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Synthesis of 5-Carbon-Substituted 1-β-D-Ribofuranosylimidazole-4-carboxamides *via* Lithiation of a Primary Carboxamide

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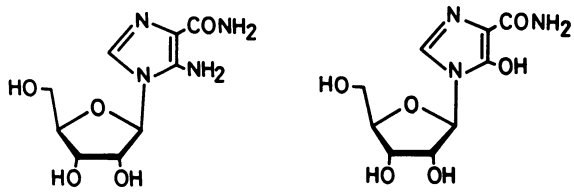
Several 5-carbon-substituted 1-β-D-ribofuranosylimidazole-4-carboxamides were synthesized *via* the direct C-5 lithiation of a protected 4-carboxamide derivative as the key reaction step. Wittig reaction of a 5-formyl derivative was also examined.

Keywords——lithiation; imidazole nucleoside; 5-substituted 1-β-D-ribofuranosylimidazole-4-carboxamide; lithium diisopropylamide; lithium 2,2,6,6-tetramethylpiperidide; Wittig reaction

Due to the considerable potential chemotherapeutic importance of 5-substituted 1-β-D-ribofuranosylimidazole-4-carboxamides as analogues of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICAR, **1**), several compounds including bredinin (**2**)[1] have



1 **2**

Fig. 1

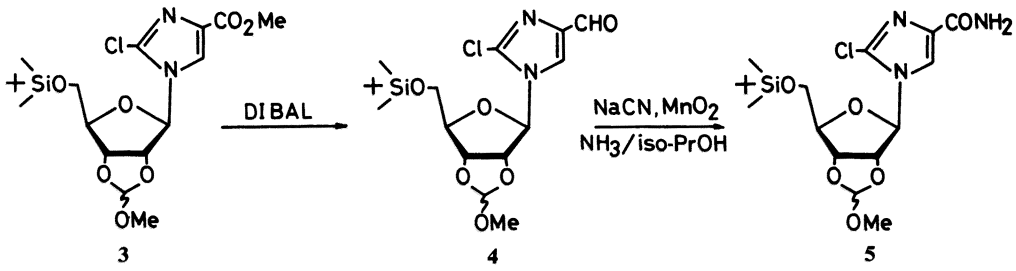
been prepared so far. Among the compounds in this class, the 5-chloro, 5-bromo, and 5-iodo derivatives were synthesized by Sandmeyer reaction of 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile followed by hydrolysis.[2] Another route to the 5-substituted derivatives is the classical condensation method, though formation of a mixture of regio-isomers is always anticipated in this case.[3]

Recently, we reported a lithiation approach to C-5 substitution of methyl 2-chloro-1-(2,3-*O*-methoxymethylidene-5-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carboxylate (**3**)[4] wherein the chlorine atom served as a protecting group during the metallation. Hydrogenolysis of the chlorine atom followed by concurrent deprotection of the methoxymethylidene and *tert*-butyldimethylsilyl (TBDMS) groups furnished the corresponding 5-substituted products, which seemed to be easily convertible to the 4-carboxamide derivatives. However, drastic conditions are required to effect ammonolysis of the ester function. For example, the ammonolysis of ethyl 5-methyl-1-β-D-ribofuranosylimidazole-4-carboxylate has been carried out in a sealed tube with liquid NH_3 for 3 d.[3d]

Consideration of the above-mentioned background led us to examine C-5 lithiation of a preformed imidazole-4-carboxamide, in the hope that it would provide a general method for the preparation of 5-substituted 1-β-D-ribofuranosylmidazole-4-carboxamides.

The method used for the ester–amide conversion, which is relatively mild, and therefore

enabled us to employ the protected nucleoside **3** as a starting material, is as follows. When **3** was reacted with diisobutylaluminium hydride (DIBAL) in tetrahydrofuran (THF)–toluene at below −70 °C for 2 h, the formyl derivative (**4**) was obtained in 95% yield. By adopting

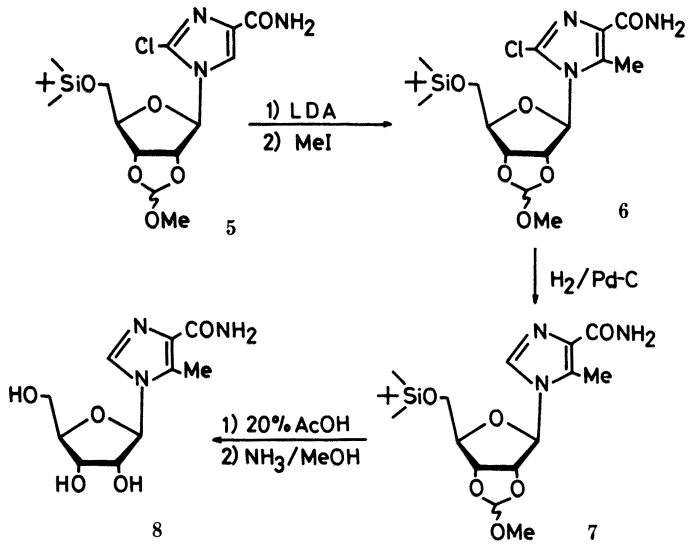


3 4 5

Chart 1

Gilman's method,[5] **4** was converted to the requisite carboxamide **5**. Thus, treatment of **4** with a suspension of NaCN in isopropanol saturated with NH_3 and then with activated MnO_2 at 0 °C for 2 h provided a 95% yield of **5** in a one-pot process (Chart 1).

Lithiation at the C-5 position of **5** was carried out by using lithium diisopropylamide (LDA), which has been successfully used for the metallation of nucleosides having a halogen substituent.[4,6-8] Compound **5** was treated with 3.8 eq of LDA and then reacted with MeI at below −80 °C for 6 h, after which 2-chloro-5-methyl-1-(2,3-*O*-methoxymethylidene-5-*O*-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxamide (**6**) was obtained in 32% yield by



5 6 7 8

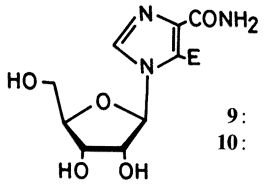
Chart 2

column chromatography on silica gel. Addition of hexamethylphosphoric triamide (HMPA) in the above reaction or the use of lithium 2,2,6,6-tetramethylpiperidide (LTMP) instead of LDA appeared to give no significant increase in the yield of **6**, and more than 40% of the starting material (**5**) was recovered in all three cases examined.

The chlorine atom thus used to protect the C-2 position from metallation was removed by hydrogenolysis in MeOH in the presence of 10% Pd–C and Et_3N (3 atm of H_2, room temperature, 24 h) to give **7** in 76% yield. Deprotection of the sugar moiety was performed as

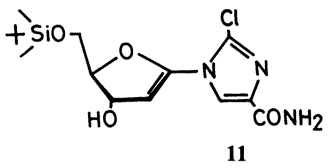
reported earlier[4] to furnish 5-methyl-1-β-D-ribofuranosylimidazole-4-carboxamide (**8**) in 74% yield as crystals (mp 178—179 °C). Physical constants of **8** were identical with those reported.[3d]

When HCO_2Me was employed as an electrophile in the reaction of the C-5 lithiated species of **5**, the 5-formylated product resulted, and this was reduced by $NaBH_4$ in a one-pot process. By following the reaction sequence illustrated in Chart 2, 5-hydroxymethyl-1-β-D-ribofuranosylimidazole-4-carboxamide (**9**: mp 155—156 °C) was isolated in 19% overall yield from **5**. Similarly, by using carbon dioxide as an electrophile, the 5-carboxylic acid **10** (mp 179—180 °C) was prepared in 17% overall yield.



9: E = CH_2OH
10: E = CO_2H

Fig. 2

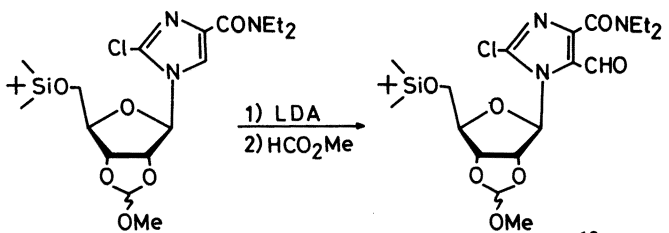


11

Fig. 3

During the LDA lithiation of **5**, we observed in the reaction mixture the presence of a polar by-product, in addition to the remaining **5** and the desired product. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of the by-product in dimethyl sulfoxide (DMSO)-d_6 showed no signals corresponding to the methoxymethylidene group and showed one D_2O-exchangeable doublet (δ 5.51 ppm) which coupled with a multiplet at δ 4.83 ppm. By comparison of the ^{1}H-NMR data with those reported for 6-amino-9-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)purine[9] and from HOMO-SD experiments, the structure of this by-product was determined as 2-chloro-1-(2-deoxy-5-*O*-TBDMS-D-*erythro*-pent-1-enofuranosyl)imidazole-4-carboxamide (**11**).[10] In the mass spectrum (MS) of **11**, a fragment ion peak corresponding to [M^+ − Bu-*tert* − H_2O] (*m/z*: 298 and 300) was observed with an intensity of *ca.* 15 times higher than that of [M^+ − Bu-*tert*] (*m/z*: 316 and 318), which is also indicative of its structure. It should be noted that **11** was also formed during the LDA lithiation of 2-chloro-1-(2,3-*O*-isopropylidene-5-*O*-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxamide.

On the other hand, when 2-chloro-1-(2,3-*O*-methoxymethylidene-5-*O*-TBDMS-β-D-ribofuranosyl)imidazole-4-*N*,*N*-diethylcarboxamide (**12**), a tertiary carboxamide, was reacted with 3.8 eq of LDA followed by HCO_2Me under conditions similar to those used for **5**, the 5-



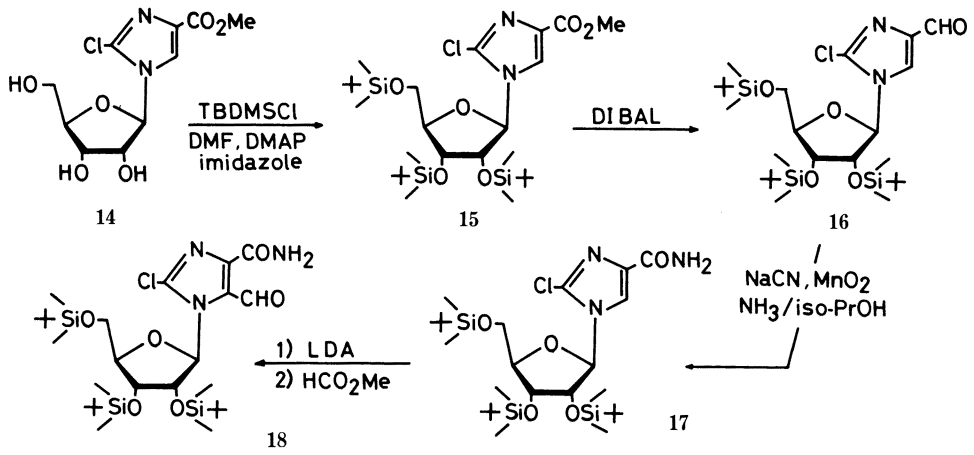
12 **13**

Chart 3

formyl derivative (**13**) was obtained in 63% yield along with a 34% recovery of **12** and the formation of the corresponding 1′,2′-unsaturated nucleoside was not observed. From these results, it became apparent that the formation of **11** and the low yield of the product in the reaction of **5** were associated with deprotonation of the 4-carboxamide group in **5**, though the

actual mechanism leading to **11** is still unknown.

We next investigated Wittig reaction of the 5-formyl 1-β-D-ribofuranosylimidazole-4-carboxamide derivative to synthesize other 5-carbon-substituted derivatives. For the preparation of the starting material for this reaction, we turned to the use of 2′,3′,5′-tris-*O*-TBDMS protection to preclude the above-mentioned elimination pathway observed in the lithiation of 2′,3′-*O*-alkylidene derivatives.



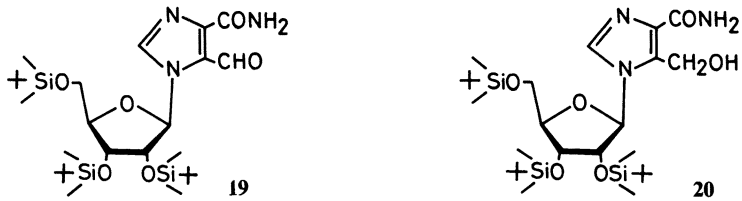
14 15 16 17 18

Chart 4

Methyl 2-chloro-1-β-D-ribofuranosylimidazole-4-carboxylate (**14**)[4] was treated with 6 eq of TBDMSCl in dimethylformamide (DMF) in the presence of imidazole (6 eq) and 4-*N*,*N*-dimethylaminopyridine (DMAP: 6 eq) to afford the 2′,3′,5′-tris-*O*-TBDMS derivative (**15**) in almost quantitative yield. Compound **15** was converted, *via* its 4-formyl derivative (**16**), to the corresponding 4-carboxamide (**17**) as shown in Chart 4.

When **17** was lithiated with 3.8 eq of LDA and then reacted with HCO_2Me, formation of the by-product, a 1′,2′-unsaturated nucleoside, was not detected on thin layer chromatography (TLC) (benzene : EtOAc = 3 : 1). However, the 5-formylated product (**18**) was obtained in only 13% yield and most of the starting material (**17**: 83%) was recovered. The use of LTMP (5 eq), a more basic lithiating agent than LDA,[11] gave a slightly increased yield (38%) which was comparable to the LDA lithiation level of **5**.

When the hydrogenolytic removal of the C-2 chlorine atom in **18** was carried out in MeOH in the presence of 10% Pd–C and Et_3N (3 atm of H_2, 3 h), both the 5-formyl (**19**) and the 5-hydroxymethyl (**20**) derivatives were formed with a preponderance of the latter (**19**: 36%



19 20

Fig. 4

vs. **20**: 48%). This unfavorable situation was easily overcome by changing the solvent to benzene and using 5% Pd–C as a catalyst. Under these conditions, the yield of **19** rose to 70%, while the formation of **20** was suppressed to 10%.

The Wittig reaction of **19** was performed in THF by using methylenetriphenylphosphorane and (carbethoxymethylene)triphenylphosphorane, respectively, to furnish **21** (77%) and **22** (59%). In the ^{1}H-NMR spectrum of **21** in $CDCl_3$, a characteristic ABX pattern (J_{AX} = 18.1 Hz, J_{BX} = 11.7 Hz, J_{AB} = 1.0 Hz) was observed, showing the presence of a vinyl group. (*E*)-Stereochemistry of **22** was deduced from its ^{1}H-NMR spectrum, the coupling constant

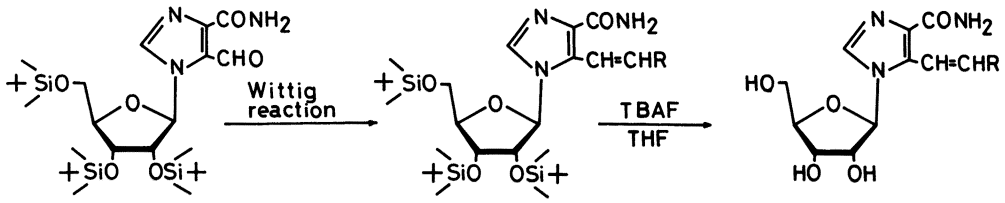


Chart 5

between vinylic protons being 16.6 Hz.

Finally, deprotection of **21** and **22** was carried out with tetrabutylammonium fluoride (TBAF) in THF to give the corresponding free nucleosides (**23** and **24**) in high yields.

In conclusion, the present work provides a general method for the preparation of various types of 5-carbon-substituted 1-β-D-ribofuranosylimidazole-4-carboxamides. Although the C-5 lithiation level is not high, presumably due to dissociation of the primary carboxamide group at the C-4 position, this method has certain advantages over the classical condensation method in that it causes no regio- and stereochemical problems. It should also be emphasized that no successful beta (or *ortho*) lithiation of a primary carboxamide has previously been reported to the best of our knowledge.[12,13]

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured with tetramethylsilane as an internal standard, with either a JEOL JNM-FX 100 or a JEOL JNM-GX 400 NMR spectrometer. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad. In the cases of 2′,3′-*O*-methoxymethylidene derivatives, ^{1}H-NMR signals of the major diastereomer are shown. MS were taken on a JEOL JMS-D 300 spectrometer. Ultraviolet (UV) spectra were recorded on a Shimadzu UV-240 spectrophotometer. Reactions at low temperature were performed using a CryoCool CC-100 apparatus (NESLAB Instrument, Inc.). Butyllithium in hexane was titrated before use by using diphenylacetic acid in THF. THF was distilled from benzophenone ketyl. Column chromatography was carried out either on silica gel (Wakogel® C-200) or on magnesium silicate (Florisil®). TLC was performed on precoated Silica gel plates 60 F_{254}, Merck.

2-Chloro-4-formyl-1-(2,3-*O*-methoxymethylidene-5-*O*-TBDMS-β-D-ribofuranosyl)imidazole (4)——A 1 M solution of DIBAL in toluene (5.6 ml) was added to a solution of **3** (687 mg, 1.5 mmol) in THF (5 ml) at below −70 °C under an Ar atmosphere. The mixture was stirred for 2 h at below −70 °C and then quenched with AcOH. The whole mixture was chromatographed on a silica gel column (benzene : EtOAc = 10 : 1) to give **4** (611 mg, 95%) as a syrup. MS *m/z*: 387, 389 (M−OMe), 361, 363 (M−Bu-*tert*), 289 (M−B). UV λ_{max}^{MeOH} nm: 256. ^{1}H-NMR ($CDCl_3$) δ: 0.11 (6H, s, SiMe), 0.89 (9H, s, SiBu-*tert*), 3.45 (3H, s, OMe), 3.91 (2H, m, CH_2-5′), 4.54 (1H, m, H-4′), 4.72 (1H, dd, H-3′), 4.91 (1H, dd, H-2′), 5.95 (1H, s, CHOMe), 6.12 (1H, d, *J* = 3.4 Hz, H-1′), 7.93 (1H, s, H-5), 9.77 (1H, s, CHO).

2-Chloro-1-(2,3-*O*-methoxymethylidene-5-*O*-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxamide (5)——A suspension of NaCN (74 mg, 1.5 mmol) in isopropanol (15 ml) saturated with NH_3 at 0 °C was stirred for 10 min at 0 °C, after which a solution of **4** (132 mg, 0.3 mmol) in isopropanol (5 ml) was added dropwise. Activated MnO_2[14] (522 mg) was added to the above mixture and the whole was stirred for 2 h at 0 °C. Filtration through Celite followed by chromatographic purification of the filtrate on a silica gel column (2% MeOH in $CHCl_3$) gave **5** (130 mg, 95%). MS *m/z*: 402, 404 (M−OMe), 376, 378 (M−Bu-*tert*), 289 (M−B), 145, 147 (B+1). UV λ_{max}^{MeOH} nm: 220. ^{1}H-NMR ($CDCl_3$) δ: 0.11 (6H, s, SiMe), 0.90 (9H, s, SiBu-*tert*), 3.44 (3H, s, OMe), 3.87 (2H, m, CH_2-5′), 4.38—4.52 (1H, m, H-4′), 4.70—5.00 (2H, m, H-2′, H-3′), 5.60, 6.85 (2H, each br, NH_2), 5.95 (1H, s, CHOMe), 6.08 (1H, d, *J* = 3.4 Hz, H-1′), 7.82 (1H, s, H-5).

2-Chloro-5-methyl-1-(2,3-*O*-methoxymethylidene-5-*O*-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxamide (6)——LDA (3.8 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 **5** (437 mg, 1.0 mmol) in THF (5 ml) was added, under positive pressure of dry Ar, at such a rate that the temperature did not exceed −80 °C. The mixtures was stirred for 1.5 h at below −80 °C, after which MeI (0.24 ml, 3.8 mmol) was added and the whole was stirred for 4 h. Another 0.14 ml (0.4 mmol) of MeI was added to the above mixture and stirring was continued for a further 2 h below −80 °C. After being quenched with AcOH, the reaction mixture was evaporated and the residue was chromatographed on a silica gel column (benzene : EtOAc = 5 : 1) to give **6** (144 mg, 32%). MS *m/z*: 416, 418 (M−OMe), 390, 392 (M−Bu-*tert*), 289 (M−B). ^{1}H-NMR ($CDCl_3$) δ: 0.09 (6H, s, SiMe), 0.91 (9H, s, SiBu-*tert*), 2.67 (3H, s, 5-Me), 3.43 (3H, s, OMe), 3.93 (2H, m, CH_2-5′), 4.24 (1H, m, H-4′), 4.90—5.10 (2H, m, H-2′, H-3′), 5.28, 6.86 (2H, each br, NH_2), 5.98 (1H, d, J = 3.9 Hz, H-1′).

5-Methyl-1-(2,3-*O*-methoxymethylidene-5-*O*-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxamide (7)——A mixture of **6** (140 mg, 0.3 mmol), Et_3N (0.1 ml, 0.8 mmol), and 10% Pd–C (50 mg) in MeOH (10 ml) was subjected to hydrogenolysis (3 atm of H_2) for 24 h at room temperature. After removal of the catalyst, the reaction mixture was purified through a silica gel column (4% MeOH in $CHCl_3$) to give **7** (98 mg, 76%). MS *m/z*: 382 (M−OMe), 356 (M−Bu-*tert*), 289 (M−B). ^{1}H-NMR ($CDCl_3$) δ: 0.09 (6H, s, SiMe), 0.90 (9H, s, SiBu-*tert*), 2.66 (3H, s, 5-Me), 3.44 (3H, s, OMe), 3.90 (2H, m, CH_2-5′), 4.41 (1H, m, H-4′), 4.70 (1H, dd, H-3′), 4.94 (1H, dd, H-2′), 5.91 (1H, d, J = 3.9 Hz, H-1′), 5.96 (1H, s, CHOMe), 5.27, 7.03 (2H, each br, NH_2), 7.62 (1H, s, H-2).

5-Methyl-1-β-D-ribofuranosylimidazole-4-carboxamide (8)——Compound **7** (75 mg, 0.2 mmol) in 20% aqueous AcOH was stirred for 24 h at room temperature. After evaporation of the solvent, the residue was treated with NH_3/MeOH (5 ml) for 5 min. Column chromatographic purification (8% MeOH in $CHCl_3$) of the mixture gave **8**, which was crystallized from EtOH to afford an analytical sample (35 mg, 74%, mp 178—179 °C). *Anal.* Calcd for $C_{10}H_{15}N_3O_5$: C, 46.69; H, 5.88; N, 16.33. Found: C, 46.96; H, 5.97; N, 16.05. MS *m/z*: 257 (M^+), 125 (B+1). UV $\lambda_{max}^{H_2O}$ nm (ε): 239 (12000), $\lambda_{min}^{H_2O}$: 205 (7600). ^{1}H-NMR (DMSO-d_6, after addition of D_2O) δ: 2.51 (3H, s, 5-Me), 3.58 (2H, m, CH_2-5′), 3.89—4.25 (3H, m, H-2′, H-3′, H-4′), 5.50 (1H, d, J = 5.9 Hz, H-1′), 7.90 (1H, s, H-5).

5-Hydroxymethyl-1-β-D-ribofuranosylimidazole-4-carboxamide (9)——The C-5 formylation of **5** (522 mg, 1.2 mmol) with HCO_2Me (0.3 ml, 4.9 mmol) was carried out for 2 h by the same procedure as described for the preparation of **6**. After being quenched with AcOH, the reaction mixture was diluted with MeOH (10 ml) and treated with $NaBH_4$ until TLC indicated complete reduction. Short-column chromatography gave the crude mixture, which was subjected to hydrogenolysis followed by deprotection as described for the preparation of **7** and **8**, respectively. This afforded a syrup, which was crystallized from MeOH to give analytically pure **9** (63 mg, 19%, mp 155—156 °C). *Anal.* Calcd for: $C_{10}H_{15}N_3O_6$: C, 43.96; H, 5.53; N, 15.38. Found: C, 44.22; H, 5.56; N, 15.56. MS *m/z*: 273 (M^+), 141 (B+1). UV $\lambda_{max}^{H_2O}$ nm (ε): 237 (17000), $\lambda_{shoulder}^{H_2O}$: 221 (10700), $\lambda_{min}^{H_2O}$: 207 (9600). ^{1}H-NMR (DMSO-d_6, after addition of D_2O) δ: 3.62 (2H, m, CH_2-5′), 3.93—4.24 (3H, m, H-2′, H-3′, H-4′), 4.53, 4.95 (2H, each d, J = 13.2 Hz, 5-CH_2OH), 5.76 (1H, d, J = 4.9 Hz, H-1′), 8.02 (1H, s, H-2).

5-Carbamoyl-3-β-D-ribofuranosylimidazole-4-carboxylic Acid (10)——The C-5 carboxylation of **5** (261 mg, 0.6 mmol) with CO_2 gas (large excess) was carried out for 30 min by the same procedure as described for the preparation of **6**. After short-column chromatography, the crude mixture was subjected to hydrogenolysis followed by deprotection as described for the preparation of **7** and **8**, respectively. Purification through DEAE cellulofine AL® (bicarbonate form, a linear gradient of 0—0.03 M $Et_3NH \cdot HCO_3$) and successive acidification through Dowex 50® (H^+ form) gave **10** (29 mg, 17%) as crystals (mp 179—180 °C). *Anal.* Calcd for $C_{10}H_{13}N_3O_7$: C, 41.82; H, 4.56; N, 14.63. Found: C, 41.65; H, 4.63; N, 14.45. MS *m/z*: 155 (B+1). UV $\lambda_{max}^{H_2O}$ nm(ε): 251 (6800), $\lambda_{min}^{H_2O}$: 235 (5900). ^{1}H-NMR (DMSO-d_6, after addition of D_2O) δ: 3.63, 3.81 (2H, each dd, CH_2-5′), 3.92—3.94 (1H, m, H-4′), 4.04—4.08 (2H, m, H-2′, H-3′), 6.49 (1H, s, H-1′), 8.69 (1H, s, H-2).

2-Chloro-1-(2-deoxy-5-*O*-TBDMS-D-*erythro*-pent-1-enofuranosyl)imidazole-4-carboxamide (11)——Physical data of this compound are as follows. MS *m/z*: 316, 318 (M−Bu-*tert*), 298, 300 (M−Bu-*tert*-H_2O). UV $\lambda_{shoulder}^{MeOH}$ nm: 250. ^{1}H-NMR (DMSO-d_6) δ: 0.02, 0.05 (6H, each s, SiMe), 0.84 (9H, s, SiBu-*tert*), 3.49 (2H, m, CH_2-5′), 4.41 (1H, m, H-4′), 4.83 (1H, m, H-3′), 5.44 (1H, d, H-2′), 5.51 (1H, d, 3′-OH), 7.60, 7.80 (2H, each br, NH_2), 7.80, (1H, s, H-5).

2-Chloro-1-(2,3-*O*-methoxymethylidene-5-*O*-TBDMS-β-D-ribofuranosyl)imidazole-4-*N*,*N*-diethylcarboxamide (12)——A solution of **4** (165 mg, 0.4 mmol) in isopropanol (5 ml) and activated MnO_2 (696 mg) were added to a suspension of NaCN (98 mg, 2.0 mmol) in isopropanol (10 ml) and Et_2NH (0.8 ml, 8.0 mmol). The mixture was stirred for 2 h at room temperature and then two 0.8 ml portions of Et_2NH were added at 2 h intervals. Filtration through Celite followed by chromatographic purification of the filtrate on a silica gel column (2% MeOH in $CHCl_3$) gave **12** (105 mg, 55%). MS *m/z*: 458, 460 (M−OMe), 432, 434 (M−Bu-*tert*), 289 (M−B). UV λ_{max}^{MeOH} nm: 224. ^{1}H-NMR ($CDCl_3$) δ: 0.10 (6H, s, SiMe), 0.89 (9H, s, SiBu-*tert*), 1.21 (6H, t, NCH_2CH_3), 3.35—3.91 (9H, m, OMe, NCH_2CH_3, CH_2-5′), 4.27—4.46 (1H, m, H-4′), 4.72—5.01 (2H, m, H-2′, H-3′), 6.06 (1H, d, J = 3.4 Hz, H-1′), 5.95 (1H, s, CHOMe), 7.68 (1H, s, H-5).

2-Chloro-5-formyl-1-(2,3-*O*-methoxymethylidene-5-*O*-TBDMS-β-D-ribofuranosyl)imidazole-4-*N*,*N*-diethylcarboxamide (13)——The C-5 formylation of **12** (95 mg, 0.2 mmol) with HCO_2Me (0.05 ml, 0.8 mmol) was carried out

for 1 h by the same procedure as described for the preparation of **6**. After being quenched with AcOH, the reaction mixture was purified by column chromatography on silica gel (benzene : EtOAc = 10—5 : 1). This afforded **13** (64 mg, 63%) and **12** (32 mg, 34%). Physical data of **13** are as follows. *Anal.* Calcd for $C_{22}H_{36}ClN_3O_7Si$: C, 51.00; H, 7.00; N, 8.11. Found: C, 51.22; H, 7.24; N, 7.93. MS *m/z*: 486, 488 (M − OMe), 460, 462 (M − Bu-*tert*). UV λ_{max}^{MeOH} nm (ε): 276 (8500), $\lambda_{shoulder}^{MeOH}$: 236 (8900), λ_{min}^{MeOH}: 256 (6900). ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s, SiMe), 0.90 (9H, s, SiBu-*tert*), 1.25 (6H, t, $NCH_2C\underline{H}_3$), 3.31—3.91 (10H, m, OMe, $NC\underline{H}_2CH_3$, H-4′, CH_2-5′), 5.00—5.13 (2H, m, H-2′, H-3′), 5.96 (1H, s, C<u>H</u>OMe), 6.37 (1H, d, *J* = 3.4 Hz, H-1′), 9.93 (1H, s, 5-CHO).

Methyl 2-Chloro-1-(2,3,5-tris-*O*-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxylate (15)——Compound **14** (2.1 g, 7.0 mmol) was added to a mixture of TBDMSCl (6.4 g, 42 mmol), imidazole (2.9 g, 42 mmol), and DMAP (5.2 g, 42 mmol) in DMF (10 ml). The mixture was stirred for 40 h at room temperature and then poured into EtOAc–H_2O. The organic layer was separated, dried (Na_2SO_4), and evaporated to dryness. Silica gel column chromatographic purification (benzene) of the residue gave **15** (4.5 g, 99%). MS *m/z*: 577, 579 (M − Bu-*tert*). UV λ_{max}^{MeOH} nm: 232. ^{1}H-NMR ($CDCl_3$) δ: 0.10, 0.11, 0.17, 0.20 (18H, each s, SiMe), 0.84, 0.93, 0.97 (27H, each s, SiBu-*tert*), 3.67—3.92 (2H, m, CH_2-5′), 3.87 (3H, s, CO_2Me), 4.09—4.29 (3H, m, H-2′, H-3′, H-4′), 5.77 (1H, d, *J* = 5.9 Hz, H-1′), 8.02 (1H, s, H-5).

2-Chloro-4-formyl-1-(2,3,5-tris-*O*-TBDMS-β-D-ribofuranosyl)imidazole (16)——This compound was prepared from **15** (4.6 g) by the same procedure as used for the preparation of **4**. Silica gel short-column chromatography (benzene : EtOAc = 10 : 1) gave **16** (2.4 g, 55%). MS *m/z*: 547, 549 (M − Bu-*tert*). UV λ_{max}^{MeOH} nm: 254. ^{1}H-NMR ($CDCl_3$) δ: 0.03, 0.11, 0.17, 0.20 (18H, each s, SiMe), 0.85, 0.94, 0.98 (27H, each s, SiBu-*tert*), 3.68—4.00 (2H, m, CH_2-5′), 4.12—4.28 (3H, m, H-2′, H-3′, H-4′), 5.79 (1H, d, *J* = 5.4 Hz, H-1′), 8.07 (1H, s, H-5), 9.78 (1H, s, 4-CHO).

2-Chloro-1-(2,3,5-tris-*O*-TBDMS-1-β-D-ribofuranosyl)imidazole-4-carboxamide (17)——This compound was prepared from **16** (2.4 g) by the same procedure as used for the preparation of **5**. Silica gel column chromatography (benzene : EtOAc = 5 : 1) gave **17** (2.0 g, 81%), which was crystallized from MeOH–H_2O (mp 133—134 °C). *Anal.* Calcd for $C_{27}H_{54}ClN_3O_5Si_3$: C, 52.27; H, 8.77; N, 6.77. Found: C, 52.55; H, 8.86; N, 7.01. MS *m/z*: 562, 564 (M − Bu-*tert*). UV λ_{max}^{MeOH} nm (ε): 223 (14300). ^{1}H-NMR ($CDCl_3$) δ: −0.27, −0.05, 0.11, 0.16, 0.19 (18H, each s, SiMe), 0.84, 0.94, 0.96 (27H, each s, SiBu-*tert*), 3.79 (2H, m, CH_2-5′), 4.07—4.27 (3H, m, H-2′, H-3′, H-4′), 5.34, 6.80 (2H, each br, NH_2), 5.76 (1H, d, *J* = 5.9 Hz, H-1′), 7.91 (1H, s, H-5).

2-Chloro-5-formyl-1-(2,3,5-tris-*O*-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxamide (18)——This compound was prepared from **17** (134 mg, 0.2 mmol), LTMP (1.0 mmol), and HCO_2Me (0.17 ml, 2.8 mmol) by the same procedure as used for the preparation of **6**. Silica gel column chromatography (benzene : EtOAc = 10 : 1) gave **18** (54 mg, 38%). MS *m/z*: 590, 592 (M − Bu-*tert*). UV λ_{max}^{MeOH} nm: 254. ^{1}H-NMR ($CDCl_3$) δ: −0.07, 0.09, 0.12 (18H, each s, SiMe), 0.78, 0.92, 0.95 (27H, each s, SiBu-*tert*), 3.62—4.20 (4H, m, H-3′, H-4′, CH_2-5′), 4.82 (1H, dd, H-2′), 5.59, 7.24 (2H, each br, NH_2), 6.45 (1H, d, *J* = 7.8 Hz, H-1′), 10.60 (1H, s, 5-CHO).

5-Formyl-1-(2,3,5-tris-*O*-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxamide (19) and 5-Hydroxymethyl-1-(2,3,5-tris-*O*-TBDMS-1-β-D-ribofuranosyl)imidazole-4-carboxamide (20)——A mixture of **18** (105 mg, 0.16 mmol), 5% Pd–C (50 mg), and Et_3N (0.2 ml) in benzene (5 ml) was hydrogenated (3 atm of H_2) at room temperature for 3 h. After removal of the catalyst, the mixture was evaporated to dryness. Silica gel column chromatography gave **19** (elution with benzene : EtOAc = 10 : 1, 69 mg, 70%) and **20** (elution with 2% MeOH in $CHCl_3$, 10 mg, 10%).

Physical data of **19** are as follows. MS *m/z*: 556 (M − Bu-*tert*). UV λ_{max}^{MeOH} nm: 275. ^{1}H-NMR ($CDCl_3$) δ: 0.06, 0.08, 0.11, 0.16, 0.18 (18H, each s, SiMe), 0.90, 0.98 (27H, each s, SiBu-*tert*), 3.76—4.12 (5H, m, H-2′, H-3′, H-4′, CH_2-5′), 5.56, 8.55 (2H, each br, NH_2), 6.31 (1H, d, *J* = 2.5 Hz, H-1′), 7.26 (overlapped with $CHCl_3$, H-2), 10.63 (1H, s, 5-CHO).

Physical data of **20** are as follows. MS *m/z*: 558 (M − Bu-*tert*). ^{1}H-NMR ($CDCl_3$) δ: −0.05, 0.10, 0.14 (18H, each s, SiMe), 0.83, 0.93, 0.95 (27H, each s, SiBu-*tert*), 3.79—3.84 (2H, m, CH_2-5′), 4.07—4.27 (3H, m, H-4′, 5-C<u>H</u>$_2$OH), 4.77—4.86 (2H, m, H-2′, H-3′), 5.53—5.75 (3H, m, H-1′, CONH, 5-$CH_2O\underline{H}$), 7.16 (1H, br, CONH), 7.74 (1H, s, H-2).

5-Vinyl-1-(2,3,5-tris-*O*-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxamide (21)——A suspension of methyltriphenylphosphonium bromide (429 mg, 1.2 mmol) in THF (3 ml) was treated with NaH (48 mg, 1.2 mmol) at 0 °C under an Ar atmosphere, and the mixture was stirred for 0.5 h at 0 °C. After being stirred for 1 h at room temperature, the mixture was again cooled to 0 °C and treated with a solution of **19** (184 mg, 0.3 mmol) in THF (5 ml). The whole reaction mixture was stirred for 13 h at room temperature and then quenched with MeOH. The mixture was partitioned between ether and H_2O. The organic layer was separated, dried (Na_2SO_4), and chromatographed on a silica gel column (benzene: EtOAc = 8 : 1) to give **21** (142 mg, 77%). MS *m/z*: 569 (M − Me), 554 (M − Bu-*tert*). UV λ_{max}^{MeOH} nm: 264. ^{1}H-NMR ($CDCl_3$) δ: 0.10, 0.11, 0.14 (18H, each s, SiMe), 0.80, 0.93, 0.96 (27H, each s, SiBu-*tert*), 3.80 (2H, m, CH_2-5′), 4.16 (1H, m, H-4′), 4.19 (1H, dd, H-3′), 4.33 (1H, dd, H-2′), 5.39, 7.05 (2H, each br, NH_2), 5.61, 5.95, 7.22 (3H, each dd, vinyl protons), 5.92 (1H, d, *J* = 6.8 Hz, H-1′), 7.83 (1H, s, H-2).

5-(2-Ethoxycarbonyl)vinyl-1-(2,3,5-tris-*O*-TBDMS-β-D-ribofuranosyl)imidazole-4-carboxamide (22)——A THF (2 ml) solution of **19** (111 mg, 0.2 mmol) was added to a suspension of (carbethoxymethylene)triphenylphosphorane (251 mg, 0.7 mmol) in THF (1.5 ml) at 0 °C under an Ar atmosphere. The mixture was stirred for 1 h at 0 °C and then for 48 h at room temperature. The reaction mixture was partitioned between ether and H_2O. The organic layer was

separated, dried (Na_2SO_4), and chromatographed on a silica gel column (benzene : EtOAc = 10 : 1) to give **22** (73 mg, 59%). MS *m/z*: 626 (M − Bu-*tert*). UV λ_{max}^{MeOH} nm: 265, 300. ^{1}H-NMR ($CDCl_3$) δ: 0.10, 0.13, 0.14 (18H, each s, SiMe), 0.80, 0.94, 0.96 (27H, each s, SiBu-*tert*), 1.29 (3H, t, $CH_2C\underline{H}_3$), 3.83 (2H, m, CH_2-5′), 4.23 (2H, q, $C\underline{H}_2CH_3$), 5.37, 7.13 (2H, each br, NH_2), 5.90 (1H, d, J = 7.3 Hz, H-1′), 6.93, 8.12 (2H, each d, vinylic protons), 7.96 (1H, s, H-2).

5-Vinyl-1-β-D-ribofuranosylimidazole-4-carboxamide (23)——A THF (3 ml) solution of **21** (109 mg, 0.2 mmol) was treated with TBAF · $3H_2O$ (199 mg, 0.6 mmol) for 0.5 h at room temperature. The whole mixture was evaporated to dryness and the residue was chromatographed on a Florisil column (20% MeOH in $CHCl_3$) to give **23** (42 mg, 86%). MS *m/z*: 269 (M^+), 137 (B + 1), 136 (B^+). UV $\lambda_{max}^{H_2O}$ nm: 260, $\lambda_{min}^{H_2O}$: 238. ^{1}H-NMR (DMSO-d_6, after addition of D_2O) δ: 3.51—3.66 (2H, m, CH_2-5′), 3.92—3.94 (1H, t, H-4′), 4.09 (1H, t, H-3′), 4.30 (1H, t, H-2′), 5.52, 5.87, 7.23 (3H, each dd, vinyl protons), 5.64 (1H, d, J = 5.1 Hz, H-1′), 8.14 (1H, s, H-2).

Compound **23** was converted to its triacetate, and the high-resolution MS was measured. High-resolution MS *m/z*: 395.1342 (M^+) Calcd for $C_{17}H_{21}N_3O_8$: 395.1329. ^{1}H-NMR ($CDCl_3$) δ: 2.09, 2.14, 2.17 (9H, each s, Ac), 4.35 (2H, m, CH_2-5′), 4.40 (1H, m, H-4′), 5.38, 7.08 (2H, each br, NH_2), 5.43 (1H, t, H-3′), 5.59 (1H, t, H-2′), 5.66, 5.84 (2H, each d, vinyl protons), 5.96 (1H, d, J = 6.2 Hz, H-1′), 7.26 (1H, dd, vinyl proton), 7.76 (1H, s, H-2).

5-(2-Ethoxycarbonyl)vinyl-1-β-D-ribofuranosylimidazole-4-carboxamide (24)——This compound was prepared from **22** (32 mg, 0.05 mmol) by the same procedure as used for the preparation of **23**. Preparative TLC ($CHCl_3$: MeOH = 5 : 1) of the reaction mixture gave **24** (15 mg, 92%), which was crystallized from EtOH (mp 104—106 °C). *Anal.* Calcd for $C_{14}H_{19}N_3O_7 \cdot 3/4H_2O$: C, 47.39; H, 5.82; N, 11.84. Found: C, 47.18; H, 5.59; N, 11.74. UV $\lambda_{max}^{H_2O}$ nm (ε): 217 (18600), 300 (15000), $\lambda_{min}^{H_2O}$: 256 (4900). ^{1}H-NMR (DMSO-d_6, after addition of D_2O) δ: 1.27 (3H, t, $CH_2C\underline{H}_3$), 3.52—3.67 (2H, m, CH_2-5′), 3.98 (1H, m, H-4′), 4.09 (1H, t, H-3′), 4.21 (2H, q, $C\underline{H}_2CH_3$), 4.36 (1H, t, H-2′), 5.67 (1H, d, J = 5.5 Hz, H-1′), 6.71, 8.21 (2H, each d, vinylic protons), 7.34, 7.61 (2H, each br, NH_2), 8.29 (1H, s, H-2).

References and Notes

1) K. Mizuno, M. Tsujino, M. Takada, M. Hayashi, K. Atsumi, K. Asano, and T. Matsuda, *J. Antibiot.*, **27**, 775 (1974); K. Fukukawa, S. Shuto, T. Hirano, and T. Ueda, *Chem. Pharm. Bull.*, **32**, 1644 (1984); *idem*, *ibid.*, **34**, 3653 (1986).
2) P. C. Srivastava, D. G. Streeter, T. R. Matthews, L. B. Allen, R. W. Sidwell, and R. K. Robins, *J. Med. Chem.*, **19**, 1020 (1976).
3) *a*) J. C. Reepmeyer, K. L. Kirk, and L. A. Cohen, *Tetrahedron Lett.*, **47**, 4107 (1975); *b*) P. C. Wyss and U. Fischer, *Helv. Chim. Acta*, **61**, 3149 (1978); *c*) P. D. Cook, R. J. Rousseau, A. M. Mian, P. Dea, R. B. Meyer, Jr., and R. K. Robins, *J. Am. Chem. Soc.*, **98**, 492 (1976); *d*) R. Alonso, J. I. Andrés, M. T. García-López, F. G. de las Heras, R. Herranz, B. Alarcón, and L. Carrasco, *J. Med. Chem.*, **28**, 834 (1985); S. G. Wood, K. G. Upadhya, N. K. Dalley, P. A. McKernan, P. G. Canonico, R. K. Robins, and G. R. Revankar, *ibid.*, **28**, 1198 (1985).
4) H. Tanaka, M. Hirayama, A. Matsuda, T. Miyasaka, and T. Ueda, *Chem. Lett.*, **1985**, 589; H. Tanaka, M. Hirayama, M. Suzuki, T. Miyasaka, A. Matsuda, and T. Ueda, *Tetrahedron*, **42**, 1971 (1986).
5) N. W. Gilman, *J. Chem. Soc., Chem. Commun.*, **1971**, 733.
6) H. Tanaka, Y. Uchida, M. Shinozaki, H. Hayakawa, A. Matsuda, and T. Miyasaka, *Chem. Pharm. Bull.*, **31**, 787 (1983).
7) H. Tanaka, A. Matsuda, S. Iijima, H. Hayakawa, and T. Miyasaka, *Chem. Pharm. Bull.*, **31**, 2164 (1983).
8) H. Tanaka, H. Hayakawa, S. Iijima, K. Haraguchi, and T. Miyasaka, *Tetrahedron*, **41**, 861 (1985).
9) M. J. Robins and R. A. Jones, *J. Org. Chem.*, **39**, 113 (1974).
10) For other reports on the formation of 1′,2′-unsaturated nucleosides: M. J. Robins and E. M. Trip, *Tetrahedron Lett.*, **38**, 3369 (1974); M. Kawana, K. Takeuchi, T. Ohba, and H. Kuzuhara, *Nucleic Acids Symposium Series*, **17**, 37 (1986).
11) LTMP is reported to be 1.6 pK units more basic than LDA: R. R. Fraser, A. Baignée, M. Bress, and K. Hata, *Tetrahedron Lett.*, **23**, 4195 (1982).
12) W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **29**, 853 (1964).
13) The present method should be regarded as an alpha lithiation of a nitrogen-activated system.
14) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, **1952**, 1094.