Hz), 4.34 (m, 1 H, H-3'), 4.24 (m, 1 H, H-4'), 3.48 (m, 2 H, H-5'a, b); Anal. Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.99; H, 4.48; N, 17.01.

**5,2'-*O*-Cycloetheno-1-(3,5-di-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (27).** Acetic anhydride (10 μl, 0.4 mmol) was added to a solution of **26** (25 mg, 0.1 mmol) in dry pyridine (2 ml) and the mixture was stirred at room temperature overnight. EtOH (1 ml) was added to the mixture to decompose an excess of acetic anhydride. The mixture was concentrated to dryness *in vacuo* and the residue was dissolved in AcOEt. The solution was washed successively with $H_2O$ and saturated aqueous NaCl. The separated organic layer was dried ($Na_2SO_4$) and concentrated to dryness *in vacuo*. The residue was coevaporated with toluene and purified by a silica gel column (1.7 x 5 cm), eluted with 20–50 % AcOEt in hexane, to give **27** (23 mg, 69% as a colorless oil): MS *m/z* 333 ($M^+$); IR 2220 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) 7.76 (s, 1 H, H-2), 6.75 (d, 1 H, vinyl proton, $J$ = 8.1 Hz), 5.79 (d, 1 H, H-1', $J_{1',2'}$ = 6.6 Hz), 5.71 (d, 1 H, vinyl proton, $J$ = 8.1 Hz), 5.53 (d, 1 H, H-3', $J_{3',2'}$ = 5.5 Hz), 4.73 (dd, 1 H, H-2', $J_{2',1'}$ = 6.6, $J_{2',3'}$ = 5.5 Hz), 4.64 (dd, 1 H, H-4', $J_{4',5'a}$ = 4.4, $J_{4',5'b}$ = 4.8 Hz), 4.22 (dd, 1 H, H-5'a, $J_{5'a,4'}$ = 4.4, $J_{5'a,b}$ = 12.1 Hz), 4.16 (dd, 1 H, H-5'b, $J_{5'b,4'}$ = 4.8, $J_{5'b,a}$ = 12.1 Hz), 2.18, 1.85 (each s, each 3 H, acetyl).

**4-Amino-1-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]-pyridine (28).** Methanolic ammonia (saturated at 0 °C, 40 ml) was added to a solution of **25** (2.28 g, 3.86 mmol) in MeOH (10 ml) and the mixture was heated at 120 °C for 3 h in a sealed tube. After the starting material was completely consumed, the reaction mixture was concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (3.2 x 13 cm), eluted with 33–75% AcOEt in hexane, to give **28** (1.78 g, 76% as a white solid). An analytical sample was prepared by crystallization from hexane as white crystals: mp 129 °C; MS *m/z* 608 ($M^+$); $^1H$ NMR ($CDCl_3$) 8.00 (s, 1 H, H-2), 7.82 (d, 1 H, H-6, $J$ = 6.0 Hz), 7.02 (d, 1 H, H-7, $J$ = 6.0 Hz), 5.78(d, 1 H, H-1', $J_{1',2'}$ = 7.1 Hz), 5.16 (br s, 2 H, $NH_2$), 4.38 (dd, 1 H, H-2', $J_{2',1'}$

= 7.1, $J_{2',3'}$ = 4.4 Hz), 4.21 (dd, 1 H, H-3', $J_{3',2'}$ = 4.4, $J_{3',4'}$ = 3.3 Hz), 4.13 (ddd, 1 H, H-4', $J_{4',3'}$ = 3.3, $J_{4',5'a}$ = 2.7, $J_{4',5'b}$ = 2.2 Hz), 3.94 (dd, 1 H, H-5'a, $J_{5'a,4'}$ = 2.7, $J_{5'a,5'b}$ = 11.5 Hz), 3.83 (dd, 1 H, H-5'b, $J_{5'b,4'}$ = 2.2, $J_{5'b,5'a}$ = 11.5 Hz), 0.98, 0.95, 0.75 (each s, each 9 H, *tert*-butyl), 0.18, 0.17, 0.12, 0.11, -0.14, -0.56 (each s, each 3 H, methyl); Anal. Calcd for $C_{29}H_{56}N_4O_4Si_3$: C, 57.19; H, 9.27; N, 9.20. Found: C, 57.03; H, 9.48; N, 9.03.

**4-Amino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridine (29).** A THF solution of TBAF (1 M, 1.8 ml, 1.8 mmol) was added to a solution of **28** (274 mg, 0.45 mmol) in dry THF (10 ml) at 0 °C. The mixture was stirred for 30 min at room temperature, and concentrated to dryness *in vacuo*. The residue was dissolved in $H_2O$ (5 ml) and put on a Amberlite XAD-4 resin column (2.7 x 34 cm), eluted with 0–60% MeOH in $H_2O$, to give **29** (120 mg, quant. as a bright yellow solid) which was crystallized from $H_2O$ as white crystals: mp 228–229° C (lit.[11] mp 229–231 °C); MS *m/z* 266 ($M^+$); UV $\lambda_{max}$ ($H_2O$) 263 nm (ε 10500); UV $\lambda_{max}$ (0.5 N HCl) 262 nm (ε 10900); UV $\lambda_{max}$ (0.5 N NaOH) 265 nm (ε 12700); $^1H$ NMR (DMSO-$d_6$) 8.29 (s, 1 H, H-2), 7.66 (d,1 H, H-6, $J$ = 5.9 Hz), 6.91 (d, 1 H, H-7, $J$ = 5.9 Hz), 6.15 (br s, 2 H, $NH_2$), 5.75 (d, 1 H, H-1', $J_{1',2'}$ = 6.2 Hz), 5.45 (d, 1 H, 2'-OH, $J_{2'\text{-OH},2'}$ = 6.2 Hz), 5.19 (d, 1 H, 3'-OH, $J_{3'\text{-OH},3'}$ = 4.4 Hz), 5.08 (dd, 1 H, 5'-OH, $J_{5'\text{-OH},5'a}$ = 5.1, $J_{5'\text{-OH},5'b}$ = 5.5 Hz), 4.31 (dt, 1 H, H-2', $J_{2',1'} = J_{2',2'\text{-OH}}$ = 6.2, $J_{2',3'}$ = 5.1 Hz), 4.09 (ddd, 1 H, H-3', $J_{3',2'}$ = 5.1, $J_{3',3'\text{-OH}}$ = 4.4, $J_{3',4'}$ = 3.3 Hz), 3.95 (dt, 1 H, H-4', $J_{4',3'}$ = 3.3, $J_{4',5'a} = J_{4',5'b}$ = 3.6 Hz), 3.66 (ddd, 1 H, H-5'a, $J_{5'a,4'}$ = 3.6, $J_{5'a,5'b}$ = 12.1, $J_{5'a,5'\text{-OH}}$ = 5.1 Hz), 3.59 (ddd, 1 H, H-5'b, $J_{5'b,4'}$ = 3.6, $J_{5'b,5'a}$ = 12.1, $J_{5'b,5'\text{-OH}}$ = 5.5 Hz); Anal. Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.29; N, 21.04. Found: C, 49.66; H, 5.34; N, 20.74.

**Acknowledgement.** This investigation was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science, and Culture of Japan.

## REFERENCES AND NOTES

1. Part 115: Aoyagi, M.; Minakawa, N.; Matsuda, A. *Tetrahedron Lett.*, in press.
2. (a) Chiang, P. K.; Richards, H. H.; Cantoni, G. L. *Mol. Pharmacol.*, **1977**, *13*, 939. (b) Chiang, P. K., Cantoni, G. L. *Biochem. Pharmacol.*, **1979**, *28*, 1897
3. (a) Bader, J. P.; Brown, N. R.; Chiang, P. K.; Cantoni, G. L. *Virology*, **1978**, *89*, 494. (b) Chiang, P. K.; Cantoni, G. L.; Shannon, W. M.; Thomas, H. J.; Montgomery, J. A. *Biochem. Biophys. Res. Commun.*, **1978**, *82*, 417.
4. Trager, W.; Tershakovec, M.; Chiang, P. K.; Cantoni, G. L. *Exp. Parasitol.*, **1980**, *50*, 83.
5. Flexner, C. W.; Hildreth, J. E.; Kuncl, R. W.; Drachman, D. B. *The Lancet*, **1992**, *339*, 438.
6. Jurgensen, C. H.; Huber, B. E.; Zimmerman, T. P.; Wolberg, G. *J. Immunol.*, **1990**, *114*, 653.
7. Allen, L. B.; Huffman, J. H.; Cook, P. D.; Meyer, R. B. Jr.; Robins, R. K.; Sidwell, R. W. *Antimicrob. Agents Chemother.*, **1977**, *12*, 114.
8. Khwaja, T. A.; Kigwana, L.; Meyer, R. B. Jr.; Robins, R. K. *Proc. Am. Assoc. Cancer Res.*, **1975**, *16*, 162.
9. (a) Ono, A.; Ueda, T. *Nucleic Acids Res.*, **1987**, *15*, 3059. (b) Ono, A.; Ohdoi, C.; Matsuda, A.; Ueda, T. *Nucleosides Nucleotides*, **1992**, *11*, 227. (c) Cosstick, R.; Li, X.; Tuil, D. K.; Williams,

D. M.; Connolly, B. A.; Newman, P. C. *Nucleic Acids Res.*, **1990**, *18*, 4771. (d) Seela, F.; Lampe, S. *Helv. Chim. Acta* , **1991**, *74*, 1790

10. Rousseau, R. T.; Townsend, L. B.; Robins, R. K. *Biochemistry*, **1966**, *5*, 756.
11. Mizuno, Y.; Tazawa, S.; Kageura, K. *Chem. Pharm. Bull.*, **1968**, *16*, 2011.
12. May, J. A. Jr.; Townsend, L. B. *J. Chem. Soc. Perkin Trans, I*, **1975**, 125.
13. Montgomery, J. A.; Shortnacy, A. T.; Clayton, S. D. *J. Heterocyclic Chem.*, **1977**, *14* , 195.
14. Cook, P. D.; Rousseau, R. J.; Main, A. M.; Dea, P.; Meyer, R. B. Jr.; Robins, R. K. *J. Am. Chem. Soc.*, **1976**, *98*, 1492.
15. Tanaka, H.; Hirayama, M.; Suzuki, M.; Miyasaka, T.; Matsuda, A.; Ueda, T. *Tetrahedron*, **1986**, *42*, 1971.
16. (a) Matsuda, A.; Minakawa, N.; Sasaki, T.; Ueda, T. *Chem Pharm Bull.*, **1988**, *36*, 2730. (b) Minakawa, N.; Takeda, T.; Sasaki, T.; Matsuda, A.; Ueda, T. *J. Med. Chem.*, **1991**, *34*, 778.
17. Hudlicky, M. "Oxidations in Organic Chemistry, ACS Monograph 186"; American Chemical Society, Washington, DC, **1990**, 202, and references therein.
18. Rf values for **6** and **7** in the same solvent system; 0.3 and 0.2, respectively.
19 A complete assignment of ribofuranose protons was established by homo spin decoupling experiments.
20. Itoh, T.; Ishihara, T.; Mizuno, Y. *Chem. Pharm. Bull.*, **1983**, *31*, 4130.