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Synthesis and Optical Properties of 2,5′-*O*-Cycloimidazole Nucleosides and Related Compounds(Nucleosides and Nucleotides. XXV[1])

Hiromichi Tanaka, Takako Takahashi, Hiroyuki Togashi, and Tohru Ueda

Faculty of Pharmaceutical Sciences, Hokkaido University[2]

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Starting from 1-β-D-ribofuranosyl-2-oxo-4-imidazoline-4-carboxylic acid (**1**), obtained from uridine, various 2,5′-*O*-cycloimidazole nucleosides have been prepared. The 2-oxo function of **1** was also converted to the 2-chloro and 2-thione functions. Whereas the circular dichroism (CD) spectra of **1** and related 2-oxo derivatives exhibited negative bands, their 5-bromo derivatives showed positive bands. All 2,5′-*O*-cycloimidazole nucleosides showed strong negative CD bands which were in contrast to the results in the 8,5′-*O*-cyclopurine nucleosides. The relationship between the sign of the CD bands and the orientation of the base moieties in imidazole nucleosides was discussed.

Keywords——bromination; uridine; imidazole nucleosides; imidazoline; cyclonucleosides; conformation; NMR; CD

Studies on the synthesis and properties of purine and pyrimidine cyclonucleosides have been important subjects in the field of nucleoside chemistry because of the usefulness of these cyclonucleosides in the transformation of the base and/or sugar moiety of naturally occurring nucleosides to the bioactive derivatives.[3] In certain case, as 2,2′-cyclocytidine,[4] the cyclonucleoside itself exhibited potent anti-leukemic activity.

Cyclonucleosides have also been utilized in the stereochemical studies of nucleosides, nucleotides, and polynucleotides as the conformationally fixed models.[5] By contrast little is explored about the chemistry of cycloimidazole nucleosides due probably to their difficult accessibility. Aminoimidazolecarboxamide (AICA) riboside and bredinin,[6] a nucleoside antibiotic, are the naturally occurring imidazole nucleosides so far accessible.

Preceding reports by Fox and co-workers[7] concerning with the interesting conversion of uridine to 1-β-D-ribofuranosyl-2-oxo-4-imidazoline-4-carboxylic acid (**1**) prompted us to investigate the synthesis and properties of the imidazole nucleosides derivatizable from **1**. The present report involves the synthesis and optical properties of several 2,5′-*O*-cycloimidazole nucleosides and related compounds.

The starting material **1** was prepared from uridine[7b] which was isolated in a form of the 2′,3′,5′-tri-*O*-acetate (**2**). This method enabled us to prepare **2** in relatively large scale by one pot synthesis from uridine. Methylation of **2** with a controlled amount of diazomethane afforded the 4-carboxylic acid methyl ester (**3**).[8] The use of an excess of the reagent afforded the *N*-methyl derivative (**4**), confirmed after deacetylation to give **5**. Deacetylation of **3** by

1) Part XXIV: A. Matsuda, M. Tezuka, K. Niizuma, E. Sugiyama, and T. Ueda, *Tetrahedron*, **34**, 2633 (1978).
2) Location: *Kita-12, Nishi-6, Kita-ku, Sapporo, 060, Japan.*
3) For recent examples, see M. Ikehara and Y. Ogiso, *Tetrahedron*, **28**, 3695 (1972); J.B. Chattopadhyaya and C.B. Reese, *J. Chem. Soc. Chem. Commun.*, **1977**, 414.
4) A. Hoshi, H. Kanzawa, K. Kuretani, M. Saneyoshi, and Y. Arai, *Gann*, **62**, 145 (1971).
5) For a recent review, see M. Ikehara and T. Ueda, *Yuki Gosei Kagaku*, **32**, 402 (1974).
6) M. Hayashi, T. Hirano, M. Yaso, K. Mizuno, and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **23**, 245 (1975).
7) *a*) B.A. Otter, E.A. Falco, and J.J. Fox, *J. Org. Chem.*, **34**, 1319 (1969); *b*) *Idem*, *ibid.*, **34**, 2636 (1969).
8) An alternate route of the preparation of **3** has been reported: P.C. Srivastava, R.J. Rousseau, and R.K. Robins, *J. Chem. Soc. Chem. Commun.*, **1977**, 151.

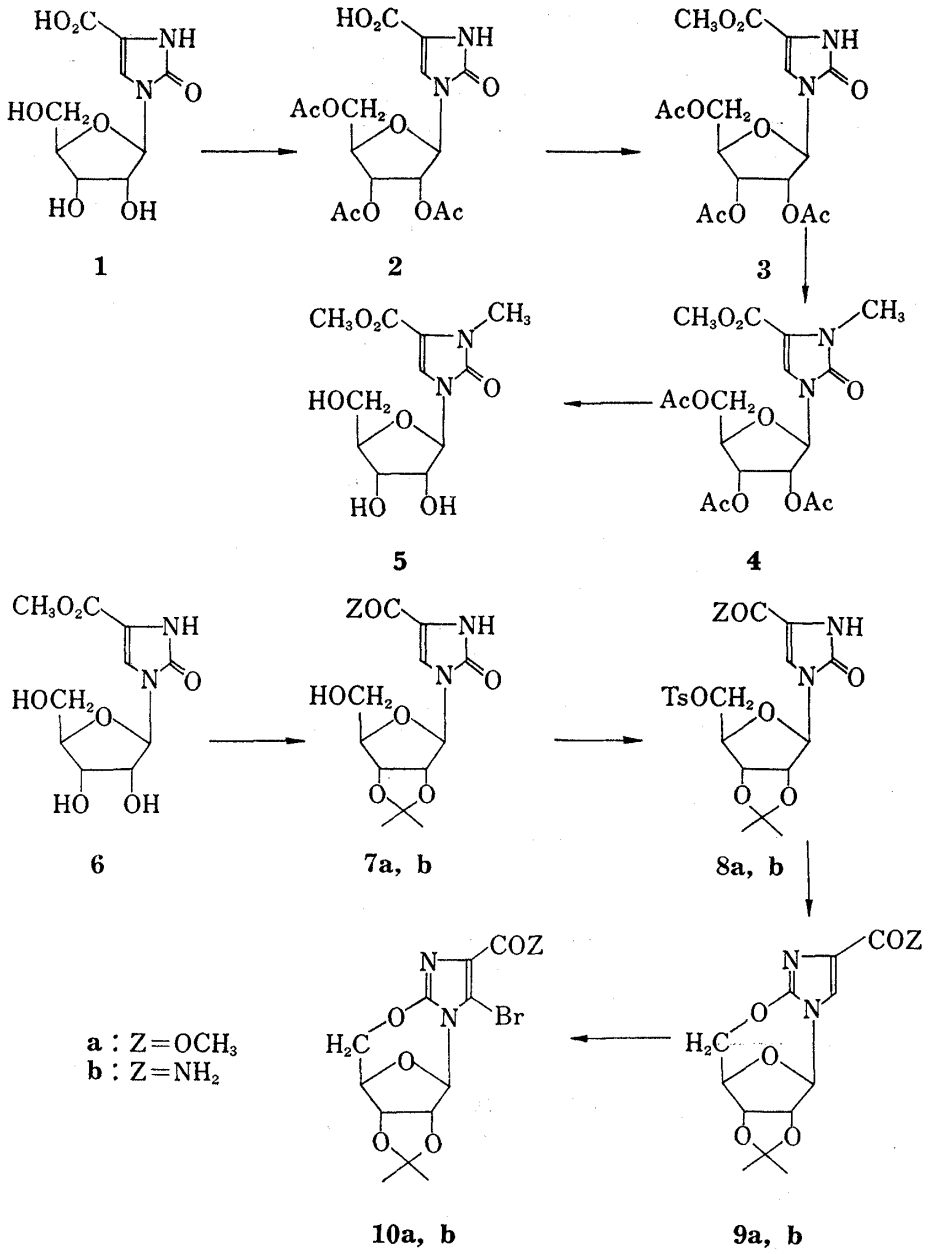
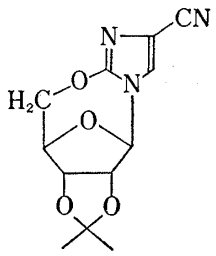


Chart 1

methoxide treatment gave the riboside **6**, which was converted to the 2′,3′-*O*-isopropylidene derivative (**7a**) in high yield. Treatment of **7a** with *p*-toluenesulfonyl chloride in pyridine afforded the 5′-*O*-tosylate (**8a**) which was then cyclized by the action of triethylamine in refluxing dioxane to give 2,5′-*O*-cyclo-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-2-oxyimidazole-4-carboxylic acid methyl ester (**9a**). The structure of **9a** was confirmed by the spectral and analytical basis. In nuclear magnetic resonance (NMR) spectra the geminal coupling of the 5′-protons in **9a** was detected which is characteristic of the 2,5′-*O*-cyclo structure. One of the 5′-protons further splits as a result of the coupling with the 4′-proton. This is indicative of the 5′-*O*-endo conformation of the cyclo linkage in **9a**.

The ammonolysis of **7a** required rather drastic conditions, heating at 100° in concentrated ammonia for 105 minutes, to give the 4-carboxamide (**7b**). The 5′-*O*-tosylation of **7b** (to give **8b**) followed by treatment with sodium hydroxide in methanol afforded the 2,5′-*O*-cyclo derivative (**9b**).

The cyclo linkages of **9a** and **9b** were found to be unexpectedly stable. The compound **9a** or **9b** resisted to the sulfhydrolysis, ammonolysis, or treatment with sodium benzoate in hexamethylphosphoric triamide. These stabilities are to be contrasted with the ready ring-opening of the 8,5′-*O*-cyclopurine nucleosides or 2,5′-*O*-cyclouridines by the aforementioned solvolyses.[5] It is conceivable that in purine nucleosides the electron-withdrawing pyrimidine ring fused with the imidazole moiety facilitates the attack of the nucleophile to the position 8 (equivalent to the position 2 in the imidazole) or the 5′-carbon. Treatment of **9a** and **9b** with bromine in methanol afforded the respective 5-bromo derivatives (**10a** and **10b**). The reaction of **10a** or **10b** with various nucleophiles also failed to cause the substitution at the position 5, or the cleavage of the cyclo linkages. For example, treatment of **10b** with liquid ammonia at 75° for 67 hr met with the quantitative recovery of the starting material.



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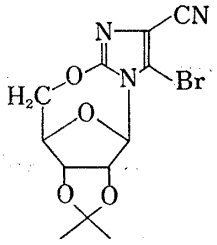

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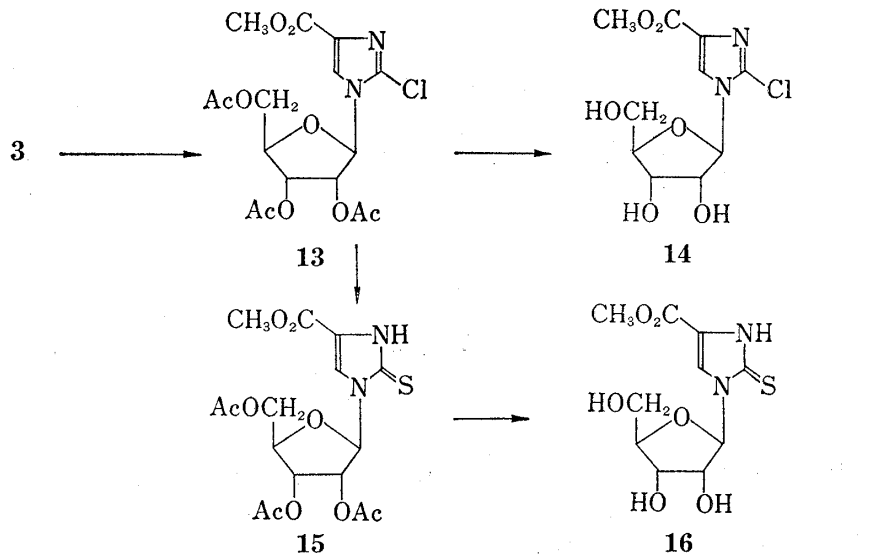
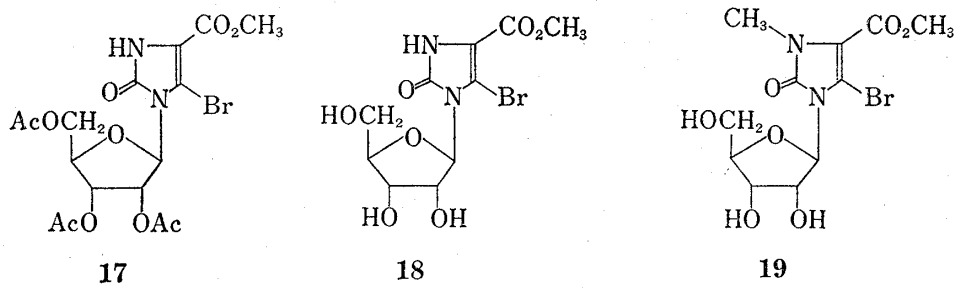
Chart 2

In order to raise the electron-withdrawing nature of the 4-substituent, **9b** and **10b** were treated with phosphoryl chloride to give the respective 4-cyano derivatives (**11** and **12**). These were also found to be stable toward the cyclo-ring opening reactions or substitution reactions at the position 5.

The alternative route to introduce a substituent into the position 2 may be the thiation of **3**. Treatment of **3** with phosphorus pentasulfide in pyridine or in dioxane, however, failed



13 **14** **15** **16**



17 **18** **19**

Chart 3

to give the expected 2-thione derivative. On the other hand, treatment of **3** with phosphoryl chloride-dimethylaniline afforded the 2-chloro compound (**13**) in high yield. Deacetylation of **13** with sodium methoxide afforded the 2-chloroimidazole riboside (**14**). Treatment of **13** with liquid hydrogen sulfide in pyridine afforded the 2-thione (**15**) in high yield, which was also deprotected to give the riboside (**16**). Compound **14** resisted to the treatment with methanolic ammonia or methoxide in methanol for the 2-substitution. This stability is in consistent with the previous finding of the inertness of 2-bromo-AICA riboside[9] toward various nucleophiles.

As a whole, the π-excessive nature of the imidazole ring reflects on the low reactivity of the 2- or 5-halogeno group as well as the 2,5′-*O*-cyclo linkage toward nucleophilic substitution regardless of the presence of the electron-withdrawing group at the position 4.

Some optical properties of the imidazole cyclonucleosides and related compounds are to be discussed here. The 2-imidazolone nucleosides can be regarded as the derivative of purine nucleosides in a sense that both are ribosylated in the imidazole part, or as that of pyrimidine nucleosides by taking account of the carbonyl group at the position 2 as in uridine and cytidine. There have been much efforts to correlate the sign of the circular dichroism (CD) bands of purine and pyrimidine nucleosides to their *syn* or *anti* conformations.[10] Most of the naturally occurring pyrimidine nucleosides exhibit positive CD spectra at their λ_{max}'s and are deduced to prefer *anti* conformation (the 2-carbonyl group being outside of the ribose ring), while 6-methyl derivatives of uridine and cytidine with negative CD signs were regarded as existing in syn conformation.[14–16] The purine nucleosides exhibiting negative CD signs were assumed to prefer *anti* conformation (the pyrimidine part of the purine ring being outside of the ribose ring).[14,17] 8-Substituted purine nucleosides tend to possess *syn* conformations.[18]

The conformations of nucleosides have also been discussed on the basis of nuclear magnetic resonance,[19] nuclear Overhauser effect,[20] dipole moments,[21] or by quantum mechanical treatment.[22] It may be generally stated that, in solution, pyrimidine nucleosides tend to have higher energy barriers between *syn* and *anti* conformers, the latter being more stable. The *syn-anti* barriers in the purine nucleosides seems to be rather low. The results of the crystal structures of various nucleosides are generally proportional to this assumption.[23]

It may be expected that the barrier of the glycosyl bond rotation in imidazole nucleosides should be similar to that of purine nucleosides. Mackenzie and Shaw reported[9b] the CD spectra of derivatives of aminoimidazolecarboxamide riboside in which they assumed the

9) *a*) G.A. Ivanovics, R.J. Rousseau, M. Kawana, P.C. Srivastava, and R.K. Robins, *J. Org. Chem.*, **39**, 3651 (1974); *b*) G. Mackenzie and G. Shaw, *J. Chem. Res.*, (*S*), **184**, (*M*), 2145 (1977).
10) The definition of *syn* or *anti* for the glycosylic torsion angles of the nucleosides are made by Donohue and Trueblood(ϕ_{CN}),[11] Sundaralingam(ϕ_{CN}),[12] and Hart and Davis(γ).[13]
11) J. Donohue and K.N. Trueblood, *J. Mol. Biol.*, **2**, 363 (1960).
12) M. Sundaralingam, *Biopolymers*, **7**, 821 (1969).
13) P.A. Hart and J.P. Davis, *J. Am. Chem. Soc.*, **93**, 753 (1971).
14) D.W. Miles, R.K. Robins, and H. Eyring, *Proc. Nat. Acad. Sci. US*, **57**, 1138 (1967).
15) D.W. Miles, M.J. Robins, R.K. Robins, M.W. Winkley, and H. Eyring, *J. Am. Chem. Soc.*, **91**, 824 (1969).
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17) D.W. Miles, R.K. Robins, and H. Eyring, *J. Phys. Chem.*, **71**, 3931 (1967).
18) M. Ikehara and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **19**, 104 (1971).
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20) P.A. Hart and J.P. Davis, *The Jerusalem Symposia on Quantum Chemistry and Biochemistry*, **5**, 297 (1973).
21) H. Weiler-Feilchenfeld, G. Zvilichovsky, E.D. Bergmann, B. Pullman, and H. Berthod, *The Jerusalem Symposia on Quantum Chemistry and Biochemistry*, **5**, 329 (1973).
22) B. Pullman and H. Berthod, *Symposium on Quantum Chemistry and Biochemistry*, **5**, 209 (1973).
23) G.A. Jeffrey and M. Sundaralingam, *Adv. Carbohyd. Chem. Biochem.*, **30**, 445 ((1974), **31**, 347 (1975), **32**, 353 (1976), and references therein.

anti conformer (the 5-amino group being outside of the ribose ring) exhibits a negative CD sign, as observed in the purine nucleosides.

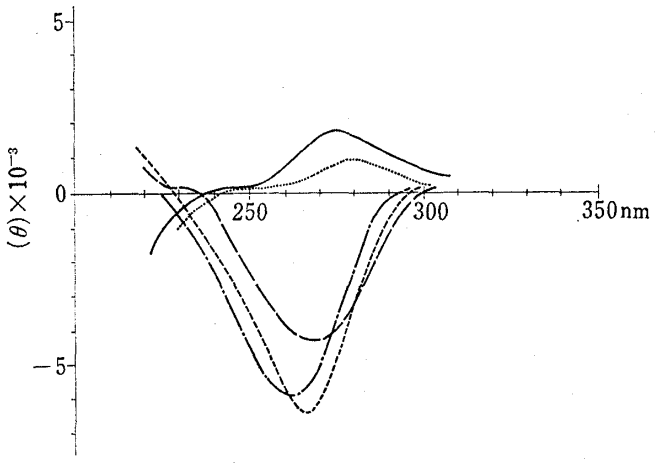

Fig. 1. CD Spectra of 2-Imidazolone Nucleosides

————: **5**, – – – –: **7a**, —·—·—: **7b**, ·····: **18**, ——— : **19**.

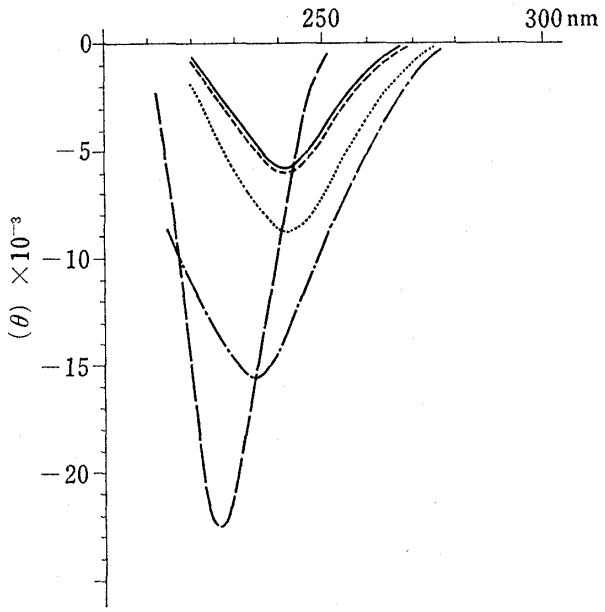

Fig. 2. CD Spectra of 2,5′-Cycloimidazole Nucleosides

– – – –: **9a**, ———: **9b**, ·····: **10b**, ————: **11**, —·—·—: **12**.

The CD spectra of the compounds prepared in the present work were shown in Fig. 1 and 2. Compounds having the 2-keto group (**5**, **7a**, **7b**) exhibited negative CD bands at their λ_{max}'s. If we assume these compounds prefer to possess the *anti* conformation (the 2-keto group being outside of the ribose ring), the introduction of the substituent at position 5 should lead to take rather *syn* form, which should reflect to the CD spectra. In fact, compound **18** and **19**, the 5-bromo derivative of **5** and **6**, showed weak but positive CD spectra at their λ_{max}'s.[24] The CD spectra of all 2,5′-*O*-cycloimidazole nucleosides (**9a**, **9b**, **10b**, **11** and **12**) showed negative CD bands, irrespective of the presence or the absence of the substituent at the position 5. It is to be noted that the CD spectra of corresponding cyclopurine nucleoside, 8,5′-*O*-cycloadenosine,[25] exhibited strong positive ellipticity. This would suggest that the assumption based on the results of purine nucleosides cannot simply be applied to the estimation of conformations of imidazole nucleosides. Since the molar ellipticities of the cyclo nucleosides (Fig. 2) are rather higher than those of usual nucleosides (Fig. 1) the latter nucleosides must be in the equilibrium of *syn-anti* conformers.

The CD spectra of 2-chloroimidazole nucleoside (**14**) showed negative sign. An imidazole-2-thione nucleoside (**16**) exhibited strong negative and positive CD band from the longer wave-length absorption region, which is similar to that of 2-thiouridine.[26]

Experimental

General Methods——Melting points were determined on a Yanagimoto Micro Melting Point Apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on Merck TLC plates (silica gel F_{254}, precoated in 0.25 mm thick) and spots were visualized by ultraviolet (UV)-lamp. Infrared (IR) spectra

24) Other 5-substituted 2-imidazolone nucleosides also exhibited positive CD spectra, H. Tanaka and T. Ueda, unpublished experiments.
25) M. Ikehara, M. Kaneko, Y. Nakahara, and S. Uesugi, *Chem. Pharm. Bull.* (Tokyo), **19**, 1381 (1971); M. Ikehara, S. Uesugi, and K. Yoshida, *Biochem.*, **11**, 830, 836 (1972).
26) T. Ueda and H. Nishino, *Chem. Pharm. Bull.* (Tokyo), **17**, 920 (1969).

were recorded on a Hitachi 215 spectrophotometer. UV spectra were recorded on a Shimadzu UV-300 spectrophotometer. Mass spectra (MS) were taken on a JEOL JMS-D300 mass spectrometer. NMR spectra were recorded on a Hitachi R-20B (60 MHz) or JEOL PS-100 (100 MHz) spectrometer using tetramethylsilane as an internal standard. The abbreviations used in the description of the splitting are as follows: s (singlet), d (doublet), t (triplet), m (multiplet), and b (broad). CD spectra were recorded on a JASCO J-40 spectropolarimeter with a data processor operating 8 accumulations. Methanol was used as the solvent throughout this experiment at room temperature (15—20°).

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-2-oxo-4-imidazoline-4-carboxylic Acid (2)——Compound **1** was prepared from 120 g of uridine according to the method reported.[7] The reaction mixture containing **1** was acidified with acetic acid and evaporated to dryness. The residue was dissolved in 1000 ml of pyridine and 1000 ml of acetic anhydride, and kept overnight at room temperature. The mixture was evaporated to leave a brown residue which was taken in aqueous saturated $NaHCO_3$, and washed with $CHCl_3$. The aqueous layer was acidified with conc. HCl to pH 1 and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and evaporated to leave a crystalline solid of **2** (80 g, 42%). Recrystallization of **2** from EtOH–hexane gave an analytically pure sample, mp 229—232°. *Anal.* Calcd. for $C_{15}H_{18}N_2O_{10}$: C, 46.63; H, 4.70; N, 7.25. Found: C, 46.41; H, 4.72; N, 7.19. MS *m/e*: 386 (M), 342 (M–CO_2), 326 (M-AcOH). UV λ_{max}^{MeOH}: 263 nm (ε, 9600). NMR (60 MHz, DMSO-d_6), δ: 2.09 (s, 6, Ac), 2.12 (s, 3, Ac), 4.33 (bs, 3, 4′,5′-H), 5.45 (m, 1, 3′-H), 5.66 (d, 1, 2′-H), 5.75 (d, 1, 1′-H, J=5 Hz), 7.56 (d, 1, 5-H, J=1.5 Hz), 10.45 (bs, 1, NH).

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-2-oxo-4-imidazoline-4-carboxylic Acid Methyl Ester (3)——To a solution of **2** (6.0 g) in MeOH was added diazomethane in ether in portionwise under stirring. The progress of the reaction was checked by TLC ($CHCl_3$–MeOH, 15: 1). After the completion of the esterification the solvent was evaporated to leave a residue which was crystallized from EtOH to afford **3** (5.8 g, 93%). Recrystallization of **3** from MeOH–ether gave a pure sample, mp 154—155°, *Anal.* Calcd. for $C_{16}H_{20}N_2O_{10}$: C, 48.00; H, 5.04; N, 7.00. Found: C, 48.11; H, 4.96; N, 6.94. MS *m/e*: 400 (M), 142 (B+1). UV λ_{max}^{MeOH}: 267 nm (ε, 12700). NMR (60 MHz, DMSO-d_6), δ: 2.10 (s, 3, Ac), 2.14 (s, 3, Ac), 2.18 (s, 3, Ac), 3.87 (s, 3, CO_2CH_3), 4.37 (bs, 3, 4′,5′-H), 5.30, 5.70 (m, 2, 2′,3′-H), 5.97 (d, 1, 1′-H, J=5.0 Hz), 7.26 (d, 1, 5-H, J=1.5 Hz), 10.10 (bs, 1, NH).

1-(β-D-Ribofuranosyl)-2-oxo-3-methyl-4-imidazoline-4-carboxylic Acid Methyl Ester (5)——To the MeOH solution of **3** was added excess diazomethane in ether. The solution was evaporated to leave a foamy residue (**4**). Without further purification **4** was dissolved in MeOH containing 0.5 molar equivalent of NaOMe and kept for 1 hr at room temperature. The solution was neutralized with Amberlite IR-120 (H^+ form) resin and the filtrate was concentrated. The residue was crystallized from EtOH–ether to give **5**, mp 201—203°. The yield of **5** from **3** was almost quantitative. *Anal.* Calcd. for $C_{11}H_{16}N_2O_7$: C, 45.83; H, 5.60; N, 9.72. Found: C, 45.75; H, 5.56; N, 9.82. MS *m/e*: 288 (M), 156 (B+1). UV λ_{max}^{MeOH}: 270 nm (ε, 12700). NMR (60 MHz, DMSO-d_6), δ: 3.39 (s, 3, NMe), 3.50—3.70 (d, 2, 5′-H), 3.80 (s, 3, CO_2CH_3), 4.0—4.3 (m, 1, 4′-H), 5.0—5.5 (m, 2, 2′,3′-H), 5.54 (d, 1, 1′-H, J=5.0 Hz), 7.26 (s, 1, 5-H).

1-(β-D-Ribofuranosyl)-2-oxo-4-imidazoline-4-carboxylic Acid Methyl Ester (6)——To a solution of **3** (20 g, 50 mmol) in MeOH was added NaOMe (4.05 g, 75 mmol) and kept for 1 hr at room temperature. The solution was neutralized with Amberlite IR-120 (H^+ form) resin and evaporated to leave a residue which was crystallized from MeOH–hexane to furnish 10.7 g (78%) of **6**, mp 187—189°, *Anal.* Calcd. for $C_{10}H_{14}N_2O_7$: C, 43.80; H, 5.15; N, 10.22. Found: C, 43.70; H, 5.23; N, 10.08. MS *m/e*: 274 (M), 142 (B+1). UV λ_{max}^{MeOH}: 268.5 nm (ε, 12500). NMR (60 MHz, DMSO-d_6), δ: 3.55 (d, 2, 5′-H), 3.73 (s, 3, CO_2CH_3), 3.70—4.30 (m, 3, 2′,3′,4′-H), 4.80—5.30 (m, 3, 2′,3′,5′-OH), 5.43 (d, 1, 1′-H, J=6.0 Hz), 7.58 (d, 1, 5-H, J=1.5 Hz), 10.85 (bs, 1, NH).

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-2-oxo-4-imidazoline-4-carboxylic Acid Methyl Ester (7a)——To a suspension of **6** (5.48 g) in acetone (500 ml) was added 70% $HClO_4$ (14.3 g) with stirring at 0° and kept for 2 hr at room temperature. The solution was neutralized by the addition of finely powdered K_2CO_3 and the insoluble inorganic salts were removed by filtration. The filtrate was evaporated and the residue was taken in MeOH, the insoluble material being removed, and the solvent was evaporated. The residue was crystallized from H_2O to give 3.96 g (63%) of **7a**, mp 153—154°. *Anal.* Calcd. for $C_{13}H_{18}N_2O_7$: C, 49.68; H, 5.77; N, 8.91. Found: C, 49.42; H, 5.87; N, 8.85. MS *m/e*: 314 (M), 299 (M–15), 142 (B+1). UV λ_{max}^{MeOH}: 267.5 nm (ε, 12500). NMR (60 MHz, DMSO-d_6), δ: 1.31 (s, 3, exo-MeC), 1.50 (s, 3, endo-MeC), 3.57 (t, 2, 5′-H), 3.77 (s, 3, CO_2CH_3), 4.0—4.3 (m, 1, 4′-H), 4.7—5.3 (m, 3, 2′,3′-H and 5′-OH), 5.66 (d, 1, 1′-H, J=2.5 Hz), 7.68 (s, 1, 5-H), 11.00 (bs, 1, NH).

Compound **7a** was also obtained from **3** (34 g) without isolation of **6** by adding the methanolyzate into acetone solution containing 70% $HClO_4$, and the yield of **7a** was 22.3 g (83.3%).

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-2-oxo-4-imidazoline-4-carboxamide (7b)——Compound **7a** (20 g) in MeOH (100 ml) and 28% aqueous NH_3 (150 ml) were placed in a steel tube and heated at 100° for 105 min. The mixture was evaporated and the residue was crystallized from H_2O to give 16.67 g (87.6%) of **7b**. Recrystallization from MeOH gave an analytically pure sample, mp 224—225.5°. *Anal.* Calcd. for $C_{12}H_{17}N_3O_6$: C, 48.16; H, 5.73; N, 14.04. Found: C, 48.08; H, 5.70; N, 13.98. MS *m/e*: 299 (M), 284 (M–15), 127 (B+1). UV $\lambda_{max}^{H_2O}$: 263.5 nm (ε, 10400); $\lambda_{max}^{1N\ NaOH}$: 282.5 nm (ε, 8200). NMR (60 MHz, DMSO-d_6), δ: 1.31

(s, 3, exo-MeC), 1.50 (s, 3, endo-MeC), 3.55 (t, 2, 5′-H), 3.90—4.30 (m, 1, 4′-H), 4.60—5.20 (m, 3, 2′,3′-H and 5′-OH), 5.61 (d, 1, 1′-H, J=2.5 Hz), 7.32 (bs, 2, $CONH_2$), 7.38 (s, 1, 5-H), 10.55 (bs, 1, NH).

2,5′-Cyclo-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-2-oxyimidazole-4-carboxylic Acid Methyl Ester (9a)——Compound **7a** (9.0 g, 28.6 mmol) was dissolved in pyridine (60 ml) and *p*-toluenesulfonyl chloride (6.0 g, 31.5 mmol) was added and kept at room temperature overnight. After adding few crops of ice and stirring for 5 min the mixture was poured into $NaHCO_3$ solution. The solution was extracted with $CHCl_3$ and the organic layer was evaporated, co-evaporated with EtOH, to furnished **8a** as a sirup, UV λ_{max}^{EtOH}: 223 and 263 nm. The crude **8a** was dissolved in dioxane (150 ml) containing triethylamine (6 ml) and the solution was refluxed for 5 hr. After removal of the solvent the residue was taken in $CHCl_3$, washed with 1 N-NaOH, dried over Na_2SO_4, and evaporated. The residue was crystallized from iso-PrOH to give 5.55 g (65.4%) of **9a**. Recrystallization from iso-PrOH afforded a pure sample, mp 140.5—141.5°. *Anal.* Calcd. for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.46. Found: C, 52.67; H, 5.48; N, 9.47. MS *m/e*: 296 (M). UV λ_{max}^{MeOH}: 240 nm (ε, 9900). IR (KBr): 1720 cm^{-1} (CO). NMR (100 MHz, $CDCl_3$), δ: 1.35 (s, 3, exo-MeC), 1.54 (s, 3, endo-MeC), 3.86 (s, 3, CO_2CH_3), 4.06 (d, 1, 5′-H, J=13 Hz), 4.45 (dd, 1, 5′-H), 4.67 (bs, 1, 4′-H), 4.77 (d, 1, 3′-H, J=5.8 Hz), 5.05 (d, 1, 2′-H), 5.67 (s, 1, 1′-H), 7.42 (s, 1, 5-H).

2,5′-Cyclo-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-2-oxyimidazole-4-carboxamide (9b)——Compound **7b** (2.9 g, 9.7 mmol) was dissolved in pyridine (22 ml) and *p*-toluenesulfonyl chloride (1.99 g, 10.4 mmol) was added at −15°, and stirred for 3 hr at room temperature. The mixture was poured into ice-water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and evaporated and coevaporated with EtOH to leave a foam of **8b**. The crude **8b** was taken in MeOH containing 5 ml of 5 N NaOH, and kept for 1 hr at room temperature. The solvent was removed and the residue was crystallized from MeOH–hexane to give 2.2 g (81.5%) of **9b**, mp 268—270°. *Anal.* Calcd. for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.38; N, 14.94. Found: C, 51.18; H, 5.43; N, 14.99. MS *m/e*: 281 (M), 266 (M−15). UV λ_{max}^{EtOH}: 238.5 nm (ε, 9000). NMR (60 MHz, DMSO-d_6), δ: 1.32 (s, 3, exo-MeC), 1.46 (s, 3, endo-MeC), 3.98 (d, 1, 5′-H, J=13.5 Hz), 3.55 (dd, 1, 5′-H), 4.70 (bs, 1, 4′-H), 4.84 (d, 1, 3′-H, J=6.0 Hz), 5.10 (d, 1, 2′-H), 6.09 (s, 1, 1′-H), 7.13 (bs, 2, $CONH_2$), 7.66 (s, 1, 5-H).

2,5′-Cyclo-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-bromo-2-oxyimidazole-4-carboxylic Acid Methyl Ester (10a)——To a solution of **9a** (102 mg, 0.34 mmol) in MeOH was added a solution (1.2 ml) of bromine (1.029 g in 20 ml of MeOH), and stirred for 30 min at room temperature. The reaction mixture was neutralized with 1 N NaOH (5 ml) and the solvent was removed under reduced pressure below 30°. The residue was partitioned with $CHCl_3$ and H_2O and the organic layer was dried over Na_2SO_4, and evaporated to leave **10a** (114 mg, 88.2%) as a foam. MS *m/e*: 376, 374 (M), 361, 359 (M−15) 295 (M−Br). UV λ_{max}^{MeOH}, 252 nm.

2,5′-Cyclo-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-bromo-2-oxyimidazole-4-carboxamide (10b)——By a similar treatment of **9b** with bromine as described above, **10b** was obtained in 88% yield, mp 255—256° from MeOH. *Anal.* Calcd. for $C_{12}H_{14}BrN_3O_5$: C, 40.01; H, 3.92; Br, 22.19; N, 11.67. Found: C, 40.07; H, 3.92; Br, 22.33; N, 11.57. MS *m/e*: 361, 359 (M), 346, 344 (M−15), 281 (M−Br). UV λ_{max}^{EtOH}: 247 nm (ε, 7800).

2,5′-Cyclo-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-2-oxyimidazole-4-carbonitrile (11)——Compound **9b** (1.9 g, 6.76 mmol) was suspended in $CHCl_3$ (30 ml) and triethylamine (3.42 g, 34 mmol), and $POCl_3$ (2.07 g, 13.5 mmol) was added dropwise at 0°. The reaction mixture was stirred for 8 hr at room temperature and added to ice-water. The mixture was extracted with $CHCl_3$ and the organic layer was dried over Na_2SO_4. The solvent was evaporated and the residue was crystallized from EtOH to give 1.58 g (88.7%) of **11**, mp 172—173°. *Anal.*Calcd. for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.95; H, 4.90; N, 15.95. MS *m/e*: 263 (M), 248 (M−15). UV λ_{max}^{EtOH}: 225 nm (ε, 9400). IR (KBr): 2240 cm^{-1} (CN).

2,5′-Cyclo-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-bromo-2-oxyimidazole-4-carbonitrile (12)——To a solution of 10b (1.8 g, 5 mmol) in $CHCl_3$ (50 ml) containing triethylamine (3 g) was added $POCl_3$ (767 mg, 5 mmol) dropwise at 0°. Stirring was continued at 0° for 30 min, then at room temperature for 2 hr. The mixture was poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4, evaporated, and the residue was crystallized from EtOH to give 939 mg (54.9%) of **12**, mp 244—246°. *Anal.* Calcd. for $C_{12}H_{12}BrN_3O_4$: C, 42.12; H, 3.54; Br, 23.36, N, 12.28. Found: C, 42.00; H, 3.57; Br, 23.35; N, N, 12.07. MS *m/e*: 343, 341 (M), 328, 326 (M−15), 262 (M–Br). UV λ_{max}^{EtOH}: 238 nm (ε, 7700). IR (KBr): 2240 cm^{-1} (CN).

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-2-chloroimidazole-4-carboxylic Acid Methyl Ester (13)——To a suspension of **3** (6.0 g) in $POCl_3$ (45 ml) was added dimethylaniline (4.5 ml) and the mixture was heated under reflux for 6 hr. Most of $POCl_3$ was removed under reduced pressure and the concentrate was poured slowly into ice-water with stirring. The ice cold mixture was extracted with $CHCl_3$ and the organic layer was washed with 0.1 N HCl followed by 50% saturated $NaHCO_3$. The $CHCl_3$ layer was dried over Na_2SO_4, evaporated, and the residue was applied to a column of silica gel (3.5×25 cm, packed with $CHCl_3$) in $CHCl_3$. The eluate with 0.5% MeOH in $CHCl_3$ was evaporated to leave **13** (5.37 g, 85.5%) as a foam. MS *m/e*: 420, 418 (M), 389, 387 (M–OMe). UV λ_{max}^{EtOH}: 226 nm. This was used for further reaction without attempting crystallization.

1-(β-D-Ribofuranosyl)-2-chloroimidazole-4-carboxylic Acid Methyl Ester (14)——The compound **13** (2.86 g) was dissolved in MeOH containing NaOMe (740 mg) and kept for 90 min at room temperature. The mixture was neutralized with Amberlite IR-120 (H^+) resin, filtered, and the filtrate was concentrated to give

colorless crystals (**14**, 1.45 g, 72.6%). Recrystallization from MeOH gave an analytically pure sample, mp 185—187°. *Anal.* Calcd. for $C_{10}H_{13}ClN_2O_6$: C, 41.03; H, 4.48; Cl, 12.11; N, 9.57. Found: C, 40.75; H, 4.51; Cl, 12.31; N, 9.53. MS *m/e*: 294, 292 (M), 162, 160 (B+1), 131, 129 (B+1-OCH_3). UV λ_{max}^{MeOH}: 234 nm (ε, 10500). NMR (100 MHz, DMSO-d_6), δ: 3.17—3.59 (m, 2, 5′-H), 3.76 (s, 3, CO_2CH_3), 3.92—4.07 (m, 2, 3′,4′-H), 4.24 (t, 1, 2′-H), 4.33—5.53 (bm, 3, 2′,3′,5′-OH), 5.61 (d, 1, 1′-H, J=5.6 Hz). $[\theta]_{239}^{MeOH}$: −6200.

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-4-imidazoline-2-thione-4-carboxylic Acid Methyl Ester (15)——Crude **13** prepared from 10 g of **3** was taken in a mixture of pyridine and liquid H_2S-pyridine (100 ml, 1: 1, v/v) and sealed in a steel tube. After heating at 60° overnight H_2S was vaporized by bubbling N_2 gas and the solvent was evaporated. The residue was taken in EtOH and concentrated to effect precipitation of **15** (5.5 g). The filtrate of the precipitate was concentrated and the residue was taken in $CHCl_3$ which was applied to a column of silica gel (100 g, packed with $CHCl_3$). The eluate with $CHCl_3$ gave further 2.2 g of **15** (total 7.7 g, 74.3% from **3**) after evaporation of the solvent. Recrystallization from EtOH gave a pure sample of **15**, mp 147—149°. *Anal.* Calcd. for $C_{16}H_{20}N_2O_9S$: C, 46.15; H, 4.84; N, 6.73; S, 7.70. Found: C, 45.86; H, 4.69; N, 6.70; S, 7.45. MS *m/e*: 416 (M), 356 (M-AcOH). UV λ_{max}^{MeOH}: 269 nm (ε, 16400), shoulder at 300 nm (ε, 8300). NMR (100 MHz, $CDCl_3$), δ: 2.12 (s, 3, Ac), 2.13 (s, 3, Ac), 2.21 (s, 3, Ac), 3.88 (s, 3, CO_2CH_3), 4.38 (bs, 2, 5′-H), 4.45 (m, 1, 4′-H), 5.33 (t, 1, 3′-H), 5.50 (t, 1, 2′-H), 6.40 (d, 1, 1′-H, J=6.4 Hz), 7.68 (s, 1, 5-H), 10.06 (bs, 1, NH).

1-(β-D-Ribofuranosyl)-4-imidazoline-2-thione-4-carboxylic Acid Methyl Ester (16)——Compound **15** (5.0 g) was dissolved in MeOH containing NaOMe (973 mg) and kept overnight at room temperature. The mixture was neutralized with Amberlite IR-120 (H^+), filtered, and the filtrate was concentrated to leave a crystalline solid of **16** (3.1 g, 89%). Recrystallization from EtOH gave an analytically pure sample, mp 194—197°. *Anal.* Calcd. for $C_{10}H_{14}N_2O_6S$: C, 41.38; H, 4.86; N, 9.65; S, 11.05. Found: C, 41.36; H, 4.82; N, 9.61; S, 10.97. MS *m/e*: 290 (M), 159 (B+2), 158 (B+1). UV λ_{max}^{MeOH}: 266 nm (ε, 12700), 292 nm (ε, 9200). NMR (100 MHz, DMSO-d_6), δ: 3.61 (t, 2, 5′-H), 3.78 (s, 3, CO_2CH_3), 3.8—4.2 (m, 2, 2′,3′-H), 6.01 (d, 1, 1′-H, J=3.9 Hz), 8.16 (d, 1, 5-H, J=1.9 Hz), 13.07 (bs, 1, NH). $[\theta]_{296}^{MeOH}$: −7250, $[\theta]_{277}$, 0, $[\theta]_{255}$, +22200, $[\theta]_{231}$, 0, $[\theta]_{222}$, −6000.

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-2-oxo-5-bromo-4-imidazoline-4-carboxylic Acid Methyl Ester (17)——To a solution of **3** (10.8 g, 27 mmol) in dioxane (200 ml) was added bromine (9.135 g in 100 ml of dioxane) at room temperature. After a while triethylamine (40 ml) was added to the mixture and evaporated to dryness. The residue was taken in EtOAc and washed with 0.1 N HCl and dried over Na_2SO_4. The solvent was evaporated and the residue was dissolved in $CHCl_3$ which was applied to a column of silica gel (200 g, packed with $CHCl_3$). The eluate with 2% EtOH in $CHCl_3$ gave 10.92 g (85%) of **17** as a foam after evaporation of the solvent. *Anal.* Calcd. for $C_{16}H_{19}BrN_2O_{10}$: C, 40.10; H, 4.00; Br, 16.68; N, 5.85. Found: C, 40.56; H, 4.10; Br, 16.20 N, 5.88. UV λ_{max}^{MeOH}: 278.5 nm. MS *m/e*: 480, 478 (M), 222, 220 (B+1). NMR (60 MHz, $CDCl_3$), δ: 2.02 (s, 3, Ac), 2.09 (s, 6, Ac), 3.86 (s, 3, CO_2CH_3), 4.0—4.5 (bs, 3, 4′,5′-H), 5.5—5.8 (m, 2, 2′,3′-H), 6.11 (d, 1, 1′-H, J=6.0 Hz), 11.02 (bs, 1, NH).

1-(β-D-Ribofuranosyl)-2-oxo-5-bromo-4-imidazoline-4-carboxylic Acid Methyl Ester (18)——Compound **17** (4.95 g) was dissolved in MeOH containing NaOMe (837 mg) and kept for 1 hr at room temperature. The mixture was neutralized with Amberlite IR-120 (H^+) resin and the filtrate was concentrated to give 2.35 g (67%) of **18** as a powder. A part of the sample was purified by the preparative TLC (silica gel, developed with $CHCl_3$–MeOH, 7: 1) and crystallized from MeOH, mp 168—172°. *Anal.* Calcd. for $C_{10}H_{13}BrN_2O_7$: C, 34.01; H, 3.68; Br, 22.63; N, 7.93. Found: C, 33.84; H, 3.75; Br, 22.46; N, 7.73. UV λ_{max}^{MeOH}: 277 nm (ε, 10500). MS *m/e*: 354, 352 (M), 222, 220 (B+1), 190, 188 (B–MeOH). NMR (60 MHz, DMSO-d_6), δ: 3.40—3.70 (m, 2, 5′-H), 3.77 (s, 3, CO_2CH_3), 3.85—4.40 (m, 2, 3′,4′-H), 4.84 (t, 1, 2′-H), 5.45 (d, 1, 1′-H, J=6.0 Hz), 11.34 (bs, 1, NH).

1-(β-D-Ribofuranosyl)-2-oxo-3-methyl-5-bromo-4-imidazoline-4-carboxylic Acid Methyl Ester (19)——Compound **18** in MeOH was added diazomethane in ether. Evaporation of the solvent gave crystals which were recrystallized from MeOH–ether to furnish pure **19**, mp 165—166°. *Anal.* Calcd. for $C_{11}H_{15}BrN_2O_7$: C, 35.98; H, 4.12; Br, 21.77; N, 7.63. Found: C, 35.83; H, 4.26; Br, 21.71; N, 7.49. MS *m/e*: 368, 366 (M), 236, 234 (B+1). UV λ_{max}^{MeOH}: 280 nm (ε, 10500). NMR (60 MHz, DMSO-d_6), δ: 3.34 (s, 3, NMe), 3.50—3.80 (m, 2, 5′-H), 3.80 (s, 3, CO_2CH_3), 3.90—4.40 (m, 2, 3′,4′-H), 4.89 (t, 1, 2′-H), 5.58 (d, 1, 1′-H).

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