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A LITHIATION ROUTE TO C-5 SUBSTITUTION OF AN IMIDAZOLE NUCLEOSIDE AND ITS APPLICATION TO THE SYNTHESIS OF 3-DEAZAGUANOSINE

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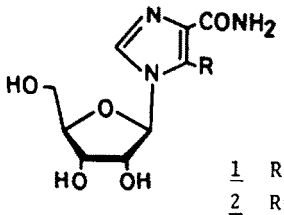
Abstract – Lithiation of a protected methyl 2-chloro-1-(β-D-ribofuranosyl)imidazole-4-carboxylate with LDA affords the C-5 anion which reacts with a wide range of electrophiles to provide various types of 5-substituted derivatives. Application of this method to the synthesis of 3-deazaguanosine, an antiviral nucleoside, is also described.

There have been many reports on the synthesis of imidazole nucleosides related to 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (1), the key intermediate in the de novo purine biosynthetic pathway.[1] Several reports suggest that introduction of C-5 substituents other than the amino group could lead to compounds such as 2-4 which exhibit significant biological activities.[2-5]

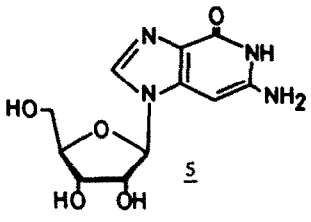
Most of these 5-substituted nucleosides have been prepared by classical condensation method.[5,6] Other procedures described in the literature include Sandmeyer reaction of 1 to give 3 (R= Cl, Br, I)[7] and photochemical transformation of 1 to 4.[8]



1 R= NH_2
2 R= Me
3 R= halogen
4 R= OH

As part of our continuing work on the utilization of lithiation for the synthetic purpose in nucleoside field,[9] we were interested in the lithiation of imidazole nucleosides which has so far been unknown. Our interest was, of course, further motivated by the fact that a general method for the substitution of imidazole nucleosides at the C-5 position was still lacking. In this paper, we would like to report that the chlorine atom at the C-2 position of an imidazole nucleoside serves as a protecting group during the lithiation with LDA and that reactions of the C-5 lithiated species with various types of electrophiles constitute an efficient method for the C-5 substitution and a new route to 3-deazaguanosine (5), an antiviral nucleoside.[10]

It is well known that lithiation of 1-substituted imidazole occurs at the carbon between nitrogen atoms.[11] Thus, to generate the C-5 anion, protection of its C-2 position may be necessary.[12] This suggests that 2-imidazolone nucleoside



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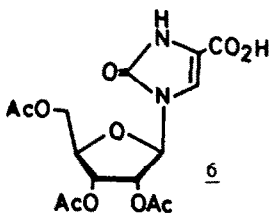

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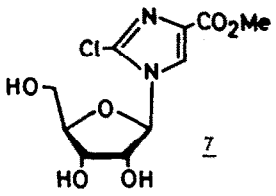


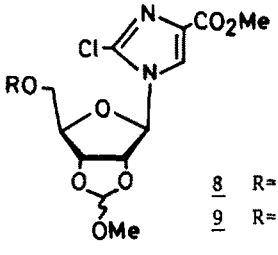
7

(6), which can be obtained from uridine in relatively large quantity,[13,14] would be useful for our purpose. That is, methyl 1-(β-D-ribofuranosyl)-2-chloroimidazole-4-carboxylate (7) accessible from 6 might be a good candidate for the lithiation at C-5, provided that the C-2 protecting group is compatible with the lithiation and removable under mild conditions.

Compound 6 was esterified (CH_2N_2/Et_2O-MeOH), chlorinated ($POCl_3$/N,N-dimethylaniline), and deacetylated (NaOMe/MeOH) according to the published procedures[14] to give 7.

The sugar hydroxyls in 7 were first protected with 2',3'-O-isopropylidene and 5'-O-methoxymethyl groups which had been successfully used for the C-6 lithiation of uridine.[9a] However, it turned out that 50% aqueous trifluoroacetic acid treatment required for removing these protecting groups caused cleavage of the glycosidic bond in the case of 7 or in any later stage of our reaction sequence. When 7 was treated with TBDMS (tert-butyldimethylsilyl) or TBDPS (tert-butyldiphenylsilyl) chloride in DMF in the presence of imidazole,[15] a mixture of tris-, bis-, and mono-O-silylated products was formed even by the use of the excess reagent. Accordingly, 2',3'-O-methoxymethylidene and 5'-O-TBDMS protecting groups were employed in the case of 7.

Compound 8 was prepared in 89% yield by ortho-ester exchange of trimethyl orthoformate with 7 in the presence of *p*-TsOH and DMF (at room temperature, for 2 h) followed by treatment of the resulting mixture with an activated silica gel to remove 5'-O-protection.[16] Silylation of 8 with TBDMSCl was carried out in pyridine (at room temperature, overnight) to give a fully protected derivative (9) in 95% yield. The PMR spectrum of 9 in $CDCl_3$ indicated that the ratio of two diastereomers was approximately 9:1 with a more shielded orthoformate proton (CH-OMe: δ 5.95 ppm), presumably exo to the ribose ring, predominant.



8 R= H
9 R= TBDMS

As LDA is a non-nucleophilic lithiating agent, which is suitable for the metallation of nucleoside having a halogen substituent,[9b,c] lithiation of 9 was carried out with this reagent. When 9 in THF was added to a THF solution of LDA (1.8 equiv) below -70 °C, a slightly yellow solution of the anion resulted. After 1 h, the reaction mixture was quenched with CD_3OD and the deuterated product was isolated by short-column chromatography on silica gel (recovery: 93%). The extent of deuterium incorporation to the C-5 position was estimated at 91% by comparing the integration of remaining H-5 (δ 7.90 and 7.93 ppm) with that of H-1' (δ 5.88 and 6.11 ppm). As can be seen from the recovery of the deuterated product, other products derived from the cleavage of C-Cl bond or the ester function in 9 were not detected in any appreciable amount in this reaction.

We next examined reactions of the lithiated species (10) with a variety of electrophilic reagents, including non-carbon electrophiles such as diphenyl di-

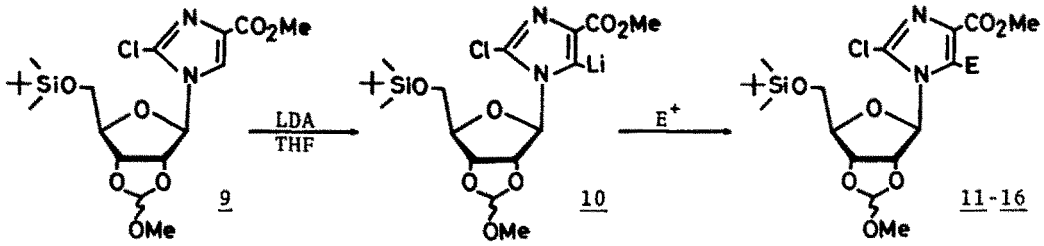


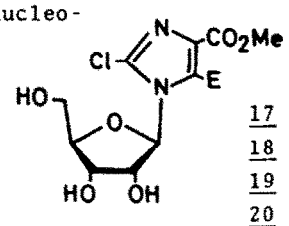
Table 1

Electrophile	E	Product	Yield (%)
MeI	Me	11	83
PhCOCl	COPh	12	86
$ClCO_2Me$	CO_2Me	13	84
PhSSPh	SPh	14	84
$ClSiMe_3$	$SiMe_3$	15	87
iodine	I	16	—

sulfide, trimethylchlorosilane, and iodine. The results are summarized in Table 1. 5-Iodinated product (16) suffered from appreciable cleavage of its glycosidic bond upon attempted purification and the pure material could not be isolated.

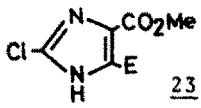
Concurrent deprotection of 2',3'-O-methoxymethylidene and 5'-O-TBDMS groups in 11-16 can be effected by treatment with aqueous acetic acid followed by methanolic ammonia in a one-pot manner to give the corresponding free nucleoside.

Thus, when a 5-substituted imidazole nucleoside was treated with 20% aqueous AcOH at room temperature for 2 days, the 5'-O-TBDMS group was also removed, producing a mixture of the corresponding free nucleoside (17-22) and its 2'- or 3'-O-formyl ester. After evaporation, the mixture was briefly treated with NH_3-MeOH (15 min) to furnish 17-22 (yields are shown in parentheses).



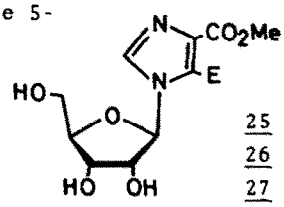
17 E= Me (75%)
18 E= COPh (74%)
19 E= CO_2Me (58%)
20 E= SPh (69%)
21 E= $SiMe_3$ (47%)
22 E= I (24%)

In the case of the formation of 19, partial cleavage of the glycosidic bond occurred during 20% aqueous AcOH treatment giving a 28% yield of 2-chloro-4,5-bis(methoxycarbonyl)imidazole (23) besides 19. In the deprotection of 15, the 5-trimethylsilyl group was partially removed upon subjecting the mixture to NH_3-MeOH and 7 was isolated in 10% yield after silica gel column chromatography. The crude mixture containing the 5-iodo derivative (16) was deprotected in a similar manner to afford 22 and the corresponding base (24) in 24% and 48% yields, respectively.



23 E= CO_2Me (28%)
24 E= I (48%)

The C-2 chlorine atom used as a protecting group during the C-5 lithiation of 9 can be removed by hydrogenolysis (3 atm of H_2) in the presence of 10% Pd-C, which is demonstrated by converting some of 5-substituted derivatives to 25-27.



25 E= Me
26 E= CO_2Me
27 E= $SiMe_3$

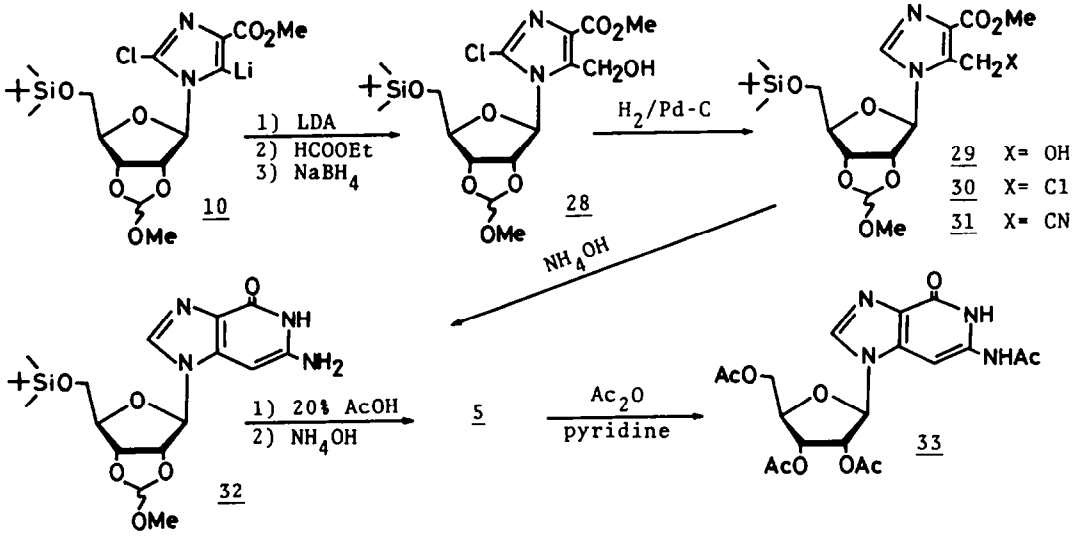
The above mentioned method for the C-5 substitution of imidazole nucleoside

in hand, we then investigated to synthesize 3-deazaguanosine, an antiviral nucleoside, from 9.

The synthesis of 3-deazaguanosine (6-amino-1-(β-D-ribofuranosyl)imidazo[4,5-c]pyridin-4(5H)-one) (5) has been reported by Cook *et al.*,[17] and it was found to be active against certain DNA and RNA viruses.[18] The method reported, however, suffered from regio- and stereochemical disadvantages when employed for the preparation of arabinofuranosyl[19] and 2'-deoxyribofuranosyl[20] derivatives of 3-deazaguanine. Accordingly, a method to transform a preformed imidazole nucleoside to a 3-deazaguanine derivative may be necessary.[21]

Compound 9 was treated with LDA as described above and the resulting 10 was subjected to the reaction with HCOOEt (below -70 °C, 1 h) to yield the 5-formyl derivative, which was reduced by $NaBH_4$ in a one-pot manner. By using these procedures, the 5-hydroxymethylated product (28) was obtained in 78% yield. The C-2 chlorine atom in 28 was removed by aforementioned hydrogenolysis to give 29 (92%). Chlorination of the hydroxymethyl group in 29 was first carried out with MsCl in the presence of a bulky acid-acceptor, 2,6-lutidine, to prevent the formation of a quaternary ammonium derivative.[22] It revealed, however, that partial deprotection of the sugar part took place during this reaction, presumably due to an acidic nature of 2,6-lutidinium salt formed. The use of Et_3N effected virtually quantitative conversion to give rise to 30 which was rather unstable. The key intermediate, 5-cyanomethyl derivative 31, was obtained in 86% yield by nucleophilic substitution of 30 with KCN in the presence of 18-crown-6 in benzene.

Cyclization of 31 to yield a protected 3-deazaguanosine (32) was conducted with 28% NH_4OH/MeOH in a sealed tube at 80 °C for 2 h.[23] Upon cooling the reaction mixture, 32 was separated as crystals (45%, mp 231-233 °C). The structure of 32 was clear from its PMR spectrum (DMSO-d_6), in which two aromatic protons appeared as singlets at 6.08 and 7.80 ppm together with two D_2O-exchangeable amino protons at 5.63 ppm. Treatment of 32 with 20% aqueous AcOH followed by dilute NH_4OH furnished 3-deazaguanosine (5: 80%) whose physical constants were identical in all respects with those reported.[17] Exclusion of the light was essential during deprotection, otherwise formation of a more polar product was observed. The structure of 3-deazaguanosine thus obtained was further confirmed by converting it to the tetraacetyl derivative 33.



EXPERIMENTAL

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. PMR spectra were measured with an internal standard of tetramethylsilane (TMS) with a JEOL JNM-FX 100 spectrometer. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad. In case where product was a mixture of two diastereomers, PMR signals of the major isomer are shown except in the case of 9. Mass spectra were taken on a JEOL JMS-D 300 spectrometer. UV spectra were recorded on a Shimadzu UV-240 spectrophotometer. Reactions at low temperature were performed using a CryoCool CC-100 (NESLAB Instrument, Inc.). Butyllithium in hexane was titrated before use by diphenylacetic acid in THF. THF was distilled from benzophenone ketyl. Column chromatography was carried out on silica gel (Wakogel® C-200) except for the preparation of 8. TLC was performed on silica gel (precoated silica gel plate 60 F_{254}, Merck).

Methyl 2-chloro-1-(2,3-O-methoxymethylidene-β-D-ribofuranosyl)imidazole-4-carboxylate (8)—— Compound 7 (3.0 g, 10.3 mmol) was suspended into a mixture of trimethyl orthoformate (90 ml), p-TsOH (244 mg), and DMF (6.0 ml). The reaction mixture was stirred at room temperature for 2 h. To the resulting solution, saturated aqueous $NaHCO_3$ was added and the whole mixture was evaporated. The residue was taken up into EtOAc-H_2O and the organic layer separated was dried (Na_2SO_4), filtered and evaporated to dryness. The whole residue was dissolved in $CHCl_3$ and applied to an activated silica gel (Mallinckrodt 2847®) column. The column was washed with $CHCl_3$ (300 ml) and kept standing for 3 days at room temperature. Elution with 1% MeOH in $CHCl_3$ gave 8 (3.1 g, 90%) as syrup.

Anal. Calcd. for $C_{12}H_{15}N_2O_7Cl$: C, 43.07; H, 4.48; N, 8.37. Found: C, 42.90; H, 4.46; N, 8.44. UV absorption in MeOH: max 234 nm (ε 10800). MS m/z: 336 and 334 (M^+), 305 and 303 (M-OMe), 162 and 160 (B+1). PMR ($CDCl_3$) δ: 3.45 (3H, s, CHOMe), 3.87 (3H, s, CO_2Me), 3.95 (2H, m, CH_2-5'), 4.48 (1H, m, H-4'), 4.83 (1H, dd, H-3'), 5.01 (1H, dd, H-2'), 5.96 (1H, s, CHOMe), 6.10 (1H, d, J= 3.4 Hz, H-1'), 7.95 (1H, s, H-5).

Methyl 2-chloro-1-(2,3-O-methoxymethylidene-5-O-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxylate (9)—— TBDMSCl (2.08 g, 13.8 mmol) was added to a solution of 8 (3.1 g, 9.2 mmol) in pyridine (30 ml). The reaction mixture was stirred overnight at room temperature. Saturated aqueous $NaHCO_3$ was added to the reaction mixture. Extraction with $CHCl_3$ followed by column chromatography on silica gel (10% EtOAc in benzene) gave 9 (4.0 g, 96%) as syrup.

Anal. Calcd. for $C_{18}H_{29}N_2O_7ClSi$: C, 48.15; H, 6.51; N, 6.24. Found: C, 48.07; H, 6.55; N, 6.17. UV absorption in MeOH: max 233 nm (ε 14800). MS m/z: 435 and 433 (M-Me), 393 and 391 (M-Bu), 289 (M-B). PMR ($CDCl_3$) δ: 0.12 (6H, s, $SiMe_2$), 0.91 (9H, s, SiBu-t), 3.36 and 3.45 (3H, each as s, CHOMe), 3.87 (3H, s, CO_2Me), 3.93 (2H, m, CH_2-5'), 4.51 (1H, m, H-4'), 4.71 (1H, dd, H-3'), 4.92 (1H, dd, H-2'), 5.88 and 6.11 (1H, each as d, H-1'), 5.95 and 6.01 (1H, each as s, CHOMe), 7.90 and 7.93 (1H, each as s, H-5).

Deuteration of methyl 2-chloro-5-lithio-1-(2,3-O-methoxymethylidene-5-O-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxylate (10)—— LDA (1.3 mmol) in THF (12 ml) was placed in a three-necked flask equipped with a gas inlet adaptor, thermometer, and rubber septum. To this, a solution of 9 (314 mg, 0.7 mmol) in THF (7 ml) was added, under positive pressure of dry argon, at such a rate that the temperature did not exceed -70 °C. After the mixture was stirred for 1 h at below -70 °C, CD_3OD (0.5 ml) was added and the whole was stirred for further 1 h. The reaction was then quenched by adding AcOH (0.1 ml). Evaporation of the solvent followed by chromatography on a silica gel column (10% EtOAc in benzene) gave the deuterated 9 (292 mg, recovery: 93%), of which PMR spectrum in $CDCl_3$ was measured. The extent of deuterium incorporation to the C-5 position was estimated at 91% by comparing the integration of remaining H-5 (δ 7.90 and 7.93 ppm) with that of H-1' (δ 5.88 and 6.11 ppm).

Methyl 2-chloro-5-methyl-1-(2,3-O-methoxymethylidene-5-O-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxylate (11)—— This compound was prepared by the procedure for the deuteration of 10. The following amounts of reagents and 479 mg (1.1 mol) of 9 in THF (7 ml) were used: LDA (1.9 mmol) in THF (12 ml), MeI (0.2 ml, 1.9 mmol). The reaction was continued for 1.5 h at below -70 °C. Silica gel column chromatography (5% EtOAc in benzene) gave 11 (410 mg, 83%) as syrup.

UV absorption in MeOH: max 235 nm. MS m/z: 464 and 462 (M^+), 176 and 174 (B+1). PMR ($CDCl_3$) δ: 0.09 (6H, s, $SiMe_2$), 0.92 (9H, s, SiBu-t), 2.64 (3H, s, 5-Me), 3.43 (3H, s, CHOMe), 3.89-3.95 (5H, m, CO_2Me and CH_2-5'), 4.32-4.26 (1H, m, H-4'), 4.97-5.01 (2H, m, H-2' and H-3'), 5.98 (1H, s, CHOMe), 6.03 (1H, d, J= 3.4 Hz, H-1').

Methyl 5-benzoyl-2-chloro-1-(2,3-O-methoxymethylidene-5-O-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxylate (12)—— This compound was prepared by the procedure for the deuteration of 10. The following amounts of reagents and 465 mg (1.0 mmol) of 9 in THF (8 ml) were used: LDA (1.8 mmol) in THF (12 ml), benzoyl chloride (0.22 ml, 1.8 mmol). The reaction was continued for 1.5 h at below -70 °C. Silica gel column chromatography (4% EtOAc in benzene) gave 12 (493 mg, 86%) as syrup.

UV absorption in MeOH: max 259 nm, shoulder 290 nm, min 240 nm. MS m/z: 539

and 537 (M-Me), 523 and 521 (M-OMe), 266 and 264 (B+1). PMR ($CDCl_3$) δ: 0.05 (6H, s, $SiMe_2$), 0.93 (9H, s, SiBu-t), 3.36 (2H, m, CH_2-5'), 3.40 (3H, s, CHOMe), 3.56 (3H, s, CO_2Me), 4.12 (1H, m, H-4'), 4.66 (1H, dd, H-3'), 5.32 (1H, dd, H-2'), 5.95 (1H, s, CHOMe), 6.17 (1H, d, J= 3.9 Hz, H-1'), 7.35-7.84 (5H, m, COPh).

Methyl 2-chloro-5-methoxycarbonyl-1-(2,3-O-methoxymethylidene-5-O-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxylate (13)—— This compound was prepared by the procedure for the deuteration of 10. The following amounts of reagents and 451 mg (1.0 mg) of 9 in THF (5 ml) were used: LDA (1.8 mmol) in THF (12 ml), methyl chloroformate (0.14 ml, 1.8 mmol). The reaction was continued for 1.5 h at below -70 °C. Silica gel column chromatography (5% EtOAc in benzene) gave 13 (431 mg, 84%) as syrup.

UV absorption in MeOH: max 251 nm, min 234 nm. MS m/z: 508 and 506 (M^+), 477 and 475 (M-OMe), 220 and 218 (B+1). PMR ($CDCl_3$) δ: 0.09 (6H, s, $SiMe_2$), 0.91 (9H, s, SiBu-t), 3.42 (3H, s, CHOMe), 3.78 (2H, m, CH_2-5'), 3.90 (6H, s, 4- and 5-CO_2-Me), 4.25 (1H, m, H-4'), 4.73 (1H, dd, H-3'), 5.24 (1H, dd, H-2'), 5.96 (1H, s, CHOMe), 6.23 (1H, d, J= 3.9 Hz, H-1').

Methyl 2-chloro-5-phenylthio-1-(2,3-O-methoxymethylidene-5-O-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxylate (14)—— This compound was prepared by the procedure for the deuteration of 10. The following amounts of reagents and 378 mg (0.8 mmol) of 9 in THF (5 ml) were used: LDA (1.4 mmol) in THF (12 ml), diphenyl disulfide (314 mg, 1.4 mmol) in THF (3 ml). The reaction was continued for 1.5 h at below -70 °C. Silica gel column chromatography (6% EtOAc in benzene) gave 14 (375 mg, 84%) as syrup.

UV absorption in MeOH: max 243 nm, shoulder 285 nm, min 222 nm. MS m/z: 558 and 556 (M^+), 527 and 525 (M-OMe), 270 and 268 (B+1). PMR ($CDCl_3$) δ: 0.09 (6H, s, $SiMe_2$), 0.89 (9H, s, SiBu-t), 3.34 (3H, s, CHOMe), 3.78 (2H, m, CH_2-5'), 3.84 (3H, s, CO_2Me), 4.22 (1H, m, H-4'), 4.83 (1H, dd, H-3'), 5.21 (1H, dd, H-2'), 5.90 (1H, s, CHOMe), 6.40 (1H, d, J= 3.9 Hz, H-1'), 7.23 (5H, m, SPh).

Methyl 2-chloro-5-trimethylsilyl-1-(2,3-O-methoxymethylidene-5-O-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxylate (15)—— This compound was prepared by the procedure for the deuteration of 10. The following amounts of reagents and 493 mg (1.1 mmol) of 9 in THF (5 ml) were used: LDA (1.9 mmol) in THF (12 ml), trimethylchlorosilane (0.25 ml, 2.7 mmol). The reaction was continued for 1.5 h at below -70 °C. Silica gel column chromatography (8% EtOAc in benzene) gave 15 (498 mg, 87%) as syrup.

UV absorption in MeOH: max 244 nm, min 238 nm. MS m/z: 507 and 505 (M-Me), 491 and 489 (M-OMe), 219 and 217 (B+1-Me). PMR ($CDCl_3$) δ: 0.08 (6H, s, $SiMe_2$), 0.45 (9H, s, 5-$SiMe_3$), 0.91 (9H, s, SiBu-t), 3.40 (3H, s, CHOMe), 3.88 (3H, s, CO_2Me), 3.90 (2H, m, CH_2-5'), 4.19 (1H, m, H-4'), 4.90 (1H, dd, H-3'), 5.27 (1H, dd, H-2'), 5.95 (1H, s, CHOMe), 6.17 (1H, d, J= 4.4 Hz, H-1').

Methyl 2-chloro-5-methyl-1-(β-D-ribofuranosyl)imidazole-4-carboxylate (17)—— 20% Aqueous AcOH (40 ml) was added to 11 (436 mg) and the mixture was stirred at room temperature for 2 days. The reaction mixture was evaporated and coevaporated with EtOH to remove the last trace of water. The residue was treated with NH_3/MeOH (20 ml) for 15 min. After evaporation, the resulting residue was chromatographed on a silica gel column (5% EtOH in $CHCl_3$) to give 17 (214 mg, 75%) as foam.

Anal. Calcd. for $C_{11}H_{15}N_2O_6Cl$: C, 43.09; H, 4.89; N, 9.14. Found: C, 43.30; H, 5.18; N, 9.13. UV absorption in H_2O: max 241 nm (ε 11700). MS m/z: 308 and 306 (M^+), 176 and 174 (B+1). PMR (DMSO-d_6) δ: 2.59 (3H, s, 5-Me), 3.57 (3H, s, CO_2Me), 3.62 (2H, m, CH_2-5'), 3.83 (1H, m, H-4'), 3.95-4.10 (1H, m, H-3'), 4.26-4.45 (1H, m, H-2'), 4.94 (1H, t, 5'-OH), 5.23 and 5.48 (2H, each as d, 2'- and 3'-OH), 5.63 (1H, d, J= 6.8 Hz, H-1').

Methyl 5-benzoyl-2-chloro-1-(β-D-ribofuranosyl)imidazole-4-carboxylate (18) —— This compound was prepared from 12 (440 mg) as described in the preparation of 17 from 11. Silica gel column chromatography (7% EtOH in $CHCl_3$) gave 234 mg (74%) of 18 as foam.

Anal. Calcd. for $C_{17}H_{17}N_2O_7Cl$: C, 51.47; H, 4.29; N, 7.06. Found: C, 51.75; H, 4.41; N, 6.77. UV absorption in H_2O: max 253 nm (ε 9800) and 322 nm (ε 4500), min 225 nm (ε 5500) and 289 nm (ε 2600). MS m/z: 266 and 264 (B+1). PMR (DMSO-d_6) δ: 2.62-3.22 (2H, m, CH_2-5'), 3.48 (3H, s, CO_2Me), 3.63 (1H, m, H-4'), 3.80 (1H, m, H-3'), 4.26 (1H, m, H-2'), 4.57 (1H, t, 5'-OH), 5.19 and 5.58 (2H, each as d, 2'- and 3'-OH), 5.64 (1H, d, J= 6.8 Hz, H-1'), 7.42-7.98 (5H, m, COPh).

Methyl 2-chloro-5-methoxycarbonyl-1-(β-D-ribofuranosyl)imidazole-4-carboxylate (19) and 2-chloro-4,5-bis(methoxycarbonyl)imidazole (23)—— These compounds were prepared from 13 (431 mg) as described in the preparation of 17 from 11. Silica gel column chromatography (8% EtOH in $CHCl_3$) gave 173 mg (58%) of 19 as foam and 52 mg (28%) of 23 which was crystallized from MeOH (mp 110-112 °C).

Physical data of 19 are as follows. Anal. Calcd. for $C_{12}H_{15}N_2O_8Cl$: C, 41.11; H, 4.28; N, 7.99. Found: C, 41.26; H, 4.44; N, 7.81. UV absorption in H_2O: max 246 nm (ε 8600). MS m/z: 220 and 218 (B+1). PMR (DMSO-d_6, after addition of D_2O) δ: 3.54 (2H, m, CH_2-5'), 3.71 (1H, m, H-4'), 3.91 (1H, m, H-3'), 3.78 and 3.86 (6H, each as s, 4- and 5-CO_2Me), 4.29 (1H, t, H-2'), 5.73 (1H, d, J= 6.8 Hz, H-1').

Physical data of 23 are as follows. Anal. Calcd. for $C_7H_7N_2O_8Cl$: C, 38.47; H, 3.20; N, 12.82. Found: C, 38.76; H, 3.36; N, 12.72. UV absorption in H_2O: max

258 nm (ε 10400), min 233 nm (ε 7200). MS m/z: 220 and 218 (M^+). PMR (DMSO-d_6) δ: 3.81 (6H, s, CO_2Me), 10.42 (1H, br, NH).

Methyl 2-chloro-5-phenylthio-1-(β-D-ribofuranosyl)imidazole-4-carboxylate (20) —— This compound was prepared from 14 (266 mg) as described in the preparation of 17 from 11. Silica gel column chromatography (5% EtOH in $CHCl_3$) gave 132 mg (69%) of 20 which was crystallized from isopropyl alcohol (mp 127-129 °C).

Anal. Calcd. for $C_{16}H_{17}N_2O_6ClS$: C, 47.96; H, 4.24; N, 6.99. Found: C, 47.68; H, 4.31; N, 6.93. UV absorption in H_2O: max 243 nm (ε 13900) and 297 nm (ε 1000), min 223 nm (ε 7700). MS m/z: 402 and 400 (M^+), 270 and 268 (B+1). PMR (DMSO-d_6) δ: 3.53 (2H, m, CH_2-5'), 3.70 (3H, s, CO_2Me), 3.77 (1H, m, H-4'), 3.96-4.12 (1H, m, H-3'), 4.50-4.68 (1H, m, H-2'), 4.82 (1H, t, 5'-OH), 5.19 and 5.45 (2H, each as d, 2'- and 3'-OH), 6.00 (1H, d, J= 6.4 Hz, H-1'), 7.13-7.39 (5H, m, SPh).

Methyl 2-chloro-5-trimethylsilyl-1-(β-D-ribofuranosyl)imidazole-4-carboxylate (21) —— This compound was prepared from 15 (470 mg) as described in the preparation of 17 from 11. Silica gel column chromatography (8% EtOH in $CHCl_3$) gave 153 mg (47%) of 21 which was crystallized from H_2O (mp 65-67 °C) and 25 mg (10%) of 7.

Physical data of 21 are as follows. Anal. Calcd. for $C_{13}H_{21}N_2O_6ClSi$: C, 42.81; H, 5.76; N, 7.68. Found: C, 43.01; H, 5.89; N, 7.60. UV absorption in MeOH: max 233 nm (ε 11400). MS m/z: 366 and 364 (M^+), 234 and 232 (B+1). PMR (DMSO-d_6) δ: 0.37 (9H, s, $SiMe_3$), 3.62 (2H, m, CH_2-5'), 3.76 (3H, s, CO_2Me), 3.80 (1H, m, H-4'), 4.02 (1H, m, H-3'), 4.51 (1H, m H-2'), 4.86 (1H, t, 5'-OH), 5.15 and 5.51 (2H, each as d, 2'- and 3'-OH), 5.71 (1H, d, J= 6.4 Hz, H-1').

Methyl 2-chloro-5-iodo-1-(β-D-ribofuranosyl)imidazole-4-carboxylate (22) and 2-chloro-4(5)-iodo-5(4)-methoxycarbonylimidazole (24) —— The lithiation reaction was carried out by using the following amounts of reagents and 497 mg (1.1 mmol) of 9 in THF (5 ml): LDA (1.9 mmol) in THF (12 ml), iodine (507 mg, 2.0 mmol as I_2). The iodination reaction was continued for 1 h at below -70 °C. The crude mixture was passed through a silica gel column (6% EtOAc in benzene) and treated as described in the preparation of 17 from 11. Silica gel column chromatography (8% EtOH in $CHCl_3$) gave 22 (109 mg, 24%), which was rather unstable, and 38 (152 mg, 48%) as crystals (mp 165-168 °C).

PMR data of 22 are as follows. PMR (DMSO-d_6) δ: 3.59 (2H, m, CH_2-5'), 3.77 (3H, s, CO_2Me), 3.84 (1H, m, H-4'), 3.97-4.23 (1H, m, H-3'), 4.47-4.65 (1H, m, H-2'), 4.88 (1H, t, 5'-OH), 5.24 and 5.53 (2H, each as d, 2'- and 3'-OH), 5.80 (1H, d, J= 6.4 Hz, H-1').

Physical data of 24 are as follows. Anal. Calcd. for $C_5H_4N_2O_2ClI$: C, 20.97; H, 1.40; N, 9.78. Found: C, 21.10; H, 1.45; N, 9.70. UV absorption in MeOH: max 267 nm (ε 10900), min 237 nm (ε 4100). MS m/z: 288 and 286 (M^+). PMR (DMSO-d_6) δ: 3.79 (3H, s, CO_2Me), 14.11 (1H, br, NH).

Methyl 5-methyl-1-(β-D-ribofuranosyl)imidazole-4-carboxylate (25) —— Hydrogenolysis of 11 (240 mg) was carried out in MeOH (13 ml) and Et_3N (0.2 ml) in the presence of 10% Pd-C (98 mg) for 24 h under 3 atm of H_2. Short-column chromatography on silica gel (10% EtOAc in benzene) gave 188 mg (85%) of the product, which was then deprotected as described above. Purification through a silica gel column (8% EtOH in $CHCl_3$) gave 25 (105 mg, 88%) as syrup.

UV absorption in H_2O: max 239 nm, min 206 nm. PMR (DMSO-d_6, after addition of D_2O) δ: 2.51 (overlapped with DMSO, 5-Me), 3.75 (2H, m, CH_2-5'), 3.87-4.24 (3H, m, H-2', H-3' and H-4'), 5.55 (1H, d, J= 5.4 Hz, H-1'), 8.00 (1H, s, H-2).

Compound 25 was converted to its triacetate, whose high resolution MS was measured. High resolution MS m/z: 398.13316 (M^+) Calcd. for $C_{17}H_{22}N_2O_9$ 398.13256. PMR ($CDCl_3$) δ: 2.11 (3H, s, Ac), 2.15 (6H, s, Ac), 2.62 (3H, s, 5-Me), 3.90 (3H, s, CO_2Me), 4.37 (3H, m, CH_2-5' and H-4'), 5.34-5.51 (2H, m, H-2' and H-3'), 5.77 (1H, d, J= 4.4 Hz, H-1'), 7.74 (1H, s, H-2).

Methyl 5-methoxycarbonyl-1-(β-D-ribofuranosyl)imidazole-4-carboxylate (26) —— Hydrogenolysis of 13 (335 mg) was carried out in MeOH (15 ml) and Et_3N (0.23 ml) in the presence of 10% Pd-C (90 mg) for 3 h under 3 atm of H_2. Short-column chromatography on silica gel (10% EtOAc in benzene) gave 293 mg (94%) of the product, which was then deprotected as described above. Purification through a silica gel column (8% EtOH in $CHCl_3$) gave 26 (155 mg, 79%) as syrup.

UV absorption in H_2O: max 250 nm, min 210 nm. PMR (DMSO-d_6, after addition of D_2O) δ: 3.57-3.64 (2H, m, CH_2-5'), 3.78 and 3.84 (6H, each as s, 4- and 5-CO_2Me), 3.90-4.20 (3H, m, H-2', H-3' and H-4'), 5.84 (1H, d, J= 3.9 Hz, H-1'), 8.35 (1H, s, H-2).

Compound 26 was converted to its triacetate, whose high resolution MS was measured. High resolution MS m/z: 442.12383 (M^+) Calcd. for $C_{18}H_{22}N_2O_{11}$ 442.12243. PMR ($CDCl_3$) δ: 2.08 (3H, s, Ac), 2.16 (6H, s, Ac), 3.91 and 3.93 (6H, each as s, 4- and 5-CO_2Me), 4.29-4.51 (3H, m, CH_2-5' and H-4'), 5.26-5.53 (2H, m, H-2' and H-3'), 6.31 (1H, d, J= 2.9 Hz, H-1'), 7.28 (1H, s, H-2).

Methyl 5-trimethylsilyl-1-(β-D-ribofuranosyl)imidazole-4-carboxylate (27) —— Hydrogenolysis of 15 (321 mg) was carried out in MeOH (15 ml) and Et_3N (0.25 ml) in the presence of 10% Pd-C (107 mg) for 5.5 h under 3 atm of H_2. Short-column chromatography on silica gel (8% EtOAc in benzene) gave 237 mg (79%) of the product, which was then deprotected as described above. Purification through a silica gel column (8% EtOH in $CHCl_3$) gave 27 (76 mg, 47%) as syrup.

UV absorption in H_2O: max 246 nm, min 223 nm. PMR (DMSO-d_6) δ: 0.36 (9H, s, $SiMe_3$), 3.58 (2H, m, CH_2-5'), 3.88 (1H, m, H-4'), 3.98-4.27 (2H, m, H-2' and H-3'), 5.06 (1H, t, 5'-OH), 5.18 and 5.45 (2H, each as d, 2'- and 3'-OH), 5.67 (1H, d, J= 5.4 Hz, H-1'), 8.25 (1H, s, H-2).

Compound 27 was converted to its triacetate, whose high resolution MS was measured. High resolution MS m/z: 456.15572 (M^+) Calcd. for $C_{19}H_{28}N_2O_9Si$ 456.15632. PMR ($CDCl_3$) δ: 0.44 (9H, s, $SiMe_3$), 2.09 (3H, s, Ac), 2.15 (3H, s, Ac), 2.17 (3H, s, Ac), 3.90 (3H, s, CO_2Me), 4.36 (3H, m, CH_2-5' and H-4'), 5.34-5.48 (2H, m, H-2' and H-3'), 6.08 (1H, d, J= 5.4 Hz, H-1'), 7.99 (1H, s, H-2).

Methyl 2-chloro-5-hydroxymethyl-1-(2,3-O-methoxymethylidene-5-O-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxylate (28)—— The lithiation reaction was carried out by using the following amounts reagents and 484 mg (1.1 mmol) of 9 in THF (5 ml): LDA (1.9 mmol) in THF (12 ml), ethyl formate (0.16 ml, 2 mmol). The reaction was continued for 1 h at below -70 °C. The reaction mixture was quenched with AcOH (0.11 ml) and allowed to warm to room temperature. The mixture containing 5-formyl derivative was diluted with MeOH (20 ml) and then treated with $NaBH_4$ (36 mg) for 30 min at room temperature. After evaporation, the whole residue was chromatographed on a silica gel column (8% EtOAc in benzene). This afforded 400 mg (78%) of 28 as syrup.

UV absorption in MeOH: max 230 nm, shoulder 240 nm. MS m/z: 449 and 447 (M-OMe), 423 and 421 (M-Bu). PMR ($CDCl_3$) δ: 0.16 (6H, s, $SiMe_2$), 0.95 (9H, s, SiBu-t), 3.70 (3H, s, CHOMe), 3.91 (3H, s, CO_2Me), 4.01 (2H, m, CH_2-5'), 4.28 (1H, m, H-4'), 4.85-5.21 (4H, m, 5-CH_2OH, H-2' and H-3'), 5.98 (1H, s, CHOMe), 6.18 (1H, d, J= 4.4 Hz, H-1').

Methyl 5-hydroxymethyl-1-(2,3-O-methoxymethylidene-5-O-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxylate (29)—— Hydrogenolysis of 28 (2.5 g) was carried out in MeOH (100 ml) and Et_3N (5.5 ml) in the presence of 10% Pd-C (521 mg) for 15 h under 3 atm of H_2. After removal of the catalyst, the reaction mixture was evaporated to dryness and the residue was chromatographed on a silica gel column (1% MeOH in $CHCl_3$) to yield 2.2 g (92%) of 29 as syrup.

UV absorption in MeOH: max 237 nm. MS m/z: 413 (M-OMe). PMR ($CDCl_3$) δ: 0.11 (6H, s, $SiMe_2$), 0.90 (9H, s, SiBu-t), 3.44 (3H, s, CHOMe), 3.91-3.95 (5H, m, CH_2-5' and CO_2Me), 4.42 (1H, m, H-4'), 4.86-4.97 (4H, m, 5-CH_2OH, H-2' and H-3'), 5.96 (1H, s, CHOMe), 6.06 (1H, d, J= 2.9 Hz, H-1'), 7.73 (1H, s, H-2).

Methyl 5-chloromethyl-1-(2,3-O-methoxymethylidene-5-O-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxylate (30)—— To a solution of 29 (1.4 g, 3.2 mmol) in DMF (6 ml) and Et_3N (0.7 ml, 5 mmol), MsCl (0.4 ml, 5.2 mmol) was added. The reaction mixture was stirred for 1.5 h at room temperature and then quenched with aqueous $NaHCO_3$. Extraction with EtOAc followed by chromatographic purification on a silica gel column (1% MeOH in $CHCl_3$) gave 30 (1.4 g, 95%) as syrup, which was unstable.

PMR ($CDCl_3$) δ: 0.10 (6H, s, $SiMe_2$), 0.90 (9H, s, SiBu-t), 3.47 (3H, s, CHOMe), 3.91-3.94 (5H, m, CH_2-5' and CO_2Me), 4.40-4.50 (1H, m, H-4'), 4.50-4.77 (1H, m, H-3'), 4.93-5.03 (1H, m, H-2'), 4.99 and 5.31 (2H, each as d, 5-CH_2Cl), 5.98 (1H, s, CHOMe), 6.15 (1H, d, J= 3.9 Hz, H-1'), 7.83 (1H, s, H-2).

Methyl 5-cyanomethyl-1-(2,3-O-methoxymethylidene-5-O-TBDMS-β-D-ribofuranosyl)-imidazole-4-carboxylate (31)—— A mixture of 30 (1.6 g, 3.4 mmol), KCN (442 mg, 6.8 mmol) and 18-crown-6 (140 mg) in dry benzene (20 ml) was stirred overnight at room temperature. After evaporation, the residue was taken up into $CHCl_3$-H_2O. The organic layer was dried (Na_2SO_4), evaporated and chromatographed on a silica gel column (1% MeOH in $CHCl_3$). This afforded 31 (1.3 g, 86%) as syrup.

UV absorption in MeOH: max 225 nm, shoulder 238 nm. MS m/z: 422 (M-OMe). IR ($CHCl_3$) cm^{-1}: 2250 (-CN). PMR ($CDCl_3$) δ: 0.09 (3H, s, SiMe), 0.10 (3H, s, SiMe), 0.89 (9H, s, SiBu-t), 3.47 (3H, s, CHOMe), 3.91-3.94 (5H, m, CH_2-5' and CO_2Me), 4.46-4.49 (1H, m, H-4'), 4.75-4.86 (1H, m, H-3'), 4.93-5.03 (1H, m, H-2'), 4.18 and 4.57 (2H, each as d, J= 17.6 Hz, 5-CH_2CN), 5.99 (1H, s, CHOMe), 6.07 (1H, d, J= 3.9 Hz, H-1'), 7.80 (1H, s, H-2).

6-Amino-1-(2,3-O-methoxymethylidene-5-O-TBDMS-β-D-ribofuranosyl)imidazo[4,5-c]pyridin-4(5H)-one (32)—— To a solution of 31 (1.0 g, 2.2 mmol) in MeOH (16 ml) was added 28% NH_4OH (24 ml). The mixture was heated at 80 °C for 2 h in a sealed tube. After cooling the reaction mixture, 32 (420 mg, 45%) was precipitated. Crystallization from isopropyl alcohol gave an analytical sample (mp 231-233 °C, dec.).

Anal. Calcd. for $C_{19}H_{30}N_4O_6Si$: C, 52.06; H, 6.84; N, 12.79. Found: C, 51.96; H, 6.97; N, 12.55. UV absorption in H_2O: max 273 nm and 300 nm, min 292 nm. MS m/z: 438 (M^+), 150 (B+1). PMR (DMSO-d_6) δ: 0.03 (6H, s, $SiMe_2$), 0.85 (9H, s, SiBu-t), 3.34 (3H, s, CHOMe), 3.75 (2H, m, CH_2-5'), 4.27 (1H, m, H-4'), 4.83 (1H, dd, H-3'), 5.06 (1H, dd, H-2'), 5.34 (1H, s, H-7), 5.60 (2H, br, NH_2), 5.83 (1H, d, J= 2.9 Hz, H-1'), 6.06 (1H, s, CHOMe), 7.78 (1H, s, H-2), 10.31 (1H, br, NH).

6-Amino-1-(β-D-ribofuranosyl)imidazo[4,5-c]pyridin-4(5H)-one (5)—— A suspension of 32 (100 mg) in 20% aqueous AcOH was stirred for 24 h at room temperature with exclusion of the light. The reaction mixture was evaporated and then coevaporated with EtOH. The residue was dissolved in 28% NH_4OH (20 ml) and stirred for 30 min at 0 °C. Evaporation of NH_3 gave an analytically pure 5 (45 mg, 80%, mp 254-256 °C, dec.).

Anal. Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.85. Found: C, 46.69; H, 5.10; N, 19.56. UV absorption in H_2O: max 273 nm and 300 nm, min 292 nm. PMR (DMSO-d_6) δ: 3.58-3.88 (2H, m, CH_2-5'), 3.92-4.32 (3H, m, H-2', H-3' and H-4'), 5.02 (1H, t, 5'-OH), 5.12 and 5.45 (2H, each as d, 2'- and 3'-OH), 5.50 (1H, d, J= 5.4 Hz, H-1'), 5.53 (1H, s, H-7), 5.58 (2H, br, NH_2), 7.90 (1H, s, H-2), 10.32 (1H, br, NH).

6-Acetylamino-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)imidazo[4,5-c]pyridin-4(5H)-one (33)—— Compound 5 (30 mg) in pyridine (0.5 ml) was treated with Ac_2O (1 ml) at room temperature overnight. Evaporation of the solvent gave 33 (45 mg, 94%), which was crystallized from EtOH (mp 249-251 °C).

Anal. Calcd. for $C_{19}H_{22}N_4O_9$: C, 50.66; H, 4.92; N, 12.44. Found: C, 50.62; H, 4.90; N, 12.35. UV absorption in H_2O: max 269 nm (ε 14900), 275 nm (ε 14600), and 305 nm (ε 14200), min 237 nm (ε 5100) and 287 nm (ε 11600). MS m/z: 450 (M^+), 192 (B+1). PMR (DMSO-d_6) δ: 2.03 (3H, s, Ac), 2.05 (3H, s, Ac), 2.10 (3H, s, Ac), 2.11 (3H, s, Ac), 4.35-4.43 (3H, m, CH_2-5' and H-4'), 5.30-5.58 (2H, m, H-2' and H-3'), 6.06 (1H, d, J= 5.9 Hz, H-1'), 6.46 (1H, s, H-7), 8.10 (1H, s, H-2), 10.33 and 11.20 (2H, each as br, NH).

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