Efficient and β-Stereoselective Synthesis of 4(5)-Methyl-5(4)-(5-amino-5-deoxy-β-D-ribofuranosyl)imidazole and Related Compounds Exhibiting Antiulcer Activity

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The reaction of 2,3,5-tri-*O*-benzyl-D-ribose with the lithium salt of an imidazole derivative gave an adduct 17*RS*. Treatment of 17*RS* with 1.5 N HCl in refluxing tetrahydrofuran gave the β-4(5)-ribofuranosylimidazole 19 (35%) and the ribosylimidazole 18 (51%). The latter was converted into β-19 in 86% yield by the Mitsunobu cyclization. This synthetic method produced only the desired β-anomer. Protection of the imidazole nitrogen of 19 with an ethoxycarbonyl group followed by debenzylation gave 21, which was successively derived to the 5′-amino derivative 1 *via* the 5′-substituted phthalimide 23, followed by hydrazine degradation in excellent yield. Compound 1 was then converted into the 5′-cyanoguanidine 2 in 79% yield. The 5′-amino derivatives 3—9 lacking a methyl group were efficiently synthesized. Among them, the cyanoguanidine 5 and phenylthiourea 8 exhibited antiulcer activities with half the efficacy of cimetidine. The molecular conformation of 5 was determined by X-ray structure analysis.

Key words imidazole C-nucleoside; Mitsunobu reaction; antiulcer activity; X-ray analysis

Histamine H_2-receptor antagonists, following the therapeutic success of cimetidine,[1] are now widely used for treatment of peptic ulcers and associated gastrointestinal disorders. For antiulcer activity, it is advantageous for the compound to have a folded conformation,[2] as shown in Fig. 1. Mitchell[2a] and Gilman[2b] *et al.* proposed that hydrogen-bonding between the imidazole nitrogen atom and the N–H group of the side chain was an important factor. An X-ray analysis[2c] of cimetidine also indicated that an N···NH bond exists between the imidazole and guanidine residue, forming a stable ten-membered ring system. Ishida and coworkers[3] also showed that 4-(2-aminophenyl)-1*H*-imidazole, which forms an intramolecular hydrogen bond, exhibited antiulcer activity with half the efficacy of cimetidine.

We recently reported[4] an efficient and stereoselective synthesis of 4(5)-(β-D-ribofuranosyl)imidazole (**10**), as well as 4(5)-(2-deoxyribofuranosyl)imidazoles (**11**) and their ethoxycarbonyl derivatives **12** and **13**, *via* the Mitsunobu cyclization[5] as the key step (Fig. 3). Since most biologically active nucleosides possess β-stereochemistry at C-1 of the sugar moiety, β-stereoselective glycosylation is important in nucleoside synthesis.[6] We used the hydrogen-bonding potential of imidazoles in the previous approach[4] to achieve β-stereoselective glycosylation. With these results in hand, we became interested in the synthesis of a novel 4(5)-methyl-5(4)-(5-amino-5-deoxy-β-D-ribofuranosyl)-imidazole (**1**) as a versatile precursor to 5′-amino derivatives. We envisioned that compound **1** and its derivatives could adopt folded conformations through intramolecular hydrogen bondings, with distances approximately equal to that (*ca.* 3 Å) of cimetidine as judged from a molecular-model examination, as shown in Fig. 2. Therefore, we expected that the 5′-aminoimidazole C-nucleoside **1**, and its cyanoguanidine derivative **2** containing cimetidine-like structure would show antiulcer activity. We report herein an efficient and β-stereoselective synthesis of **1** and **2**. Further, in connection with this study, 5′-amino derivative C-nucleosides **3**—**9** lacking the methyl group in the imidazole moiety were synthesized from ethyl 4-(β-D-ribofuranosyl)-imidazole-1-carboxylate (**12**)[4b] and ethyl 4-(2-deoxy-β-D-ribofuranosyl)imidazole-1-carboxylate (**13**).[4b]

Synthesis of 4(5)-Methyl-5(4)-(5-amino-5-deoxy-β-D-ribofuranosyl)imidazole and Related Compounds The bromide **15** was easily prepared by the reaction of 2-(*tert*-butyldimethylsilyl)-5-methyl-*N*,*N*-dimethylimidazole-1-sulfonamide (**14**)[7] with *N*-bromosuccinimide (NBS).[8] Imidazole anions are generated relatively readily on C-2 and C-5 by direct metalation and metal-halogen exchange, but generation of the thermodynamically less stable C-4 anion is much more difficult.[9] Therefore, halogen-metal exchange of the bromide **15** was first examined by trapping of a protected 2,3,5-tri-*O*-benzyl-D-ribose (**16**)[10] under various conditions. The best yield (72%) of the adduct **17*RS***, which was a 2:3 epimeric mixture, was obtained under the conditions given in Chart 1. Although deprotection of the corresponding adduct lacking the methyl group proceeded smoothly,[4] that of **17*RS*** under reflux in HCl–tetrahydrofuran (THF) afforded the desired β-anomer **19** directly in 35% yield, together with the open-chain diol **18**[11] (51%), which was a 1:10 mixture of **18*R*** and **18*S***. The process of acidic

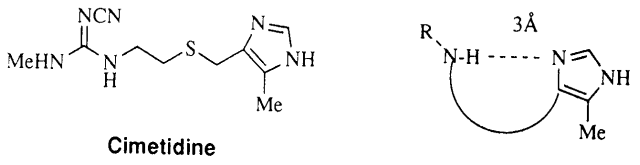

Fig. 1

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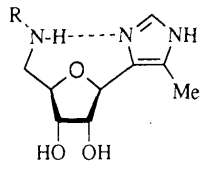
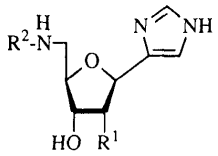
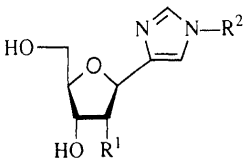


1: R = H
2: R = -C(=NCN)-NHMe



3 : R^1 = OH R^2 = H
4 : R^1 = R^2 = H
5 : R^1 = OH, R^2 = —C(=NCN)—NHMe
6 : R^1 = H, R^2 = —C(=NCN)—NHMe
7 : R^1 = OH, R^2 = —C(=S)—NHMe
8 : R^1 = OH, R^2 = —C(=S)—NHPh
9 : R^1 = OH, R^2 = —C(=O)—NHPh

Fig. 2



10 : R^1 = OH, R^2 = H
11 : R^1 = R^2 = H
12 : R^1 = OH, R^2 = CO_2Et
13 : R^1 = H, R^2 = CO_2Et

Fig. 3

cyclization is dealt with in detail in the next section. Mitsunobu cyclization of **18** using *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD)–Bu_3P[12] also afforded the *β*-anomer **19** in 86% yield. We recently demonstrated[4] that the Mitsunobu cyclization of a mixture of *R*- and *S*-diols corresponding to the demethyl derivatives of **18** produced exclusively the *β*-anomer. Therefore, the *β*-stereochemistry of **19** could be assigned at this stage. Treatment of **19** thus obtained with ethyl chloroformate, followed by separation by column chromatography afforded two regioisomers of the ethoxycarbonyl group; ethyl 5-methyl-4-(2,3,5-tri-*O*-benzyl-*β*-D-ribofuranosyl)-imidazole-1-carboxylate (*β*-**20a**) in 95% yield and a small amount of *β*-**20b** (5%). The correlation of *β*-**20a** and *β*-**20b** was proved by their conversion into 4(5)-methyl-5(4)-(*β*-D-ribofuranosyl)imidazole (**22**) *via* debenzylation followed by removal of the ethoxycarbonyl group. The C-1′-proton signals of **20a** and **20b** resonated at 4.96 ppm and 5.40 ppm, respectively. The signal of the methyl protons of **20a** (δ 2.42 ppm) appeared at lower field than that observed for **20b** (δ 2.20 ppm). These results presumably reflect the shielding effects of the ethoxycarbonyl group.

On the other hand, when **18** was treated with methanesulfonyl chloride (MsCl) in pyridine,[13] *β*-**20a** and *α*-**20**[14] were obtained in 41% and 26% yields, respectively. The low stereoselectivity of this glycosylation may be due to the generation of an isoimidazole intermediate.[4] The C-1′ configurations of the two compounds were assigned as follows. Firstly, according to Hudson's rule,[15] the optical rotation values of *α*-anomers are more positive than those of *β*-anomers. Further, in accord with the previous statements[16] and our experience,[4] *β*-anomers are less polar in TLC than the corresponding *α*-anomers. Further, based on ^{1}H-NMR,[17] the C-1′ protons of the *β*-anomers of imidazole C-nucleosides resonate at higher field than those of *α*-anomers.[4b] The same correlations were observed for *β*-**20a** and *α*-**20**, as summarized in Table 1. The correctness of the assignment was indicated by the observation of a 3% nuclear Overhauser effect (NOE) between the C-1′ and C-4′ protons in the imidazole C-nucleoside **21** obtained by debenzylation of **20a** with $Pd(OH)_2$–cyclohexene. Importantly, the glycosylations under the acidic and the Mitsunobu conditions produced only the desired *β*-imidazole C-nucleosides without *α*-anomer contamination.

We next tried a selective synthesis of the 5′-substituted phthalimide **23** using the Mitsunobu reaction (Chart 2). Reaction of **21** with 1 molar eq each of diethyl azodicarboxylate (DEAD), Ph_3P, and phthalimide in THF did not proceed. However, the use of excess[18] DEAD (3.5 eq), Ph_3P (3.5 eq), and phthalimide (1.1 eq) afforded the desired **23** in quantitative yield. Double deprotection of **23** with hydrazine hydrate afforded the 5′-amino derivative **1** in 43% overall yield from the starting protected D-ribose **16**. An NOE experiment on **1** indicated a 7% NOE between the 1′-H and 4(5)-Me. The methyl group directed outside the molecule can serve for hydrogen bonding. The amine **1** was easily converted into the cyanoguanidine **2** by treatment with dimethyl *N*-cyanodithioiminocarbonate followed by methylamine in 79% yield.

We further directed our attention to synthesizing the C-nucleosides **3**—**9** lacking the methyl group, starting from imidazole C-nucleosides **12**[4] and **13**[4] (Chart 3). Conversion of **12** into the phthalimide **24**, followed by deprotection with hydrazine hydrate afforded the 5′-amino compound **3** (86%), which was subsequently transformed into the 5′-cyanoguanidine **5**. Treatment of **3** with phenyl or methyl isothiocyanate or phenyl isocyanate afforded the 5′-thioureas **7**, **8**, or the 5′-urea **9**, which could serve as bioisosters of cyanoguanidines.[19] In the case of the 2′-deoxy compound **13**, use of 1.1 eq each of phthalimide,

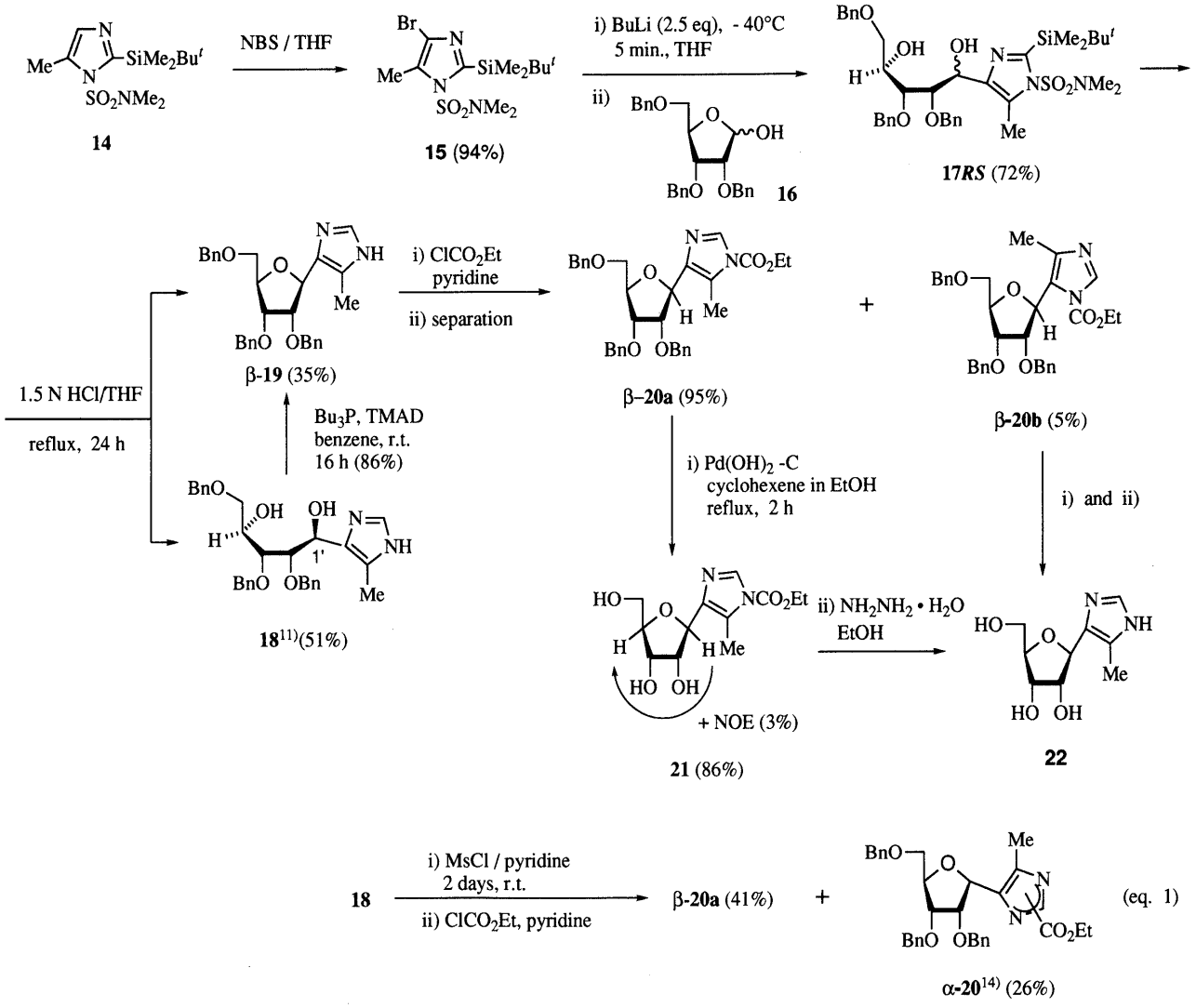


Chart 1

Table 1. $[\alpha]_D$, TLC, and ^{1}H-NMR Data for **β-20a** and **α-20**

	β-20a	**α-20**
$[\alpha]_D$[a]	−12.60° (c=6.27)	+73.76° (c=0.87)
Rf values[b]	0.56	0.32
^{1}H-NMR (C-1′)[c] δ, $J_{1',2'}$ (Hz)	4.96 (6.6)	5.18 (2.6)

a) Measured in $CHCl_3$. *b*) Measured in EtOAc–*n*-hexane (1 : 1). *c*) $CDCl_3$–TMS.

DEAD, and Ph_3P gave **25** (95%), which similarly afforded the amine **4** and cyanoguanidine **6**.

Cyclization of the Adduct 17 under Acidic Condition Few cyclizations of ribosylheterocycles under acidic conditions are known.[6b,13] We thus examined the stereoselective formation of the β-anomer **19** from the 2 : 3 epimeric mixture of **17*RS*** under acidic conditions (Chart 4). Although chromatographic separation of each epimer was difficult, desilylation of **17*RS*** with Bu_4NF, followed by SiO_2 column chromatography gave the less polar **26*R*** (37%) and polar **26*S*** (59%) without difficulty. The C-1′ configurations of **26*R*** and **26*S*** were assigned by analogy with our previous results[4]; the *R* isomers are less polar in TLC than the *S* isomers. Yokoyama *et al.* reported that reaction of a 1′*R*/*S*-mixture of 2-ribosylthiophenes or furans with MsCl–pyridine gave an α/β-mixture of ribofuranosyl heterocycles in ratios that coincided with those of the two epimers.[13] The reaction was therefore applied to the ribosylimidazoles (**26*R*, 26*S***) to assign the respective C-1′ configurations (Chart 4). Compounds **26*R*** and **26*S*** preferentially provided β-**27** and α-**27**, respectively, though the reaction did not proceed cleanly. Refluxing of **26*R*** in 1.5 N HCl for 22 h produced the β-anomer **19** and the unsubstituted diol **18*R*** in 60% and 21% yields, respectively. On the other hand, the same treatment of **26*S*** gave only the diol **18*S*** (80%), which could be converted into the β-anomer **19** by Mitsunobu cyclization in 88% yield. Accordingly, it is apparent that the β-anomer **19** was obtained from the *R*-isomer **17*R*** under acidic conditions, but not from the *S*-isomer **17*S***.

This fact may be explained as illustrated in Chart 5. Acidic cyclization of the deprotected diol **18*R*** proceeds smoothly to give the β-anomer **19** *via* an *SN2* process, but that of **18*S*** would not be favorable because of the steric hindrance between the methylimidazole and 4′-hydroxy group.

Chronotropic Response on Guinea Pig Atrium The nine synthesized compounds **1**—**9** were tested for *in vitro*

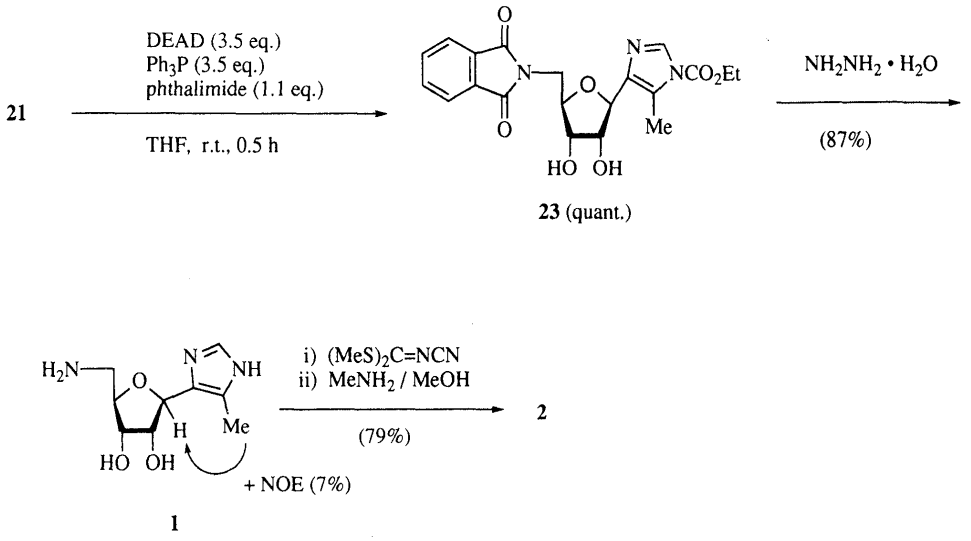


Chart 2

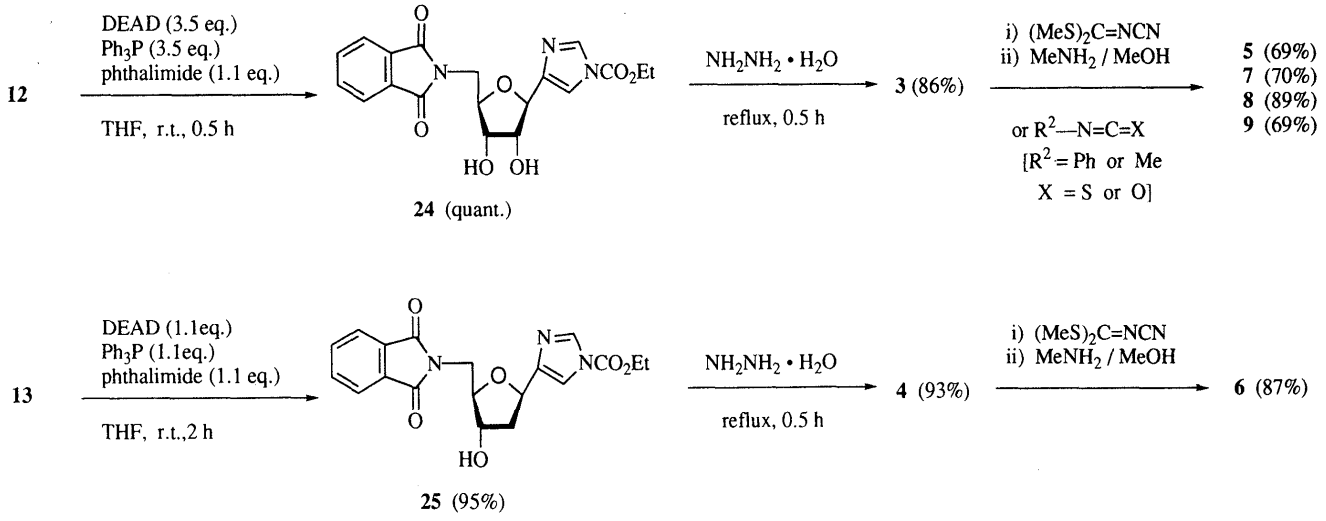


Chart 3

H_2-receptor antagonist activities using chronotropic response on guinea pig atrium, but the expected H_2-activities were not observed. Since H_2-receptor mediates the stimulation of the spontaneous beating rate of the guinea pig atrium, this result shows that none of compounds **1**—**9** interacts with the H_2-receptor.

Antiulcer Activity The effects of compounds **1**—**9** were examined on rat gastric ulcers produced by restraint and water-immersion stress. Among them, the cyanoguanidine **5** and phenylthiourea **8** exhibited antiulcer activities about half that of cimetidine, as summarized in Table 2. This means that the antiulcer activity of **5** and **8** does not arise through H_2-receptor antagonist activity, but through another mechanism.

X-Ray Structure Analysis of 5 Attempts to prepare single crystals of the 5′-amino compounds **1**, **3**, and **4**, which could have intramolecular hydrogen bonding, failed. Fortunately, the cyanoguanidine **5**, exhibiting antiulcer activity, was successfully crystallized by the vapor-diffusion method. Thus, it was analyzed by X-ray crystallography to determine the stereochemical conformation. The result is illustrated in Fig. 4, which was drawn with the graphics program ORTEP II.[20] The molecular structure of **5** is shown as a stereoscopic presentation in which the atomic numbering scheme is also given. Regarding the existence of an intramolecular hydrogen bond, the distance of N(6)···N(3) was 4.06 Å and the angle N(6)-H···N(3) was 89.8°. The criteria for a hydrogen bond are that the angle N(6)-H···N(3) should be greater than 90°, and the distance N(6)···N(3) should not exceed 3.3 Å for a short hydrogen bond or 4.0 Å for a long one.[21] Accordingly, this bond almost meets the criteria for long hydrogen bond. In addition, this study indicated a C2′-exo envelope conformation for the sugar moiety and an *E*-geometry for the cyanoguanidine moiety, as shown in Fig. 4.

In conclusion, an efficient and β-stereoselective synthesis of 4(5)-methyl-5(4)-(5-amino-5-deoxy-β-D-ribofuranosyl)-imidazole **1** and its 5′-cyanoguanidine **2** was achieved using the acidic and the Mitsunobu conditions as key steps. In the examination of the acidic cyclization, it was clarified that β-anomer **19** was produced only from the *R*-isomer of the adduct **17*RS***. As an extension of this study, the imidazole C-nucleosides **3**—**9** lacking the methyl group

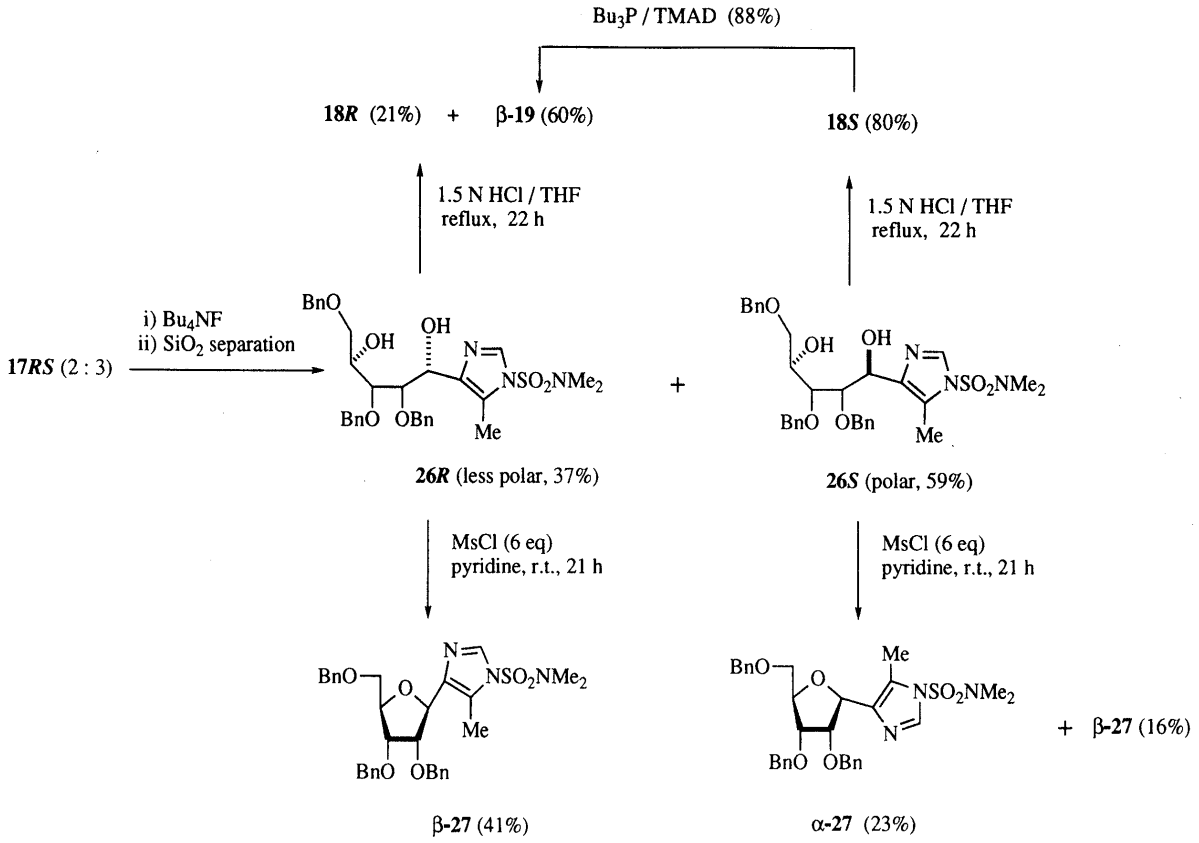


Chart 4

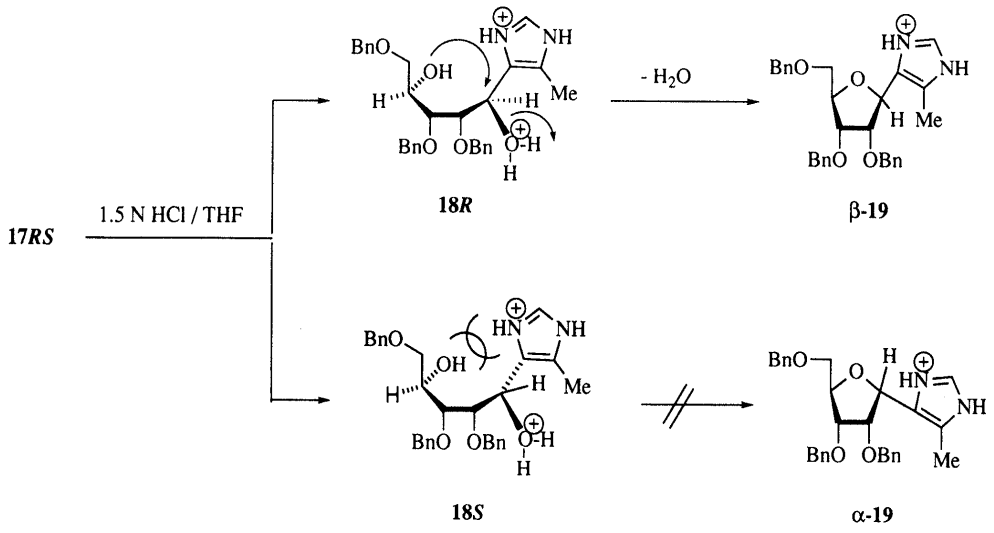


Chart 5

Table 2. *In Vivo* Anti-ulcer Activities of Compounds **5**, **8** and Cimetidine on Water Immersion Stress-Induced Ulceration in Rats

Drug	Dose (mg/kg)	*n*	Total length of ulcer (mm)	Inhibition (%)
Control	—	9	8.81±2.47	—
5	50	6	5.47±1.65	38.0
Cimetidine	50	6	2.30±1.95*	83.9
Control	—	9	16.39±2.54	—
8	50	6	10.38±0.87	36.6

n is number of data. The values represent the mean±S.E. *, $p<0.05$.

were successfully synthesized. The nine synthesized nucleosides unexpectedly showed no significant *in vitro* H_2-receptor antagonist activity. However, the cyanoguanidine **5** and phenylthiourea **8** exhibited antiulcer activities about half that of cimetidine. An X-ray structure analysis of **5** revealed its stereochemical conformation.

Experimental

The melting points were determined on a Yanagimoto micromelting points apparatus and are uncorrected. Optical rotations measurements were recorded at 20 °C with a JASCO DIP-181 digital polarimeter. The ORD spectra were recorded with a JASCO ORD/UV-5 spectrometer. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer.

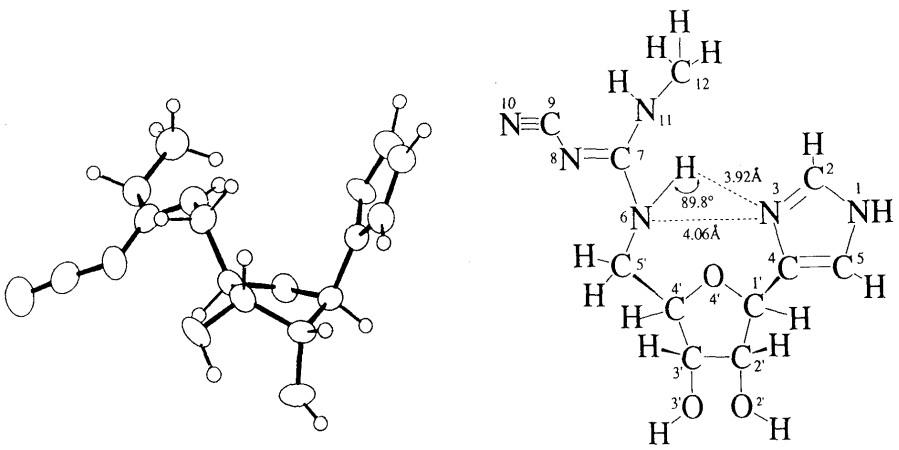


Fig. 4. Stereo Presentation of the Molecular Structure of **5** and the Numbering System

In the right figure, the distances and angle of the putative hydrogen bond are present. The hydrogen bond is shown by dotted lines.

Table 3. Crystal Data for Compound **5**

Molecular formula	$C_{11}H_{16}N_6O_3$
Molecular weight	280.287
Crystal color, external form	Colorless, platelet
Crystal dimensions (mm)	$0.3 \times 0.5 \times 0.1$
Crystal system	Monoclinic
Space group	$P2_1$
Cell dimensions a (Å)	6.5911 (8)
b (Å)	13.961 (2)
c (Å)	7.0471 (9)
β (degree)	102.303 (9)
V (Å^3)	633.5 (1)
Z value	2
D_x (g/cm^3)	1.4692

^{1}H- and ^{13}C-NMR spectra were taken with tetramethylsilane as an internal standard on a Varian Gemini-200 spectrometer in $CDCl_3$ unless otherwise noted. Low-resolution and high-resolution mass spectra (HR-MS) were determined with Hitachi M-80 and M-4000H instruments. All reactions with air- and moisture-sensitive compounds were carried out under an argon atmosphere. Unless otherwise noted, all extracts were dried over Na_2SO_4, and the solvent was removed in a rotary evaporator under reduced pressure. For column chromatography, FL-60D and Chromatorex NH-DM 1020 (Fuji Silysia Chemical Ltd.) were used. THF was distilled from sodium/benzophenone.

2-(*tert*-Butyldimethylsilyl)-4-bromo-5-methyl-*N*,*N*-dimethylimidazole-1-sulfonamide (15) NBS (408 mg, 2.29 mmol) was added in small portions at room temperature to a solution of **14** (695 mg, 2.29 mmol) in THF (10 ml), and the mixture was stirred for 1 h. The reaction mixture was diluted with EtOAc, and the solution was washed with 10% K_2CO_3. The organic layer was dried, then the solvent was evaporated. The residual oil was purified by column chromatography (EtOAc : *n*-hexane = 1 : 11) to give **15** (820 mg, 94%) as a white solid, which was recrystallized from EtOAc–*n*-hexane to give colorless crystals, mp 108 °C. IR (KBr) cm^{-1}: 1376, 1160 (SO_2). ^{1}H-NMR δ: 0.36 (s, 6H, $SiMe_2$), 1.01 (s, 9H, Si *tert*-Bu), 2.34 (s, 3H, Me), 2.88 (s, 6H, SO_2NMe_2). ^{13}C-NMR δ: −3.3, 11.2, 18.9, 27.7, 38.2, 119.7, 127.4, 154.7. MS (EI) *m/z*: 382 ($M^+ + 1$). *Anal.* Calcd for $C_{12}H_{24}N_3O_2SSiBr$: C, 37.69; H, 6.36; N, 10.99. Found: C, 37.34; H, 6.16; N, 11.06.

2-(*tert*-Butyldimethylsilyl)-5-methyl-4-(2,3,5-tri-*O*-benzyl-D-ribosyl)-*N*,*N*-dimethylimidazole-1-sulfonamide (17*RS*) A solution of 1.6 M BuLi–*n*-hexane (1.6 ml, 2.5 mmol) was added dropwise to a pre-cooled solution of **15** (955 mg, 2.5 mmol) in THF (25 ml) at −40 °C, and the resulting mixture was stirred for 5 min (at this time, the temperature of the reaction mixture spontaneously rose to −30 °C). A solution of **16** (420 mg, 1.0 mmol) in THF (5 ml) was added over 3 min at −30 °C. The dry ice bath was removed, and the reaction mixture was stirred at room temperature for 2 h. Then, the reaction was quenched with MeOH (1 ml), and THF was evaporated off. The residue was dissolved in EtOAc–*n*-hexane (3 : 1), and the solution was washed with H_2O, dried, and evaporated to give a crude oil. This was purified by flash chromatography on silica gel with EtOAc–*n*-hexane (3 : 17 to 1 : 2) to give **17*RS*** (521 mg, 72%) as a pale yellow oil. ^{1}H-NMR indicated the product to be a 2 : 3 mixture of *R*- and *S*-isomers. IR (neat) cm^{-1}: 3420 (OH), 1372, 1170 (SO_2). ^{1}H-NMR δ: 0.37 (d, 6H, Me × 2), 1.00 (s, 9H, Si *tert*-Bu), 2.22 [s, 9/5 H, Me (1′*S*)], 2.30 [s, 6/5H, Me (1′*R*)], 2.74 [s, 18/5H, SO_2NMe_2 (1′*S*)], 2.79 [s, 12/5H, SO_2NMe_2 (1′*R*)], 3.47—3.87 (m, 4H, 3′,5′-H, OH), 3.97 (dd, 1H, J = 7.5, 5.0 Hz, 2′-H), 4.10—4.83 (m, 7H, CH_2Ph, 4′-H), 4.89 [d, 3/5H, J = 7.5 Hz, 1′-H (1′*S*)], 4.98 [br s, 2/5H, 1′-H (1′*R*)], 7.03—7.44 (m, 15H, Ph). MS (SIMS) *m/z*: 724 ($M^+ + 1$). HR-MS (SIMS) *m/z*: 724.3446 (Calcd for $C_{38}H_{54}N_3O_7SSi$: 724.3449).

4(5)-Methyl-4(5)-(2,3,5-tri-*O*-benzyl-D-ribosyl)imidazole (18) and 4(5)-Methyl-4(5)-(2,3,5-tri-*O*-benzyl-D-ribofuranosyl)imidazole (β-19) A solution of **17*RS*** (3.02 g, 4.18 mmol) in THF (40 ml) was refluxed with 1.5 N HCl (50 ml) for 24 h and then cooled. After neutralization with 30% NH_4OH, the mixture was extracted with EtOAc by the salting-out technique. The extract was dried and evaporated to give an oil, which was subjected to chromatography. Elution with EtOAc–*n*-hexane (9 : 1) gave β-**19** (700 mg, 35%) as a pale yellow oil, while elution with MeOH–EtOAc (1 : 19) gave a 1 : 10 mixture (1.067 g, 51%) of **18*R*** and **18*S***[11] as a white amorphous product.

β-**19**: IR (neat) cm^{-1}: 1120, 1084 (C–O). ^{1}H-NMR δ: 2.10 (s, 3H, Me), 3.69 (dd, 1H, J = 10.3, 1.3 Hz, 5′-H_a), 3.86—3.98 (m, 1H, overlapped with 2′-H, 5′-H_b), 3.98 (dd, J = 10.3, 2.4 Hz, overlapped with 5′-H_b, 2′-H), 4.33—4.54 [m, 3H, 1.5 × (CH_2Ph)], 4.58—4.77 [m, 3H, 1.5 × (CH_2Ph)], 5.20 (d, 1H, J = 2.4 Hz, 1′-H), 6.68 (s, 1H, 2-H), 7.17—7.43 (m, 15H, Ph). MS (EI) *m/z*: 484 (M^+). HR-MS *m/z*: 484.2362 (Calcd for $C_{30}H_{32}N_2O_4$: 484.2360).

18*S*: ^{1}H-NMR ($CDCl_3 + D_2O$) δ: 2.08 (s, 3H, Me), 3.59 (dd, 1H, J = 9.8, 5.6 Hz, 5′-H_a), 3.68 (dd, 1H, J = 9.8, 3.1 Hz, 5′-H_b), 3.80 (dd, 1H, J = 7.7, 2.8 Hz, 3′-H), 4.02 (dd, 1H, J = 7.0, 2.8 Hz, 2′-H), 4.17 (m, 1H, 4′-H), 4.33—4.63 (m, 6H, CH_2Ph), 5.00 (d, 1H, J = 7.0 Hz, 1′-H), 7.10—7.46 (m, 16H, 2-H, Ph). {The coexistence of the minor product **18*R*** was indicated in the ^{1}H-NMR spectrum [*e.g.* 4.78 (dd, J = 11.0, 1.5 Hz, CH_2Ph). The full data are shown in the paragraph on the hydrolysis of **26*R***]} MS (SIMS) *m/z*: 503 ($M^+ + 1$). HR-MS (SIMS) *m/z*: 503.2544 (Calcd for $C_{30}H_{35}N_2O_4$: 503.2544).

Conversion of 18 into β-19 Using Mitsunobu Cyclization A stirred solution of **18** (1.054 g, 2.10 mmol) in dry benzene (40 ml) was treated with Bu_3P (0.67 ml, 2.52 mmol) at room temperature. Then, TMAD (0.43 g, 2.52 mmol) was added rapidly and the resulting mixture was stirred for 16 h at room temperature. The insoluble material was removed by filtration, and the filtrate was concentrated to give a residue, which was purified by flash chromatography with EtOAc–*n*-hexane (13 : 2) to give β-**19** (870 mg, 86%).

Ethyl 5-Methyl-4-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)imidazole-1-carboxylate (β-20a) and Ethyl 4-Methyl-5-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)imidazole-1-carboxylate (β-20b) Ethyl chloroformate (0.33 ml, 3.43 mmol) was added in one portion to a solution of β-**19** (1.51 g, 3.12 mmol) containing pyridine (0.25 ml, 3.12 mmol) and 4-dimethylaminopyridine (38 mg, 0.31 mmol) in benzene (35 ml) and the mixture was refluxed for 50 min. After addition of H_2O (1 ml) followed

by evaporation of the benzene, the resulting residue was extracted with EtOAc. The extract was washed with H_2O and brine, dried, and then evaporated. The residual oil was purified by flash chromatography using EtOAc–*n*-hexane (1 : 3 to 1 : 1) to give **β-20a** (1.65 g, 95%) and **β-20b** (86 mg, 5%) in that order.

β-20a (less polar): Colorless oil. $[\alpha]_D$: −12.6° (c=6.27, $CHCl_3$). IR (neat) cm^{-1}: 1758 (N–CO–O). ^{1}H-NMR δ: 1.44 (t, 3H, J=7.0 Hz, $COOCH_2C\underline{H}_3$), 2.42 (s, 3H, Me), 3.59 (d, 2H, J=5.4 Hz, 5′-H), 4.07 (dd, J=5.4, 4.1 Hz, 3′-H), 4.29 (dd, J=9.9, 5.4 Hz, 4′-H), 4.36—4.71 (m, 8H, 2′-H, CH_2Ph, $COC\underline{H}_2CH_3$), 4.96 (d, 1H, J=6.6 Hz, 1′-H), 7.18—7.40 (m, 15H, Ph), 8.03 (s, 1H, 2-H). ^{13}C-NMR δ: 11.2, 14.7, 64.6, 71.2, 72.5, 73.0, 73.9, 75.9, 78.6, 80.9, 82.2, 120.8—128.8, 137.4, 137.6, 138.6, 138.7, 149.8. MS (EI) m/z: 556 (M^+). HR-MS m/z: 556.2570 (Calcd for $C_{33}H_{36}N_2O_6$: 556.2571).

β-20b (more polar): Colorless oil. $[\alpha]_D$: +5.5° (c=4.75, $CHCl_3$). IR (neat) cm^{-1}: 1760 (N–CO–O). ^{1}H-NMR δ: 1.35 (t, 3H, J=7.0 Hz, $COOCH_2C\underline{H}_3$), 2.22 (s, 3H, Me), 3.58 (dd, 1H, J=10.7, 5.4 Hz, 5′-H_a), 3.66 (dd, 1H, J=10.7, 4.5 Hz, 5′-H_b), 4.04 (dd, 1H, J=6.6, 6.0 Hz), 4.16—4.43 (m, 5H), 4.43—4.75 (m, 5H), 5.40 (d, 1H, J=7.2 Hz, 1′-H), 7.10—7.46 (m, 15H, Ph), 8.03 (s, 1H, 2-H). MS (EI) m/z: 556 (M^+). HR-MS m/z: 556.2560 (Calcd for $C_{33}H_{36}N_2O_6$: 556.2571).

Ethyl 5-Methyl-4-(β-D-ribofuranosyl)imidazole-1-carboxylate (21) A mixture of **β-20a** (1.05 g, 1.89 mmol), 20% $Pd(OH)_2$–C (526 mg), and cyclohexene (15.3 ml, 151 mmol) in EtOH (50 ml) was refluxed for 3.5 h. After removal of the catalyst by filtration through Celite, the filtrate was evaporated to give a residue, which was purified by column chromatography [MeOH–EtOAc (1 : 10)] to give **21** (414 mg, 86%) as a white amorphous product. IR (neat) cm^{-1}: 3700—2300 (OH), 1762 (N–CO–O). ^{1}H-NMR (CD_3OD) δ: 1.43 (t, 3H, J=7.4 Hz, $COOCH_2C\underline{H}_3$), 2.45 (s, 3H, Me), 3.63 (dd, J=12.1, 3.9 Hz, 5′-Ha), 3.79 (dd, 1H, J=12.1, 3.2 Hz, 5′-H_b), 3.95 (dt, 1H, J=3.9, 3.2 Hz, 4′-H), 4.16 (m, 2H, 2′, 3′-H), 4.48 (q, 2H, J=7.4 Hz, $COOC\underline{H}_2CH_3$), 4.74 (dt, 1H, J=7.4, 3.7 Hz, 1′-H), 8.23 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ: 10.9, 14.6, 64.1, 65.9, 73.1, 76.8, 77.8, 87.5, 128.9, 138.3, 139.0, 150.7. MS (SIMS) m/z: 287 (M^+ + 1). HR-MS (SIMS) m/z: 287.1248 (Calcd for $C_{12}H_{19}N_2O_6$: 287.1242).

4(5)-Methyl-4(5)-(β-D-ribofuranosyl)imidazole (22) A mixture of **21** (81 mg, 0.28 mmol) and hydrazine hydrate (14 μl, 0.28 mmol) in EtOH (5 ml) was refluxed for 1 h. The solvent was evaporated to give a residue, which was purified by column chromatography [Chromatorex NH-DM 1020, MeOH–EtOAc (3 : 7)] to give **22** (55 mg, 92%) as a white amorphous product. ORD (c=2.50, MeOH) [α] (nm): −40.0° (589), −80.0° (435), −132.0° (365), −312.0° (290). ^{1}H-NMR (CD_3OD) δ: 2.25 (s, 3H, Me), 3.67 (dd, 1H, J=11.8, 3.9 Hz, 5′-H_a), 3.80 (dd, 1H, J=11.8, 3.3 Hz, 5′-H_b), 3.93 (dd, 1H, J=6.6, 3.3 Hz, 4′-H), 4.05—4.20 (m, 2H, 2′, 3′-H), 4.75 (d, 1H, J=6.8 Hz, 1′-H), 7.57 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ: 10.2, 64.0, 73.0, 77.1, 78.0, 87.1, 129.4, 132.1, 135.5. MS (EI) m/z: 214 (M^+). HR-MS m/z: 214.0955 (Calcd for $C_9H_{14}N_2O_4$: 214.0953).

Conversion of 18 into β-20a and α-20 Using MsCl–Pyridine A solution of the diol **18** (262 mg, 0.50 mmol) and $MeSO_2Cl$ (0.23 ml, 3.0 mmol) in pyridine (4 ml) was stirred for 2 d at room temperature. After addition of cold H_2O (1 ml), the mixture was extracted with a mixture of EtOAc–*n*-hexane (4 : 1), and the extract was washed with brine, dried, and evaporated. The residue was purified by column chromatography using EtOAc for elution to give a yellow oil, which was dissolved in benzene (10 ml) containing pyridine (0.02 ml, 0.25 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol). To this solution was added ethyl chloroformate (0.023 ml, 0.25 mmol), and the whole was subsequently refluxed for 30 min. After addition of H_2O followed by evaporation of benzene, the resulting residue was extracted with EtOAc–*n*-hexane (7 : 3). The extract was washed with H_2O and brine, dried, and evaporated to give a crude oil, which was purified by column chromatography using EtOAc–*n*-hexane (3 : 7) to give **β-20a** (48 mg, 41%), which was identical with an authentic sample prepared from **β-19**, from the first fraction and **α-20** (31 mg, 26%) as an oil from the second fraction. $[\alpha]_D$: +73.8° (c=0.88, $CHCl_3$). IR (neat) cm^{-1}: 1760 (N–CO–O). ^{1}H-NMR δ: 1.43 (t, 3H, J=7.5 Hz, $COOCH_2C\underline{H}_3$), 2.45 (s, 3H, Me), 3.62 (dd, 1H, J=10.9, 3.8 Hz, 5′-H_a), 3.78 (dd, 1H, J=10.9, 2.3 Hz, 5′-H_b), 4.17 (ddd, 1H, J=6.2, 3.9, 2.6 Hz, 2′-H), 4.22 (s, 1H, 3′-H), 4.26 (s, 2H, CH_2Ph), 4.32—4.66 (m, 7H, 4′-H, $COOC\underline{H}_2CH_3$, CH_2Ph), 5.18 (d, 1H, J=2.6 Hz, 1′-H), 7.08—7.40 (m, 15H, Ph), 8.04 (s, 1H, 2-H). MS m/z: 556 (M^+). HR-MS m/z: 556.2555 (Calcd for $C_{30}H_{36}N_2O_6$: 556.2571).

Ethyl 5-Methyl-4-(5-deoxy-5-phthaloylamino-β-D-ribofuranosyl)imidazole-1-carboxylate (23) Phthalimide (54 mg, 0.37 mmol) and Ph_3P (312 mg, 1.19 mmol) were dissolved in a solution of **21** (98 mg, 0.34 mmol) in THF (8 ml). To this mixture, DEAD (0.2 ml, 1.19 mmol) was added slowly with stirring. The reaction mixture was stirred at room temperature for 30 min, then the reaction was quenched with two drops of H_2O, and the whole was evaporated to give a residue, which was subsequently extracted with EtOAc. The extract was dried, and evaporated to give a crude oil, which was purified by flash chromatography with EtOAc–*n*-hexane (3 : 2) to give **23** (143 mg, quant.) as a white amorphous product. IR (film) cm^{-1}: 3400 (OH), 1752 (N–CO–O), 1706 (CO–N–CO). ^{1}H-NMR δ: 1.40 (t, 3H, J=7.0 Hz, $COOCH_2C\underline{H}_3$), 2.40 (s, 3H, Me), 3.57 (br s, 2H, OH), 3.98 (d, 2H, J=5.0 Hz, 5′-H), 4.17 (q, 1H, J=5.0 Hz), 4.40 (m, 4H), 4.79 (d, 1H, J=4.0 Hz, 1′-H), 7.66—7.74 (m, 2H, phthalimide), 7.77 (s, 1H, 2-H), 7.78—7.84 (m, 2H, phthalimide). MS (SIMS) m/z: 416 (M^+ + 1).

4(5)-Methyl-4(5)-(5-amino-5-deoxy-β-D-ribofuranosyl)imidazole (1) A solution of **23** (495 mg, 1.19 mmol) and $NH_2NH_2 \cdot H_2O$ (0.15 ml, 3.00 mmol) in EtOH (50 ml) was refluxed for 100 min, and Chromatorex NH-DM 1020 (4 g) was then added to the hot solution. The solvent was evaporated to give a coated silica gel, which was subsequently placed in a column (Chromatorex NH-DM 1020). Chromatography using MeOH–EtOAc (1 : 15 to 1 : 1) as the eluent gave **1** (219 mg, 87%) as a white amorphous product. $[\alpha]_D$: −27.5° (c=1.40, MeOH). IR (Nujol) cm^{-1}: 3700—2200 (OH, NH), 1600 (NH). ^{1}H-NMR (CD_3OD) δ: 2.25 (s, 3H, Me), 2.82 (dd, 1H, J=13.4, 6.4 Hz, 5′-H_a), 2.93 (dd, 1H, J=13.4, 4.4 Hz, 5′-H_b), 3.85 (m, 1H, 4′-H), 4.00 (dd, 1H, J=6.2, 4.9 Hz, 3′-H), 4.16 (dd, 1H, J= 6.8, 6.2 Hz, 2′-H), 4.75 (d, 1H, J=6.8 Hz, 1′-H), 7.55 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ: 10.3, 45.2, 73.8, 76.5, 78.7, 86.3, 129.7, 131.8, 135.7. MS (SIMS) m/z: 214 (M^+ + 1). HR-MS (SIMS) m/z: 214.1186 (Calcd for $C_9H_{16}N_3O_3$: 214.1191).

1-Cyano-2-methyl-3-{5-deoxy-1-[4(5)-methyl-1*H*-imidazol-4(5)-yl]-β-D-ribofuranos-5-yl}guanidine (2) A solution of **1** (68 mg, 0.32 mmol) and dimethyl *N*-cyanodithioiminocarbonate (57 mg, 0.35 mmol) in MeOH (8 ml) was stirred for 4 h at room temperature. After evaporation of the solvent, the residue was dissolved in 40% $MeNH_2$ in MeOH (8 ml) and the resulting mixture was stirred for 13 h at room temperature. The solvent was evaporated to give a residual oil, which was chromatographed [Chromatorex NH-DM 1020, MeOH–EtOAc (1 : 4)] to give **2** (74 mg, 79%) as a white amorphous product. $[\alpha]_D$: +2.6° (c=1.27, MeOH). IR (KBr) cm^{-1}: 3300 (OH), 2160 (CN), 1584 (C=N). ^{1}H-NMR (CD_3OD) δ: 2.26 (s, 3H, Im-CH_3), 2.76 (s, 3H, NHMe), 3.45 (dd, 1H, J=13.8, 6.2 Hz, 5′-H_a), 3.54 (dd, 1H, J=13.8, 6.2 Hz, 5′-H_b), 4.00 (m, 1H, 4′-H), 4.08 (dd, 1H, J=5.5, 4.3 Hz, 3′-H), 4.18 (dd, 1H, J=6.2, 5.5 Hz, 2′-H), 4.79 (d, 1H, J=6.2 Hz, 1′-H), 7.60 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ: 9.9, 29.0, 45.7, 74.0, 76.6, 78.9, 84.2, 120.3, 128.4, 133.0, 135.8, 162.7. MS (SIMS) m/z: 295 (M^+ + 1). HR-MS (SIMS) m/z: 295.1526 (Calcd for $C_{12}H_{19}N_6O_3$: 295.1517).

Ethyl 4-(5-Deoxy-5-phthaloylamino-β-D-ribofuranosyl)imidazole-1-carboxylate (24) Phthalimide (24 mg, 0.16 mmol) and Ph_3P (136 mg, 0.52 mmol) were dissolved in a solution of **12** (40 mg, 0.15 mmol) in THF (5 ml). Then, DEAD (80 μl, 0.52 mmol) was added and the resulting mixture was stirred for 2.5 h at room temperature to give **24** (59 mg, quant.) by the same procedure as used for the preparation of **23**: mp 146—149 °C (EtOH). IR (KBr) cm^{-1}: 3450 (OH), 1765 (N–CO–O), 1720 (CO–N–CO). ^{1}H-NMR δ: 1.43 (t, 3H, J=7.0 Hz, $COOCH_2C\underline{H}_3$), 3.99 (s, 1H, 5′-H_a), 4.01 (s, 1H, 5′-H_b), 4.10—4.29 (m, 3H, 2′, 3′, 4′-H), 4.46 (q, 2H, J=7.0 Hz, $COOC\underline{H}_2CH_3$), 4.85 (d, 1H, J=3.3 Hz, 1′-H), 7.44 (s, 1H, 5-H), 7.68—7.86 (m, 4H, phthalimide), 7.98 (s, 1H, 2-H). *Anal.* Calcd for $C_{19}H_{19}N_3O_7$: C, 56.85; H, 4.77; N, 10.47. Found: C, 56.68; H, 4.78; N, 10.52.

4(5)-(5-Amino-5-deoxy-β-D-ribofuranosyl)imidazole (3) A solution of **24** (709 mg, 1.77 mmol) and $NH_2NH_2 \cdot H_2O$ (0.21 ml, 4.42 mmol) in EtOH (70 ml) was refluxed for 30 min to give **3** (302 mg, 86%) as a white amorphous product by the same procedure as used for the preparation of **1**: $[\alpha]_D$: −21.9° (c=1.55, MeOH). IR (Nujol) cm^{-1}: 3300 (OH), 1590 (NH). ^{1}H-NMR (CD_3OD) δ: 2.80 (dd, 1H, J=13.4, 6.6 Hz, 5′-H_a), 2.93 (dd, 1H, J=13.4, 4.0 Hz, 5′-H_b), 3.88 (m, 1H, 4′-H), 3.97 (t, 1H, J=5.4 Hz, 3′-H), 4.15 (t, 1H, J=5.6 Hz, 2′-H), 4.76 (d, 1H, J=5.8 Hz, 1′-H), 7.10 (s, 1H, 5-H), 7.68 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ: 44.8, 73.7, 76.5, 80.1, 85.3, 118.4, 137.1, 138.2. MS (SIMS) m/z: 200 (M^+ + 1). HR-MS (SIMS) m/z: 200.1022 (Calcd for $C_8H_{14}N_3O_3$: 200.1034).

(*E*)-1-Cyano-2-methyl-3-{5-deoxy-1-[1*H*-imidazol-4(5)-yl]-β-D-ribofuranos-5-yl}guanidine (5) By the same procedure as described for the preparation of **2**, the amine **3** (158 mg, 0.80 mmol) was converted

into **5** (154 mg, 69%) as a white amorphous product: $[\alpha]_D$: +6.5° (c=1.49, MeOH). IR (Nujol) cm^{-1}: 2160 (CN), 1580 (C=N). ^{1}H-NMR (CD_3OD) δ: 2.75 (s, 3H, NHMe), 3.44 (dd, 1H, J=14.7, 6.0 Hz, 5′-H_a), 3.54 (dd, 1H, J=14.7, 4.2 Hz, 5′-H_b), 3.97—4.12 (m, 2H, 3′, 4′-H), 4.16 (dd, 1H, J=5.4, 5.0 Hz, 2′-H), 4.80 (d, 1H, J=5.4 Hz, 1′-H), 7.12 (s, 1H, 5-H), 7.72 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ: 28.9, 45.5, 74.0, 76.9, 80.6, 83.9, 117.5, 120.2, 137.5, 139.3, 162.7. MS (SIMS) m/z: 281 (M^++1). HR-MS (SIMS) m/z: 281.1360 (Calcd for $C_{11}H_{17}N_6O_3$: 281.1361).

4(5)-[5-Deoxy-5-(*N*-methylthioureido)-β-D-ribofuranosyl]imidazole (7) A solution of **3** (159 mg, 0.80 mmol) and methyl isothiocyanate (90 mg, 1.20 mmol) in MeOH (20 ml) was stirred at room temperature for 14 h. After evaporation of the solvent, the residue was purified by column chromatography [Chromatorex NH-DM 1020, MeOH–EtOAc (1 : 9 to 1 : 3)] to give **7** (153 mg, 70%) as a white amorphous product: $[\alpha]_D$: −21.1° (c=2.45, MeOH). IR (neat) cm^{-1}: 3700—2200 (OH), 1560, 1111 [NHC(S)NH]. ^{1}H-NMR (CD_3OD) δ: 2.93 (s, 3H, NHMe), 3.80 (br d, 2H, J=10.0 Hz, 5′-H), 4.00—4.20 (m, 3H, 2′, 3′, 4′-H), 4.75 (d, 1H, J=5.0 Hz, 1′-H), 7.15 (s, 1H, 5-H), 7.77 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ: 31.5, 47.8, 73.8, 76.9, 80.2, 84.4, 118.3, 137.5, 138.8, 184.9. MS (SIMS) m/z: 273 (M^++1). HR-MS (SIMS) m/z: 273.1024 (Calcd for $C_{10}H_{17}N_4O_3S$: 273.1020).

4(5)-[5-Deoxy-5-(*N*-phenylthioureido)-β-D-ribofuranosyl]imidazole (8) The same procedure as described for the preparation of **7** provided **8** (44 mg, 89%) as a white amorphous product from **3** (30 mg, 0.15 mmol) and phenyl isothiocyanate (27 μl, 0.22 mmol) in MeOH (2 ml). $[\alpha]_D$: −10.1° (c=1.00, MeOH). IR (KBr) cm^{-1}: 3260 (OH), 1535, 1105 [NHC(S)NH]. ^{1}H-NMR (CD_3OD) δ: 3.91 (m, 2H, 5′-H), 4.05—4.18 (m, 3H, 2′-, 3′-, 4′-H), 4.76 (d, 1H, J=5.5 Hz, 1′-H), 7.08 (s, 1H, 5-H), 7.18 (dd, 1H, J=15.2, 7.3 Hz, Ph), 7.33 (d, 4H, J=7.3 Hz, Ph), 7.65 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ: 48.1—50.6 (overlapped with the solvent), 74.0, 76.9, 80.3, 84.0, 118.3, 125.7, 126.9, 130.4, 137.4, 138.7, 140.0, 183.0. MS (SIMS) m/z: 335 (M^++1). HR-MS (SIMS) m/z: 335.1179 (Calcd for $C_{15}H_{19}N_4O_3S$: 335.1177).

4(5)-[5-Deoxy-5-(*N*-phenylureido)-β-D-ribofuranosyl]imidazole (9) The same procedure as described for the preparation of **7** provided **9** (118 mg, 69%) as a white amorphous product from **3** (107 mg, 0.54 mmol) and phenyl isocyanate (65 μl, 0.59 mmol) in MeOH (5 ml). $[\alpha]_D$: −37.1° (c=1.10, MeOH). IR (KBr) cm^{-1}: 3300 (OH), 1662, 1595 [NHC(O)NH]. ^{1}H-NMR (CD_3OD) δ: 3.45 (dd, 1H, J=14.1, 3.9 Hz, 5′-H_a), 3.57 (dd, 1H, J=14.1, 4.9 Hz, 5′-H_b), 3.96—4.05 (m, 2H, 3′, 4′-H), 4.17 (dd, 1H, J=5.4, 6.6 Hz, 2′-H), 4.75 (d, 1H, J=6.6 Hz, 1′-H), 6.97 (m, 1H, Ph), 7.14 (d, 1H, J=0.7 Hz, 5-H), 7.17—7.42 (m, 4H, Ph), 7.73 (d, 1H, J=0.7 Hz, 2-H). ^{13}C-NMR (CD_3OD) δ: 43.2, 73.9, 76.9, 80.0, 85.1, 118.7, 120.4, 123.7, 130.1, 137.4, 138.5, 141.2, 158.7. MS (SIMS) m/z: 319 (M^++1). HR-MS (SIMS) m/z: 319.1412 (Calcd for $C_{15}H_{19}N_4O_4$: 319.1405).

Ethyl 4-(2,5-Dideoxy-5-phthaloylamino-β-D-ribofuranosyl)imidazole-1-carboxylate (25) The same procedure as described for the preparation of **23** provided **25** (1.795 g, 95%) as a white amorphous product from **13** (1.31 g, 5.12 mmol), DEAD (0.96 ml, 5.63 mmol), Ph_3P (1.48 g, 5.63 mmol), and phthalimide (828 mg, 5.63 mmol). IR (KBr) cm^{-1}: 3400 (OH), 1762 (CO–N–CO), 1712 (N–CO–N). ^{1}H-NMR δ: 1.43 (t, 3H, J=7.0 Hz, $COOCH_2C\underline{H}_3$), 2.30 (dd, 2H, J=7.0, 4.5 Hz, 2′-H), 3.00 (br s, 1H, OH), 3.88 (m, 2H, 5′-H), 4.18 (m, 1H, 4′-H), 4.45 (m, 3H, 3′-H, $COO\underline{C}H_2CH_3$), 5.16 (t, 1H, J=7.0 Hz, 1′-H), 7.38 (s, 1H, 5-H), 7.64—7.75 (m, 2H, phthalimide), 7.78—7.89 (m, 2H, phthalimide), 8.00 (s, 1H, 2-H). ^{13}C-NMR δ: 14.7, 40.6, 40.8, 64.9, 74.6, 74.9, 84.2, 114.4, 123.8, 132.5, 134.5, 137.5, 144.8, 149.0, 169.0. MS (SIMS) m/z: 386 (M^++1). HR-MS (SIMS) m/z: 386.1352 (Calcd for $C_{19}H_{20}N_3O_6$: 386.1351).

4(5)-(5-Amino-2,5-dideoxy-β-D-ribofuranosyl)imidazole (4) The same procedure as used for the preparation of **1** provided **4** (336 mg, 93%) as a white amorphous product from **25** (760 mg, 1.97 mmol). $[\alpha]_D$: +33.9° (c=1.60, MeOH). ^{1}H-NMR (CD_3OD) δ: 2.13 (ddd, 1H, J=13.2, 5.9, 2.5 Hz, 2′-H_a), 2.27 (ddd, 1H, J=13.2, 10.2, 6.1 Hz, 2′-H_b), 2.81 (dd, 1H, J=13.2, 7.1 Hz, 5′-H_a), 2.95 (dd, 1H, J=13.2, 7.1 Hz, 5′-H_b), 3.89 (dt, 1H, J=7.1, 4.2 Hz, 4′-H), 4.24 (dt, 1H, J=6.1, 2.5 Hz, 3′-H), 5.17 (dd, 1H, J=10.2, 5.9 Hz, 1′-H), 7.07 (s, 1H, 5-H), 7.66 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ: 42.4, 45.5, 75.1, 75.3, 89.0, 118.0, 137.2, 139.7. MS (SIMS) m/z: 184 (M^++1). HR-MS (SIMS) m/z: 184.1091 (Calcd for $C_8H_{14}N_3O_2$: 184.1085).

1-Cyano-2-methyl-3-[2,5-dideoxy-1-(1*H*-imidazol-4-yl)-β-D-ribofuranos-5-yl]guanidine (6) The same procedure as described for the preparation of **2** provided 1-cyano-3-{2,5-dideoxy-1-[1*H*-imidazol-4(5)-yl]-β-D-ribofuranos-5-yl}-2-methylisothiourea (244 mg, 87%) [IR (KBr) cm^{-1}: 3250 (OH), 2167 (CN), 1558 (C=N). ^{1}H-NMR (CD_3OD) δ: 2.11 (ddd, 1H, J=11.5, 5.5, 1.5 Hz, 2′-H_a), 2.27 (ddd, 1H, J=11.5, 9.0, 5.0 Hz, 2′-H_b), 2.60 (s, 3H, SMe), 3.50 (dd, 1H, J=14.0, 6.5 Hz, 5′-H_a), 3.67 (dd, 1H, J=14.0, 5.0 Hz, 5′-H_b), 4.07 (m, 1H, 4′-H), 4.27 (m, 1H, 3′-H), 5.18 (dd, 1H, J=9.0, 5.5 Hz, 1′-H), 7.10 (s, 1H, 5-H), 7.70 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ: 14.8, 42.0, 47.5, 75.2, 75.7, 85.8, 117.4, 117.7, 137.3, 140.2. 173.4] as a white amorphous product from **4** (183 mg, 1.0 mmol) and dimethyl *N*-cyanodithioiminocarbonate (162 mg, 1.0 ml) in MeOH (10 ml). The methylisothiourea (194 mg, 0.69 mmol) thus obtained was treated with 40% $MeNH_2$–MeOH (7 ml) to give **6** (187 mg, quant.) as a white amorphous product; $[\alpha]_D$: +48.3° (c=3.00, MeOH). IR (KBr) cm^{-1}: 3300 (OH), 2168 (CN), 1590 (C=N). ^{1}H-NMR (CD_3OD) δ: 2.12 (ddd, 1H, J=12.3, 6.1, 2.6 Hz, 2′-H_a), 2.27 (ddd, 1H, J=12.3, 10.2, 5.6 Hz, 2′-H_b), 2.73 (s, 3H, NHMe), 3.29—3.39 (overlapped with the solvent, 1H, 5′-H_a), 3.45 (dd, 1H, J=13.7, 5.3 Hz, 5′-H_b), 3.99 (ddd, 1H, J=7.9, 5.3, 2.3 Hz, 4′-H), 4.29 (dt, 1H, J=5.3, 2.6 Hz, 3′-H), 5.18 (dd, 1H, J=10.2, 6.1 Hz, 1′-H), 7.10 (s, 1H, 5-H), 7.70 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ: 28.9, 42.0, 46.0, 75.0, 75.8, 87.3, 117.3, 120.3, 137.2, 140.2, 162.6. MS (SIMS) m/z: 265 (M^++1). HR-MS (SIMS) m/z: 265.1420 (Calcd for $C_{11}H_{17}N_6O_2$: 265.1412).

5-Methyl-4-(2,3,5-tri-*O*-benzyl-D-ribosyl)-*N*,*N*-dimethylimidazole-1-sulfonamide (26*R* and 26*S*) A 1 M THF solution of Bu_4NF (0.84 ml, 0.84 mmol) was added slowly to a solution of **17*RS*** (597 mg, 0.83 mmol) in THF (15 ml) at 0 °C, and the mixture was stirred for 10 min at room temperature. Ice was then added to the mixture, and the solvent was evaporated to afford a residue, which was extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The crude oil was purified by column chromatography [EtOAc–*n*-hexane (2 : 3)] to give **26*R*** (185 mg, 37%) and **26*S*** (299 mg, 59%). **26*R*** (less polar); IR (neat) cm^{-1}: 3420 (OH), 1390, 1168 (SO_2). ^{1}H-NMR δ: 2.30 (s, 3H, Me), 2.83 (s, 6H, SO_2NMe_2), 3.43—3.76 (m, 4H, 2′, 3′, 5′-H), 4.27—4.52 (m, 4H, 4′-H, CH_2Ph), 4.86 (d, 1H, J=11.2 Hz, CH_2Ph), 5.00 (d, 1H, J=7.2 Hz, 1′-H), 7.23—7.46 (m, 15H, Ph), 7.77 (s, 1H, 2-H). MS (SIMS) m/z: 610 (M^++1). **26*S*** (more polar); IR (neat) cm^{-1}: 3300 (OH), 1388, 1168 (SO_2). ^{1}H-NMR δ: 2.25 (s, 3H, Me), 2.77 (s, 6H, SO_2NMe_2), 3.64 (dd, 1H, J=9.5, 5.7 Hz, 5′-H_a), 3.73 (dd, 1H, J=9.5, 3.1 Hz, 5′-H_b), 3.97 (dd, 1H, J=8.6, 1.8 Hz, 3′-H), 4.05 (dd, 1H, J=8.6, 1.8 Hz, 2′-H), 4.24 (d, 2H, J=11.7 Hz, 4′-H, OH), 4.45—4.77 (m, 6H, CH_2Ph), 4.92 (d, 1H, J=8.6 Hz, 1′-H), 7.05—7.43 (m, 15H, Ph), 7.81 (s, 1H, 2-H). MS m/z: 610 (M^++1).

Conversion of 26*R* into β-27 Using MsCl–Pyridine A solution of the diol **27** (124 mg, 0.20 mmol) and $MeSO_2Cl$ (0.1 ml, 1.20 mmol) in pyridine (10 ml) was stirred for 21 h at room temperature. After addition of H_2O (1 ml), the mixture was extracted with EtOAc, and the extract was washed with H_2O, dried, and evaporated. The residue was purified by column chromatography [EtOAc–*n*-hexane (1 : 1)] to give **β-27** (48 mg, 41%) as a colorless oil. IR (neat) cm^{-1}: 1388, 1170 (SO_2). ^{1}H-NMR δ: 2.36 (s, 3H, Me), 2.90 (s, 6H, SO_2NMe_2), 3.59 (d, 2H, J=5.1 Hz, 5′-H), 4.06 (dd, 1H, J=5.3, 4.0 Hz, 3′-H), 4.24—4.41 (m, 2H, 2′, 4′-H), 4.44—4.72 (m, 6H, 3×CH_2Ph), 4.92 (d, 1H, J=6.7 Hz, 1′-H), 7.15—7.45 (m, 15H, Ph), 7.82 (s, 1H, 2-H).

Reaction of 26*S* with MsCl–Pyridine By the same procedure as above, **26*S*** (119 mg, 0.20 mmol) was converted into **β-27** (18 mg, 16%) and **α-27** (26 mg, 23%). **α-27** (more polar); oil. IR (neat) cm^{-1}: 1391, 1165 (SO_2). ^{1}H-NMR δ: 2.42 (s, 3H, Me), 2.78 (s, 6H, SO_2NMe_2), 3.60 (dd, 1H, J=11.0, 3.8 Hz, 5′-H_a), 3.77 (dd, 1H, J=11.0, 2.7 Hz, 5′-H_b), 4.12—4.66 (m, 9H, 2′, 3′, 4′-H, CH_2Ph), 5.19 (d, 1H, J=2.7 Hz, 1′-H), 7.10—7.47 (m, 15H, Ph), 7.87 (s, 1H, 2-H).

Hydrolysis of 26 A solution of **26*R*** (92 mg, 0.15 mmol) in THF (6 ml) was refluxed with 1.5 N HCl (10 ml) for 22 h to give β-**19** (44 mg, 60%) and **18*R*** (16 mg, 21%) by the same procedure as described for the preparation of **18**.[11] **18*R*** (more polar); ^{1}H-NMR δ: 2.10 (s, 3H, Me), 3.41—3.77 (m, 4H, 2′, 3′, 5′-H), 4.14—4.63 (m, 6H, 4′-H, 2×CH_2Ph, OH), 4.78 (dd, 2H, J=11.0, 1.5 Hz, CH_2Ph), 5.04 (d, 1H, J=6.0 Hz, 1′-H), 7.11—7.50 (m, 16H, 2-H, Ph). By the same procedure as above, **26*S*** (188 mg, 0.31 mmol) was hydrolyzed to **18*S*** (125 mg, 80%) as a white amorphous product.

Conversion of 18*S* into β-19 Using Mitsunobu Cyclization The same procedure as described for Mitsunobu cyclization of **18**[11] provided **β-19** (107 mg, 88%) from **18*S*** (125 mg, 0.25 mmol), Bu_3P (0.08 ml, 0.30 mmol), and TMAD (52 mg, 0.30 mmol).

Chronotropic Response on Guinea Pig Atrial Preparation Male Hartley guinea pigs weighing between 460 and 790 g were stunned by a

blow to the head and killed by exsanguination. The atrial preparation was mounted under 0.5 g of tension in a 20-ml organ bath containing Krebs–Henseleit solution at 30 °C and continuously gassed with a mixture of 95% O_2 and 5% CO_2. Heart rate was picked up with an isometric force displacement transducer (SB-1T; Nihon Kohden, Tokyo) and recorded (Recti-Horiz; NEC-Sanei, Tokyo) *via* a carrier amplifier (RP-5; Nihon Kohden) and a heart-rate counter (AT-600G, Nihon Kohden).

Cumulative administration of histamine (3×10^{-8} to 1×10^{-3} M) was performed at 60 min intervals. After two constant control curves were obtained, one of compounds **1** to **9** or cimetidine was applied for 10 min prior to further cumulative administration of histamine. The chronotropic response was reported as a percentage of the response without drug from the same preparation. Each concentration of drug was tested in 4 separate preparations.

Antiulcer Activity Male Wistar strain rats weighing between 190 and 210 g were deprived of food for 18 h before the experiments and given access to water only. The drugs were suspended in 0.5% methylcellulose solution and given orally before the experiment. Rats were placed in a stainless steel cage (Natsume, Tokyo) and immersed vertically to the level of the xiphoid process in a water bath maintained at 23 °C for 7 h. After the immersion, the animals were killed under anesthesia with ether and the stomachs were removed and immersed in 0.3% (w/v) formalin solution for 10 min to fix the inner and outer layers of the gastric walls. The length (mm) of each stress-induced ulcer was measured under a dissection microscope. Student's *t* test was used to determine the statistical significance of differences.

Crystallization of Compound 5 The vapor diffusion, hanging-drop method was adopted for the crystallization. The first crystallization solution contained 8% of compound **5**. The crystal formed was too small for the X-ray crystallography. However, a 23% solution of **5** afforded a colorless platelet-like crystal with dimensions of $0.3 \times 0.5 \times 0.1$ mm. It gave good diffraction peaks up to 0.87 Å resolution. In these experiments, 2-methyl-2,4-pentanediol was used as the precipitant. The concentrations in the crystallization solution and the reservoir solution were 30% and 70%, respectively.

X-Ray Structure Determination The intensity data was measured on a Rigaku AFC-5R diffractometer using graphite-monochromated CuK_α radiation ($\lambda = 1.5418$ Å) with a scan rate 8° min^{-1} in 2θ range 0° to 125° and scan width of $\delta(2\theta) = (1.1 + 0.15 \tan\theta)$. Background intensities were measured for 3 s at each end of a scan. Crystal data are shown in Table 3. A total of 968 reflections (941 independent reflections) were collected using the $\omega - 2\theta$ scan method. The structure was solved by the direct method using MULTAN 87.[22] The structure was refined by a block-diagonal least-squares procedure with 890 reflections ($F_O > 2.0\sigma|F_O|$). Calculations were carried out with the UNICS system[23] using the program LSBL for the refinement. The final refinement converged to residual $R = 0.0422$ and $R_W = 0.0517$.

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