Synthesis of 4(5)-[5-(Aminomethyl)tetrahydrofuran-2-yl- or 5-(Aminomethyl)-2,5-dihydrofuran-2-yl]imidazoles by Efficient Use of a PhSe Group: Application to Novel Histamine H_3-Ligands[1]

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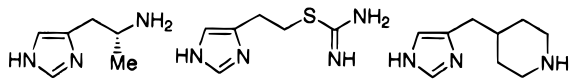
(+)-4(5)-[(2*R*,5*S*)-(5-Aminomethyl)tetrahydrofuran-2-yl]imidazole **1** and its C2′ epimer (−)-**2**, which are the 5′-amino derivatives of a novel imidazole C-nucleoside, were synthesized *via* β- and α-2′-phenylselenenyl nucleosides **15** and **16**. The anomers **15** and **16** were provided by a new synthetic method for C-nucleosides *via* the elimination of PhSeCl and selenocyclization from diol intermediates **12** and **14**, starting from L-glutamic acid. Their *ent*-**1** and *ent*-**2** (imifuramine), the latter of which was indicated as a novel type of histamine H_3-agonist confirmed by an *in vivo* brain microdialysis method, were synthesized by the same methodology from D-glutamic acid. The four isomers (**3**, **4**, *ent*-**3**, and *ent*-**4**) of a 4(5)-[(5-aminomethyl)-2,5-dihydrofuran-2-yl]imidazole were also synthesized *via* the oxidative elimination of the PhSe group of the key intermediates (**15**, **16**, *ent*-**15**, and *ent*-**16**). In connection with this study, 4(5)-(5-aminomethylfuran-2-yl)-1*H*-imidazole (**5**) was also synthesized starting from D-ribose.

The histamine H_3(H_3) receptors[2] exist at the varicosities and endings of the histaminergic fibers in the brain and modulate the synthesis and release of histamine as an autoreceptor.[3] Moreover, H_3-receptors have been shown to be heteroreceptors[4d] that modulate the release of a number of different neurotransmitters.[4] Therefore, histamine neurons play an important role in the arousal, learning, and memory mechanisms, working together with other neuromodulatory systems.[5−8] H_3-antagonists are now expected to be potential drugs for memory degenerative disorders such as Alzheimer's disease.[4] This type of receptor can be also found in many peripheral tissues. Since the first H_3-agonist (*R*)-α-methylhistamine[2] was shown to possess inhibitory action against airway smooth muscle contraction,[9,10] the H_3-agonists are regarded as a target for new therapeutics of bronchial asthma.[11] Besides (*R*)-α-methylhistamine, imetit and immepip, which are potent and selective agonists for the H_3-receptors, have been extensively used as a pharmacological tool.[4]



(R)-α-Methylhistamine Imetit Immepip

Theoretical calculations of histamine or some H_3-agonists have emphasized the importance of an intramolecular hydrogen bonding between the cationic primary amine and the N atom of the imidazole.[12,13] The ^{1}H NMR study on putative intramolecular hydrogen bonding for two H_3-agonists was recently reported.[14] However, the function of the intramolecular hydrogen bonding for activation of the H_3-receptor has not been experimentally demonstrated. On the other hand, 2-(1*H*-imidazol-4-yl)-cyclopropylamine (cyclopropylhistamine) has been reported as a H_3-agonist in a patent application by Arrang *et al.*[15] Unfortunately, the stereochemical identity of the

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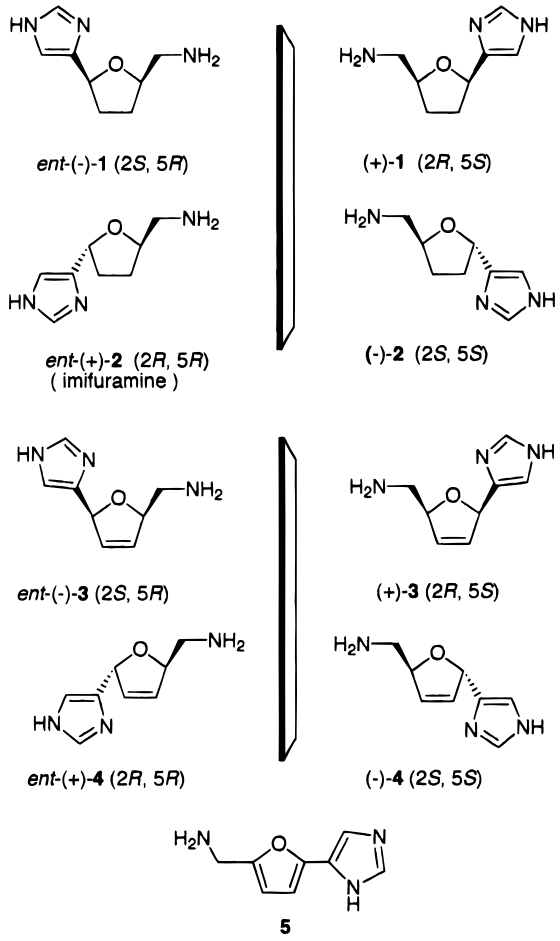
material tested was not reported. Recently, two groups[16,17] independently reported the synthesis[18] and evaluation of the H_3-agonistic activity of *trans*-cyclopropylhistamine. Khan *et al.*[16] determined that the *trans*-(1*R*,2*R*)-isomer was 1 order of magnitude more active than the (1*S*,2*S*)-isomer. Contrary to the results reported, Timmerman *et al.*[17] concluded that the (1*S*,2*S*)-isomer was about 10 times more active than its enantiomer.

As an outcome of the many structure−activity relationship studies in this drug discovery area,[4] it has been suggested that H_3-receptor agonists exhibit three common and essential structural features: an imidazole headgroup, a spacer, and an amino group. We recently reported[19,20] an efficient and stereoselective synthesis of β-imidazole C-nucleosides bearing 4(5)-substituted imidazole as a common structural unit, using the Mitsunobu cyclization. Hence, we became interested in the synthesis of novel *trans*- and *cis*-2,5-disubstituted tetrahydrofurans bearing imidazole and amino groups as an H_3-receptor activation model. We envisioned that, while the *cis* isomer **1** or its enantiomer *ent*-**1** could adopt a folded conformation through intramolecular hydrogen bonding, the trans isomer **2** or *ent*-**2** would take an extended conformation. The enhanced lipophilicity of these compounds lacking the hydroxy groups in the sugar moiety may also accentuate membrane permeability. Since only a limited number of imidazole C-nucleosides and their derivatives has been known so far,[19,20] we first endeavored to find a simple and efficient synthetic method of 2′,3′-dideoxyimidazole C-nucleosides to supply these compounds for biological evaluation. We recently communicated[1] the synthesis of novel *cis*- and *trans*-4(5)-[5-(aminomethyl)tetrahydrofuran-2-yl]imidazoles (**1**, **2**) and their enantiomers (*ent*-**1**, *ent*-**2**) using a synthetic method characterized by use of a PhSe group for the formation of the tetrahydrofuran ring. It is of particular interest that the preliminary results of an *in vivo* brain microdialysis[23] indicated that, among them, only *ent*-(+)-**2** (imifuramine) exhibited H_3-agonistic activity. The activity of imifuramine measured by the microdialysis was approximately equal to that of immepip.[24] We now disclose the details of the synthesis of the four isomers and further report the synthesis of the four stereoisomers (**3**, **4**, *ent*-**3**, and *ent*-**4**) of a novel 4(5)-[5-(aminomethyl)-2,5-dihydrofuran-2-yl]imidazole and 4(5)-(5-aminomethylfuran-2-yl)-1*H*-imidazole (**5**), which were conformationally restricted due to a planar dihydrofuran and furan rings, as part of our synthetic studies directed toward the preparation of new H_3 receptor ligands.



5

Results

(*S*)-Benzyloxymethyl-γ-butyrolactone **6** was easily synthesized from L-glutamic acid as described by Taniguchi et al.[25] Introduction of a phenylselenyl group into lactone **6** by the Chu procedure[26] gave C2α-and C2β-selenolactones **7** (52%) and **8** (30%) (Scheme 1). The poor α/β ratio was not of consequence in this synthetic method, since the two isomers could be favorably used as substrates for key intermediates **15** and **16**. Reduction of major lactone **7** with diisobutylaluminum hydride (DIBAL) gave lactol **9**. The reaction of **9** with lithium salt **11**[19] of the bis-protected imidazole resulted in a diol **12** (73%) with a C1′*S* configuration, together with C1′ epimer **13** (10%). The C1′ stereochemical assignments to **12** and **13**, respectively, were based on the analogy of our precedent.[19b] In ^{1}H NMR, their C1′ configurations were assigned by a small $J_{1',2'}$ coupling constant (2.7 Hz) of minor isomer **13** compared to that of **12** (5.9 Hz) having a 1′,2′-antiparallel orientation. The *anti* selectivity for **12** may be accounted for by a chelation−cyclic model as illustrated in Figure 1.

When we next tried deprotection of the imidazole moiety in the diol **12** in aqueous HCl−THF,[19] β- and

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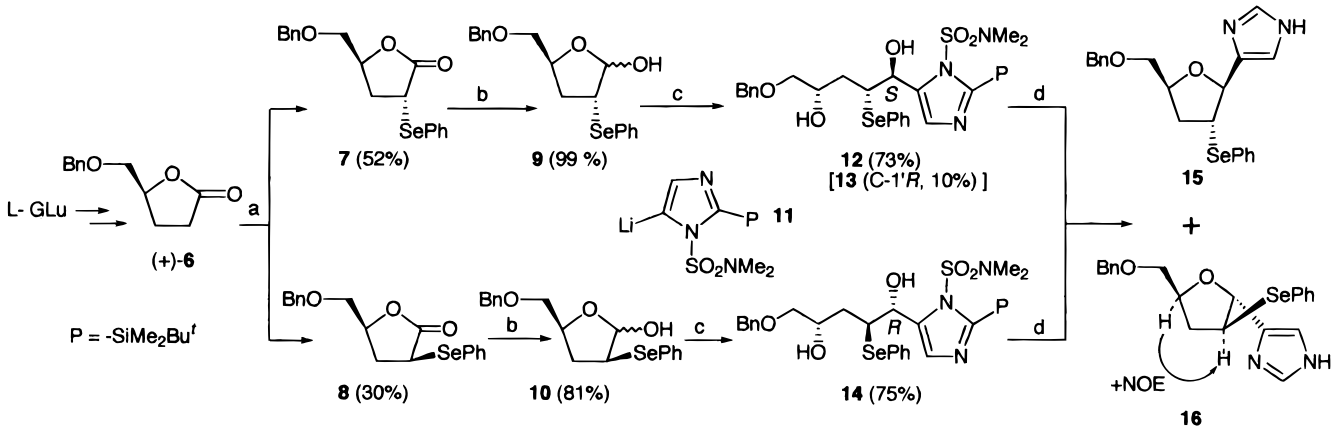
Scheme 1[a]



[a] Reagents: (a) (i) LHMDS, TMSCl; (ii) PhSeBr; (b) DIBAL (c) (i) **11**; (d) (i) aqueous 1.5 N HCl−THF; (ii) benzene, reflux, Dean−Stark water separator; yields **15** (42%), **16** (56%) from **12**; **15** (35%), **16** (53%) from **14**.

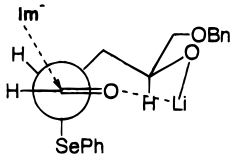
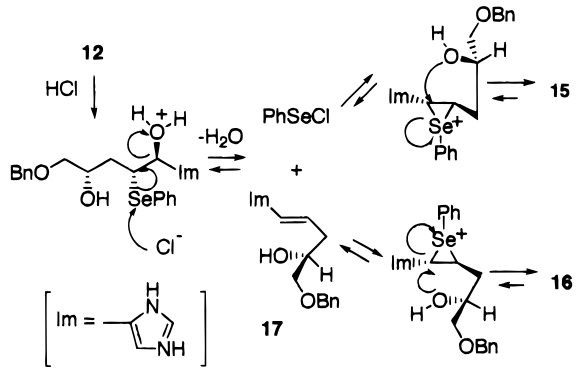


Figure 1. Anti selectivity for **12** by a chelation−cyclic model.

Scheme 2



α-C2′-phenylseleneyl nucleosides **15** (22%) and **16** (38%) were generated, together with *trans*-homoallylic alcohol **17** (26%). On the other hand, if the water in the reaction mixture was removed as an azeotrope with benzene, the yields of **15** and **16** were improved to 42% and 56%, respectively. In this case, the isolation of the α- and *β*-anomers could be easily done by SiO_2 column chromatography, presumably due to the presence of the large PhSe group directly bound to the THF ring. This result facilitated our subsequent reactions, since we have often encountered considerable difficulty in the isolation of the two anomers.[19] In ^{1}H NMR, the two C5′ protons (*δ* 3.58, 3.80) of *β*-anomer **15** were individually observed and shifted downfield compared to those (*δ* 3.46) of α-anomer **16**. These results presumably reflect the rotational hindrance of the C4′-C5′ bond and deshielding effects due to imidazole. The correctness of the assignment was indicated by the positive nuclear Overhauser effect (NOE) between the C2′- and C4′-protons in **16**. The formation of **15** and **16** can be reasonably rationalized by the postulated mechanism shown in Scheme 2. The reaction of **12** with HCl generates the homoallylic alcohol **17** by a *trans*-stereospecific elimination of PhSeCl. Recombination of **17** and PhSeCl proceeds to give the *β*- and α-anomers **15** and **16** through selenium-induced cyclization at both faces of the double bond of **17**. This is well supported by the fact that the reaction of the **17** with PhSeCl smoothly proceeded to give **15** (31%) and **16** (55%) in refluxing THF. Although such cyclization appears to be inconsistent with Baldwin's protocol,[27] being formally a 5-*endo*-*trig* process, it may be explained by the fact that this is an electrophile-driven rather than a nucleophile-driven cyclization.[28] In the case of the epimeric diol **13** having a 1′,2′-*syn* configuration, the cyclization did not proceed under refluxing HCl−THF, and only a linear diol having unsubstituted imidazole resulted.

The minor lactone **8** effectively supplied *β* anomer **15** and α anomer **16** by a parallel sequence of reactions**.** Addition of 5-lithioimidazole **11** to C2*β*-lactol **10** afforded only diol **14** with C1′*R* configuration. The cyclization of **14** cleanly provided the anomers **15** and **16** in 35% and 53% yields, respectively. To date, this synthetic approach for the preparation of C-nucleosides using a combination of the elimination of PhSeCl and selenocyclization has not been reported.[29]

After the *N*-ethoxycarbonylation[20] of the *β*-anomer **15**, the phenylselenenyl group at the C2′ position of the resulting **18** was removed to give 2′,3′-dideoxynucleoside **19** by treatment with *n*-Bu_3SnH and Et_3B (Scheme 3).[26] Debenzylation of **19** with $Pd(OH)_2$−C in cyclohexene gave a dideoxynucleoside **20**, which was subsequently subjected to phthaloylimination[20] using the Mitsunobu reaction. Although the reaction of **20** with diethyl azodicarboxylate (DEAD), Ph_3P, and phthalimide was inert, we found that the use of diisopropyl azodicarboxylate (DIAD) and 4-(dimethylamino)phenyldiphenylphosphine successfully proceeded to give phthalimide **21** in 92% yield. Double deprotection of **21** with hydrazine hydrate yielded the desired 4(5)-[(2*R*,5*S*)-5-(5-aminomethyl)tetrahydro-

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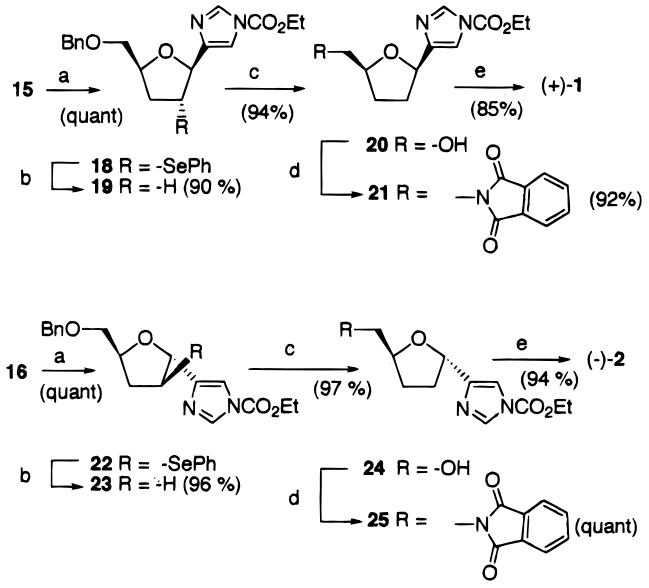
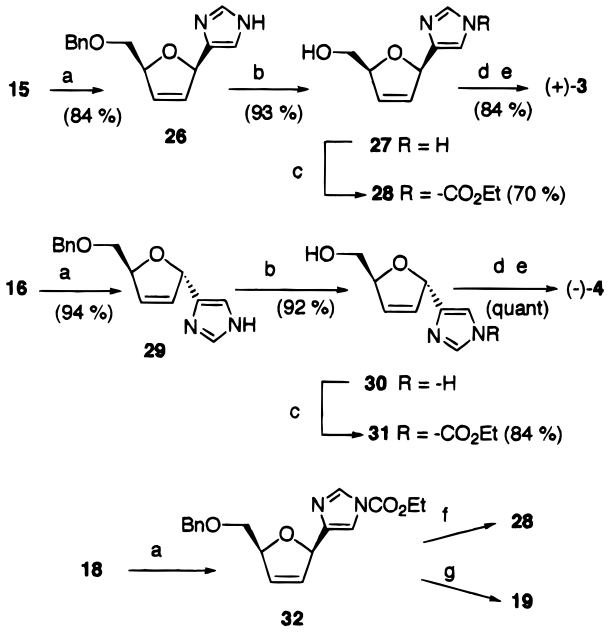
Scheme 3[a]



[a] Reagents: (a) $ClCO_2Et$; (b) Et_3B, Bu_3SnH; (c) $Pd(OH)_2$−C, cyclohexene; (d) DIAD, 4-$Me_2NC_6H_4PPh_2$, phthalimide; (e) hydrazine·H_2O.

Scheme 4[a]



[a] Reagents: (a) H_2O_2, pyridine (cat.); (b) sodium naphthalenide; (c) $ClCO_2Et$; (d) phthalimide, DEAD, Ph_3P; (e) CH_3NH_2 in EtOH; (f) TMSI or BCl_3; (g) $Pd(OH)_2$−C, cyclohexene.

furan-2-yl]imidazole (**1**) in 66% overall yield from **15**. Thus, synthesis of trans isomer **2** was attained in 87.5% overall yield from α-anomer **16** via a route similar to that employed for **15**. The structures of β- and α-anomers **1** and **2** were determined on the basis of comparison of their ^{1}H NMR. The C4′-H (δ 4.17) in **2** was observed in a lower field in comparison with that (δ 4.04) in **1**, because of the deshielding effect of the proton that was *syn* to the imidazole ring.[30] It is important to note that simply switching the starting material to D-glutamic acid allows the synthesis of enantiomers of **1** and **2**. Accordingly, *ent*-**1** and *ent*-**2** (imifuramine) were synthesized through the respective intermediates *ent*-**15** and *ent*-**16** by the same reaction sequence described herein.

The finding of imifuramine, which is a novel type of histamine H_3-agonist, encouraged us to synthesize the unsaturated compounds **3**, **4**, and their enantiomers from the selenonucleosides **15** or **16**. As 2′-phenylselenenyl nucleoside is prone to produce a C2′−C3′ double bond by facile oxidative elimination,[26] the *N*-(ethoxycarbonyl)-compound **18** was converted to the 2′,3′-unsaturated nucleoside **32** by treatment with H_2O_2/pyridine (Scheme 4). However, the selective debenzylation of **32** with conventional reagents TMSI[31] or BCl_3[32] in CH_2Cl_2 gave the desired alcohol **28** in poor yields. Treatment of **32** with $Pd(OH)_2$−C in cyclohexene indicated the susceptibility of the double bond toward hydrogenation, giving a saturated compound **19**.

After various trials, we found an alternative route using single electron-transfer reduction to the alcohol **27**. Treatment of **15** with H_2O_2/pyridine afforded β-anomer **26** (84%) having a C2′,3′ double bond. The debenzylation of **26** with lithium in liquid ammonia at −78 °C followed by workup with NH_4Cl brought about the expected alcohol **27** in low yield.[33] However, treatment of **26** with 15 equiv of sodium naphthalenide[34] in DME at room temperature for 15 min produced the unsaturated imidazole **27** in 93% yield. The *N*-ethoxycarbonylation of **27** afforded the intermediate **28**, which was subsequently transformed into the crude phthalimide compound under Mitsunobu conditions. The phthalimide was treated with methylamine[35] in ethanol to afford (+)-4(5)-[(2*R*,5*S*)-5-(aminomethyl)-2,5-dihydrofuran-2-yl]imidazole (**3**) in 84% overall yield from **27**. In a similar manner, the unsaturated derivative (−)-**4** was synthesized from the α-anomer **16**, as shown in Scheme 4. The *ent*-**3** and *ent*-**4** were led from the selenonucleosides *ent*-**15** and *ent*-**16**, respectively.

Synthesis of 4(5)-(5-aminomethylfuran-2-yl)-1*H*-imidazole (**5**) was carried out by using the synthetic method of 1-(5-imidazoyl)ribofuranoid glycals, which we had previously reported[36] (Scheme 5). The reaction of crude α-D-ribofuranosyl chloride **34**,[37] prepared from protected D-ribose **33**,[38] with 2 equiv of the lithium salt **11** affords a labile furanoid glycal **35** bearing an imidazole moiety. Subsequent treatment of **35** with silica gel in CH_2Cl_2 resulted in a furan formation to give **36** in 36% overall yield from **33**. The formed **36** was successively transformed into an aminomethyl compound **38** by desilylation with Bu_4NF, phthalimination under Mitsunobu conditions, and deprotection with hydrazine hydrate. Hydrolysis of **38** with 1.5 N aqueous HCl afforded the furylimidazole **5** in 77% overall yield from **36**.

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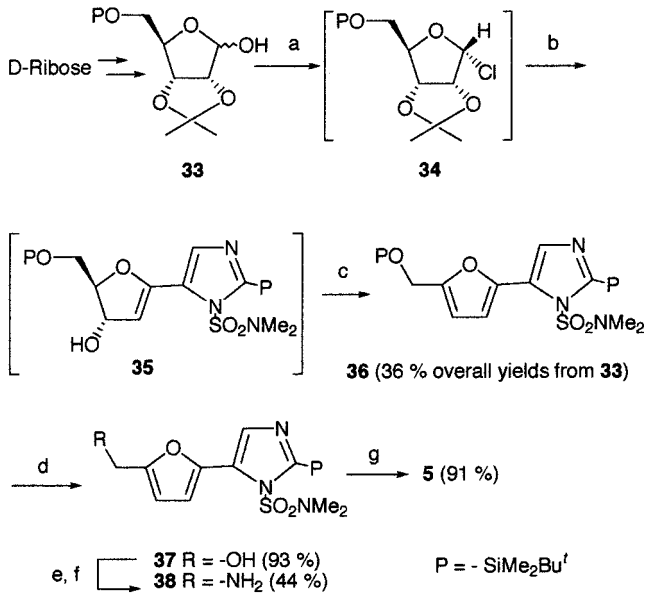
Scheme 5[a]



[a] Reagents: (a) (i) CCl_4, $(Me_2N)_3P$, −70 °C; (ii) −70 °C to rt; (b) **11** (2.0 equiv), −70 °C to reflux, (c) SiO_2, CH_2Cl_2, 3 days; (d) Bu_4NF; (e) phthalimide, Ph_3P, DEAD; (f) hydrazine·H_2O; (g) 1.5 N HCl.

In summary, the respective four possible stereoisomers of two novel imidazole C-nucleoside derivatives were synthesized by the efficient use of a PhSe group. This synthetic approach should enable the supply of a variety of derivatives by which their biological activity can be assessed. The evaluation for H_1- and H_2- as well as H_3-receptors of the nine compounds synthesized is in progress in our laboratories and will be reported in due course.

Experimental Section

General Procedures. The melting points were determined on a hot-stage apparatus and are uncorrected. The ORD spectra were recorded at 25 °C. ^{1}H and ^{13}C NMR spectra were taken with tetramethyllsilane. 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. Chromatography was performed on a silica gel. THF was distilled from sodium−benzophenone.

5-*O*-Benzyl-3-deoxy-2-*Se*-phenyl-2-seleno-D-*erythro*-pentonic Acid γ-Lactone (7) and 5-*O*-Benzyl-3-deoxy-2-*Se*-phenyl-2-seleno-D-*threo*-pentonic Acid γ-Lactone (8). According to Chu's procedure,[26] lithium hexamethyldisilazide (1 M in THF) (13.4 mL, 13.4 mmol) was added dropwise over 5 min to a solution of (+)-**6**[25] (2.512 g, 12.2 mmol) in THF (25 mL) at −70 °C with stirring. After the reaction mixture was stirred for 1 h at the same temperature, TMSCl (1.93 mL, 15.3 mmol) was added, and the reaction mixture was allowed to reach rt and stirred for 30 min at this temperature. The reaction mixture was again cooled to −70 °C, and a solution of phenylselenenyl bromide (4.319 g, 18.3 mmol) in THF (10 mL) was added. The dark brown color of the phenylselenenyl bromide disappeared as it was added and finally persisted at the end. The reaction mixture was diluted with diethyl ether (100 mL), washed with H_2O (50 mL × 5) until the ether layer was light yellow in color, dried, filtered, and concentrated. The resulting oily residue was purified by column chromatography using a gradient solvent system from 5% to 40% EtOAc in hexane to give **7** (2.296 g, 52%) followed by **8** (1.307 g, 30%). **7**: oil; IR (neat, cm^{-1}) 1765 (COO); ^{1}H NMR ($CDCl_3$) δ 2.24 (ddd, 1H, *J* = 5.1, 7.3, 13.8 Hz), 2.55 (ddd, 1H, *J* = 6.6, 8.9, 13.8 Hz), 3.46 (dd, 1H, *J* = 4.1, 11.0 Hz), 3.60 (dd, 1H, *J* = 3.1, 11.0 Hz), 4.01 (dd, 1H, *J* = 5.1, 8.9 Hz), 4.41 (m, 1H), 4.48 (s, 2H), 7.10−7.75 (m, 10H); EIMS *m*/*z* 362 (M^+); HRMS *m*/*z* 362.0417 (calcd for $C_{18}H_{18}O_3Se$ 362.0420); EIMS *m*/*z* 362 (M^+). **8**: oil; IR (neat, cm^{-1}) 1765 (COO); ^{1}H NMR ($CDCl_3$) δ 2.12 (ddd, 1H, *J* = 7.3, 8.7, 13.8 Hz), 2.67 (ddd, 1H, *J* = 7.3, 9.7, 13.8 Hz), 3.36 (dd, 1H, *J* = 5.1, 10.9 Hz), 3.44 (dd, 1H, *J* = 4.2, 10.9 Hz), 3.93 (dd, 1H, *J* = 8.7, 9.9 Hz), 4.46 (s, 2H), 4.53 (m, 1H), 7.18−7.37, 7.58−7.65 (m, 10H); EIMS *m*/*z* 362 (M^+); HRMS *m*/*z* 362.0416 (calcd for $C_{18}H_{18}O_3Se$ 362.0420).

5-*O*-Benzyl-3-deoxy-2-*Se*-phenyl-2-seleno-α- and -β-D-*erythro*-pentofuranose (9). To a solution of **7** (1.76 g, 4.87 mmol) in dry toluene (50 mL) at −70 °C was added a 1 M solution of DIBAL in toluene (6.33 mL, 6.33 mmol) over 20 min. After being stirred for 10 min at −70 °C, the reaction mixture was quenched with MeOH (10 mL) and further stirred at room temperature. Saturated $NaHCO_3$ solution (2 mL) was then added to the reaction mixture with stirring. After anhydrous $MgSO_4$ was added to the resulting suspension, the reaction mixture was stirred for a while, filtered through a Celite pad, and washed with EtOAc. The solvent was evaporated, and the residue was purified by column chromatography [EtOAc−hexane (1:4)] to give **9** (1.74 g, 99%) as a colorless oil: IR (KBr, cm^{-1}) 3340 (OH); ^{1}H NMR ($CDCl_3$) δ 1.99 (dd, 1/2H, *J* = 7.6, 14.1 Hz), 2.26 (dd, 1/2H, *J* = 6.7, 9.1 Hz), 2.53 (quint, 1/2H, *J* = 7.6, 14.1 Hz), 3.15 (d, 1/2H, *J* = 4.1 Hz), 3.36−3.50, 3.59−3.72 (m, 3H), 3.96 (d, 1/2H, *J* = 8.6 Hz), 4.38−4.63 (m, 3H), 5.33 (d, 1/2H, *J* = 8.6 Hz), 5.46 (t, 1/2H, *J* = 4.1 Hz), 7.22−7.34, 7.45−7.55 (m, 10H).

5-*O*-Benzyl-3-deoxy-2-*Se*-phenyl-2-seleno-α- and -β-D-*threo*-pentofuranose (10). Using a procedure used for **9**, lactone **8** (1.49 g, 4.13 mmol) was converted to **10** (1.21 g, 81%) as a colorless oil: IR (KBr, cm^{-1}) 3370 (OH); ^{1}H NMR ($CDCl_3$) δ 2.08−2.63 (m, 2H), 3.30−3.67 (m, 3H), 3.77 (br, 1/2H), 4.16 (d, 1/2H, *J* = 7.6 Hz), 4.20−4.32, 4.39−4.62 (m, 3H), 5.37 (dd, 1/2H, *J* = 3.7, 6.6 Hz), 5.55 (s, 1/2H), 7.20−7.57 (m, 10H).

5-[(1*S*,2*R*,4*S*)-5-Benzyloxy-1,4-dihydroxy-2-*Se*-phenyl-2-selenopentyl]-2-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethyl-1*H*-imidazolesulfonamide (12) and Its C-1′ Epimer (13). A solution of 2-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethyl-1*H*-imidazolesulfonamide (1.35 g, 4.68 mmol) in THF (14 mL) was cooled to −70 °C and treated dropwise with 1.6 M BuLi−hexane (2.92 mL, 4.68 mmol), and the reaction mixture was warmed to −50 °C over 50 min to precipitate the white lithium salts **11**. The resulting suspension was again cooled to −70 °C, and a solution of **9** (0.51 g, 1.42 mmol) in THF (8 mL) was added. The reaction mixture was stirred at the same temperature for 5 min. The dry ice bath was removed, and the reaction mixture was stirred at room temperature to dissolve the salts. After 1 h, the resulting yellow solution was quenched with H_2O, and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc, and the solution was washed with H_2O, dried, and evaporated to give a crude oil. Flash chromatography on silica gel using 30% EtOAc in hexane as eluent gave **12** (0.67 g, 73%) and **13** (0.09 g, 10%). **12** (less polar): recrystallized from hexane to give colorless needles; mp 95−96 °C; IR (KBr, cm^{-1}) 3180 (OH), 1380, 1175 (SO_2); ^{1}H NMR ($CDCl_3$) δ 0.33 (s, 6H), 0.90 (s, 9H), 1.66 (ddd, 1H, *J* = 3.0, 5.5, 15.1 Hz), 1.88 (ddd, 1H, *J* = 4.5, 9.4, 15.4 Hz), 2.65 (s, 6H), 3.00 (s, 1H), 3.21 (t, 1H, *J* = 8.8 Hz), 3.32 (dd, 1H, *J* = 3.7, 9.2 Hz), 3.86 (q, 1H, *J* = 4.9 Hz), 4.17 (br, 1H), 4.46 (s, 2H), 4.65 (d, 1H, *J* = 6.2 Hz), 5.20 (t, 1H, *J* = 5.9 Hz), 7.13−7.36, 7.49−7.53 (m, 11H). Anal. Calcd for $C_{29}H_{43}N_3O_5SSeSi$: C, 53.36; H, 6.64; N, 6.44. Found: C, 53.13; H, 6.61; N, 6.37. **13:** IR (neat, cm^{-1}) 3360 (OH), 1370, 1180 (SO_2). ^{1}H NMR ($CDCl_3$) δ 0.35 (s, 6H, *J* = 6.0 Hz), 0.92 (s, 9H), 1.77−1.95 (m, 2H), 2.70 (s, 6H), 3.01 (br, 1H), 3.33 (dd, 1H, *J* = 7.7, 9.4 Hz), 3.44 (dd, 1H, *J* = 4.1, 9.4 Hz), 3.62 (m, 1H), 4.35 (m, 1H), 4.50 (s, 3H), 5.10 (t, 1H, *J* = 2.7 Hz), 7.06−7.37 (m, 10H), 7.47 (s, 1H); SIMS *m*/*z* 654 ($M^+ + 1$).

5-[(1*R*,2*S*,4*S*)-5-Benzyloxy-1,4-dihydroxy-2-*Se*-phenyl-2-selenopentyl]-2-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethyl-1*H*-imidazolesulfonamide (14). The same procedure as described for the synthesis of **12** provided **14** (0.30 g, 75%) as a colorless oil from **10** (0.22 g, 0.60 mmol) and the lithium salt **11** (1.63 mmol). **14**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.33 (s,

6H), 0.91 (s, 9H), 1.57 (m, 1H), 1.86 (m, 1H), 2.49 (s, 1H), 2.55 (s, 6H), 3.25 (dd, 1H, J = 7.7, 8.8 Hz), 3.41 (dd, 1H, J = 3.0, 8.8 Hz), 3.94 (m, 1H), 4.16 (br, 1H), 4.48 (s, 2H), 5.09 (s, 1H), 7.14−7.34, 7.53−7.59 (m, 11H).

4(5)-(5-*O*-Benzyl-3-deoxy-2-*Se*-phenyl-2-seleno-*β*-D-*erythro*-pentofuranosyl)imidazole (15) and 4(5)-(5-*O*-Benzyl-3-deoxy-2-*Se*-phenyl-2-seleno-α-*threo*-pentofuranosyl)-imidazole (16). Method A. A solution of **12** (151 mg, 0.23 mmol) in THF (1.5 mL) was refluxed with 1.5 N HCl (1.5 mL) for 15 h and then cooled. After neutralization by addition of NH_4OH, the solvent was evaporated to give a residue, which was extracted with EtOAc. The extract was washed with H_2O and brine, dried, and evaporated. The residual oil was chromatographed using EtOAc for elution to give **15** (21 mg, 22%), **16** (36.4 mg, 38%), and then (*E*)-4(5)-[(4S)-5-*O*-benzyoxy-4-hydroxy-1-pentenyl)]imidazole (**17**) (17 mg, 28%), in turn. **15** (less polar): colorless oil; ORD (*c* 1.93, EtOH) [α] (nm) −33.7° (589), −38.9° (550), −49.2° (500), −64.8° (450), −85.5° (400), −129.5° (350), −268.4° (300); ^{1}H NMR ($CDCl_3$) δ 2.05 (ddd, 1H, J = 4.8, 6.9, and 13.6 Hz), 2.47 (dt, 1H, J = 7.7, 13.6 Hz), 3.58 (dd, 1H, J = 3.5, 10.4 Hz), 3.80 (m, 2H), 4.40 (m, 1H), 4.52 (s, 2H), 4.98 (d, 1H, J = 4.8 Hz), 6.70 (s, 1H), 7.00 (s, 1H), 7.13−7.45 (m, 10H); EIMS m/z 414 (M^+); HRMS m/z 414.0849 (calcd for $C_{21}H_{22}N_2O_2Se$ 414.0845). **16**: oil that solidified on standing. This was recrystallized from EtOAc−hexane to give **16** as colorless needles: mp 120−121 °C; ORD (*c* 1.58, EtOH) [α] (nm) +30.4° (589), +30.4° (550), +41.1° (500), +44.3 ° (450), +60.1° (400), +82.3° (350), +158.2° (308); ^{1}H NMR ($CDCl_3$) δ 1.90 (ddd, 1H, J = 8.5, 9.8, 12.7 Hz), 2.49 (dt, 1H, J = 6.8, 12.7 Hz), 3.46 (d, 2H, J = 4.9 Hz), 3.91 (dt, 1H, J = 8.1, 9.8 Hz), 4.33 (m, 1H), 4.49 (s, 2H), 4.84 (d, 1H, J = 8.1 Hz), 6.70 (s, 1H), 7.06−7.40 (m, 11H). Anal. Calcd for $C_{21}H_{22}N_2O_2Se$: C, 61.02; H, 5.36; N, 6.78. Found: C, 61.08; H, 5.30; N, 6.57. **17**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.33 (t, 2H, J = 6.8 Hz), 3.37 (dd, 1H, J = 7.5, 9.6 Hz), 3.50 (dd, 1H, J = 3.4, 9.6 Hz), 3.88 (m, 1H), 4.50 (s, 2H), 6.10 (dt, 1H, J = 7.4, 16.1 Hz), 6.32 (d, 1H, J = 16.2 Hz), 6.86 (s, 1H), 7.28 (s, 5H), 7.49 (s, 1H).

Method B. A solution of **12** (1.32 g, 2.03 mmol) in THF (24 mL) was refluxed with 1.5 N HCl (9 mL) for 1 h and then diluted with benzene (50 mL). The resulting mixture was further refluxed to remove water for 1 h as an azeotrope using a Dean−Stark water separator. Workup and purification described above gave **15** (0.35 g, 42%) and **16** (0.46 g, 56%).

The diol **14** (180 mg, 0.28 mmol) could be converted into **15** (40 mg, 35%) and **16** (60 mg, 53%) by method B.

Ethyl 4-(5-O-Benzyl-2,3-dideoxy-2-*Se*-phenyl-2-seleno-*β*-D-*erythro*-pentofuranosyl)imidazole-1-carboxylate (18). A solution of β-anomer **15** (40 mg, 0.1 mmol), ethyl chloroformate (18 μL, 0.19 mmol), pyridine (15 μL, 0.19 mmol), and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in benzene (2 mL) was refluxed for 15 min. After addition of H_2O, the solvent was evaporated and the residue was extracted with EtOAc. The extract was washed with H_2O and brine, dried, and evaporated. The residual oil was purified by flash column chromatography using EtOAc−hexane (7:13) for elution to give **18** (48 mg, quant) as a colorless oil: IR (Nujol, cm^{-1}) 1765 (COO); ^{1}H NMR ($CDCl_3$) δ 1.47 (t, 3H, J = 7.1 Hz), 2.08 (dt, 1H, J = 6.8, 13.2 Hz), 2.34 (dt, 1H, J = 7.6, 13.2 Hz), 3.55 (d, 2H, J = 5.1 Hz), 3.92 (dt, 1H, J = 6.7, 7.8 Hz), 4.29 (m, 1H), 4.38 (q, 2H, J = 7.1 Hz), 4.52 (s, 2H), 4.78 (d, 1H, J = 6.8 Hz), 7.11−7.29, 7.42−7.48 (m, 11H), 7.98 (s, 1H); EIMS m/z 486 (M^+); HRMS m/z 486.1056 (calcd for $C_{24}H_{26}N_2O_4Se$ 486.1056).

Ethyl 4-(5-*O*-Benzyl-2,3-dideoxy-*β*-D-*glycero*-pentofuranosyl)imidazole-1-carboxylate (19). A mixture of **18** (100 mg, 0.21 mmol), Et_3B (0.23 mL, 0.23 mmol), and Bu_3SnH (0.09 mL, 0.31 mmol) in benzene (7 mL) was stirred at room temperature for 90 min. The benzene was removed under reduced pressure. The residue was dissolved in CH_3CN, and the solution was washed with hexane and evaporated to give a crude oil. Flash chromatography using EtOAc−hexane (7:13) for elution gave **19** (61 mg, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.35 (t, 3H, J = 7.1 Hz), 1.71−2.30 (m, 4H), 3.52 (ddd, 2H, J = 5.5, 9.9, and 11.9 Hz), 4.18 (quint, 1H, J = 5.9 Hz), 4.39 (q, 2H, J = 5.5 Hz), 4.54 (s, 2H), 4.91 (t, 1H, J = 6.5 Hz), 7.22−7.31 (m, 6H), 8.01(s, 1H); EIMS m/z 330 (M^+); HRMS m/z 330.1578 (calcd for $C_{18}H_{22}N_2O_4$ 330.1578).

Ethyl 4-(2,3-Dideoxy-*β*-D-*glycero*-pentofuranosyl)imidazole-1-carboxylate (20). A mixture of **19** (113 mg, 0.34 mmol), 20% $Pd(OH)_2$−C (79 mg), and cyclohexene (1.0 mL, 10.26 mmol) in EtOH (15 mL) was refluxed for 1 h. After filtration through a Celite pad, the filtrate was evaporated to give a residue that was purified by column chromatography using EtOAc to give **20** (77 mg, 94%) as a colorless oil: ^{1}H NMR (CD_3OD) δ 1.46 (t, 3H, J = 7.1 Hz), 1.83−2.39 (m, 4H), 3.59 (dd, 1H, J = 5.3, 11.8 Hz), 3.72 (dd, 1H, J = 4.0, 11.8 Hz), 4.14 (m, 1H), 4.52 (q, 2H, J = 7.1 Hz), 4.93 (overlapped with H_2O in CD_3OD, 1′-H), 7.54 (s, 1H), 8.25 (s, 1H); EIMS m/z 241 (M^+ + 1); HRMS m/z 241.1184 (calcd for $C_{11}H_{17}N_2O_4$ 240.1187).

Ethyl 4-(5-Phthaloylamino-2,3,5-trideoxy-*β*-D-*glycero*-pentofuranosyl)imidazole-1-carboxylate (21). Phthalimide (71 mg, 0.48 mmol) and 4-dimethylaminophenyldiphenylphosphine (207 mg, 0.64 mmol) were dissolved in a solution of **20** (77 mg, 0.32 mmol) in THF (5 mL). To this mixture was added DIAD (0.13 mL, 0.64 mmol) with a stirring. The reaction mixture was stirred at room temperature for 12 h, and then the whole was evaporated to give a residue, which was subsequently dissolved in EtOAc. The solution was washed with H_2O and brine, dried, and evaporated to give a crude oil. It was purified by flash chromatography with EtOAc−hexane (2:3) to give a colorless oil **21** (110 mg, 92%) that solidified on standing. This was recrystallized from EtOAc−hexane to give white leaflets: mp 96−97 °C; ORD (*c* 2.06, EtOH) [α] (nm) +104.4° (589), +121.4° (550), +151.8° (500), +201.9° (450), +276.7° (400), +405.3° (350), +535.8° (330); ^{1}H NMR ($CDCl_3$) δ 1.35 (t, 3H, J = 7.1 Hz), 1.64−1.83 (m, 1H), 1.92−2.29 (m, 3H), 3.72 (dd, 1H, J = 5.2, 13.9 Hz), 3.84 (dd, 1H, J = 7.1, 13.7 Hz), 4.30 (m, 1H), 4.38 (q, 2H, J = 7.1 Hz), 4.88 (t, 1H, J = 6.3 Hz), 7.44 (s, 1H), 7.57−7.65 (m, 2H), 7.71−7.77 (m, 2H), 7.94 (s, 1H). Anal. Calcd for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.18; N, 11.38. Found: C, 61.59; H, 5.23; N, 11.24.

(+)-4(5)-[(2*R*,5*S*)-(5-Aminomethyl)tetrahydrofuran-2-yl]imidazole (1). A solution of **21** (57 mg, 0.16 mmol) and $NH_2NH_2{\cdot}H_2O$ (38 μL, 0.78 mmol) in EtOH (4 mL) was refluxed for 90 min and then cooled. A small amount of 10% Pd−C was then added to the solution, and the reaction mixture was further refluxed for 60 min. After removal of the catalyst by filtration through a Celite pad, a small amount of silica gel was added to the filtrate. 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 (3:17) as the eluent gave (+)-**1** (23 mg, 85%) as a colorless oil: ORD (*c* 0.60, EtOH) [α] (nm) +23.3° (589), +25.0° (550), +30.0° (500), +37.7° (450), +47.7° (400), +70.0° (350), +106.4° (300), +206.7° (250); IR (Nujol, cm^{-1}) 3350, 1585 (NH); ^{1}H NMR (CD_3OD) δ 1.68−2.35 (m, 4H), 2.75 (m, 2H), 4.04 (m, 1H), 4.93 (overlapped with H_2O in CD_3OD, 1′−H), 7.03 (s, 1H), 7.65 (s, 1H); ^{13}C NMR (CD_3OD) 29.9, 33.1, 47.3, 76.6, 82.1, 118.0, 137.0, 140.3; EIMS m/z 167(M^+); HRMS m/z 167.1060 (calcd for $C_8H_{13}N_3O$ 167.1058).

Ethyl 4-(5-*O*-Benzyl-2,3-dideoxy-2-*Se*-phenyl-2-seleno-α-D-*threo*-pentofuranosyl)imidazole-1-carboxylate (22). By the same procedure as used for the preparation of **18**, α-anomer **16** (116 mg, 0.28 mmol) was converted to **22** (149 mg, 100%) as a colorless oil: IR (Nujol, cm^{-1}) 1765 (COO); ^{1}H NMR ($CDCl_3$) δ 1.37 (t, 3H, J = 7.2 Hz, CH_3), 1.96 (ddd, 1H, J = 8.4, 10.1, 12.8 Hz), 2.52 (dt, 1H, J = 7.2, 12.9 Hz), 3.47 (d, 2H, J = 5.1 Hz), 3.95 (dt, 1H, J = 8.2, 10.2 Hz), 4.30−4.45 (m, 1H), 4.40 (q, 2H, J = 7.2 Hz), 4.50 (s, 2H), 4.80 (d, 1H, J = 8.2 Hz), 7.08−7.44, (m, 11H), 7.98 (s, 1H); HRMS m/z 486.1057 (calcd for $C_{24}H_{26}N_2O_4Se$ 486.1056); EIMS m/z 486 (M^+).

Ethyl 4-(5-*O*-Benzyl-2,3-dideoxy-α-D-*glycero*-pentofuranosyl)imidazole-1-carboxylate (23). A mixture of **22** (149 mg, 0.31 mmol), Et_3B (0.34 mL, 0.34 mmol), and Bu_3SnH (0.12 mL, 0.46 mmol) in benzene (8 mL) was treated at room temperature as described for the preparation of **19** to give **23** (97 mg, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.36 (t, 3H, J = 7.1 Hz), 1.67−1.78 (m, 1H), 1.86−2.32 (m, 3H), 3.48 (d, 2H, J = 5.0 Hz), 4.28−4.45 (m, 1H), 4.39 (q, 2H, J = 7.1

Hz), 4.54 (s, 2H), 4.99 (t, 1H, J = 6.4 Hz), 7.21−7.30 (m, 6H), 8.02 (s, 1H); EIMS m/z 330 (M^+).

Ethyl 4-(2,3-Dideoxy-α-D-*glycero*-pentofuranosyl)imidazole-1-carboxylate (24). The mixture of **23** (48 mg, 0.14 mmol), cyclohexene (0.44 mL, 4.32 mmol), and 20% $Pd(OH)_2$−C (29 mg) in EtOH (6 mL) was refluxed to give **24** (33 mg, 97%) as a colorless oil by the same procedure for the preparation for **20**: ^{1}H NMR (CD_3OD) δ 1.46 (t, 3H, J = 7.0 Hz), 1.76−2.40 (m, 4H), 3.57 (dd, 1H, J = 5.6, 11.9 Hz), 3.65 (dd, 1H, J = 4.2, 11.9 Hz), 4.27 (m, 1H), 4.52 (q, 2H, J = 7.0 Hz), 5.02 (t, 1H, J = 7.0 Hz), 7.50 (s, 1H), 8.25 (s, 1H); EIMS m/z 240 (M^+).

Ethyl 4-(5-Phthaloylamino-2,3,5-trideoxy-α-D-*glycero*-pentofuranosyl)imidazole-1-carboxylate (25). A mixture of **24** (67 mg, 0.28 mmol), phthalimide (61 mg, 0.42 mmol), 4-dimethylaminophenyldiphenylphosphine (179 mg, 0.56 mmol), and DIAD (0.11 mL, 0.56 mmol) was stirred overnight at room temperature to give **25** (103 mg, quant) as a colorless oil: ORD (c 2.47, EtOH) [α] (nm) +36.5° (589), +43.8° (550), +53.6° (500), +71.8° (450), +99.8° (400), +145.3° (357); ^{1}H NMR ($CDCl_3$) δ 1.34 (t, 3H, J = 7.1 Hz), 1.66−1.84 (m, 1H), 1.98−2.41 (m, 3H), 3.62 (dd, 1H, J = 5.2, 13.5 Hz), 3.83 (dd, 1H, J = 7.9, 13.5 Hz), 4.47 (q, 2H, J = 7.0 Hz), 4.51 (m, 1H), 5.04 (t, 1H, J = 6.1 Hz), 7.23 (s, 1H), 7.60−7.69 (m, 2H), 7.75−7.81 (m, 2H), 8.00 (s, 1H); EIMS m/z 369 (M^+).

(−)-4(5)-[(2*S*,5*S*)-(5-Aminomethyl)tetrahydrofuran-2-yl]imidazole (2). By the same procedure for the preparation of **1**, phthalimide **25** (105 mg, 0.28 mmol) was converted into **2** (44 mg, 94%) as a colorless oil: ORD (c 1.25, EtOH) [α] (nm) −5.4° (589), −9.0° (550), −12.2° (500), −15.0° (450), −23.0° (400), −42.9° (350), −102.7° (300), −272.3° (266); IR (Nujol, cm^{-1}) 3350, 1585 (NH); ^{1}H NMR (CD_3OD) δ 1.61−1.82 (m, 1H), 2.02−2.38 (m, 3H), 2.73 (d, 2H), 4.17 (m, 1H), 5.02 (t, 1H, J = 6.5 Hz), 7.02 (s, 1H), 7.64 (s, 1H); ^{13}C NMR (CD_3OD) δ 30.6, 33.5, 47.1, 76.0, 81.5, 117.9, 137.0, 140.4; HRMS m/z 167.1075 (calcd for $C_8H_{13}N_3O$ 167.1058); EIMS m/z 167 (M^+).

4(5)-(5-*O*-Benzyl-2,3-dideoxy-β-D-*glycero*-pento-2-enofuranosyl) imidazole (26). A solution of **15** (296 mg, 0.72 mmol) in CH_2Cl_2 (25 mL) containing a catalytic amount of pyridine (1 drop) was cooled in an ice−water bath. A 35% solution of hydrogen peroxide (0.37 mL) diluted with water (0.74 mL) was added dropwise to the above solution over a period of 20 min with stirring. The temperature of the reaction mixture was allowed to come to 20 °C slowly, and the mixture was stirred at this temperature for an additional 2 h. The reaction mixture was diluted with CH_2Cl_2, washed with water, saturated $NaHCO_3$ solution, and finally water. After the reaction mixture was dried, the solvent was removed and the residue was chromatographed over a column of silicagel using 5% MeOH in EtOAc for elution to give **26** (155 mg, 84%) as an oil: ^{1}H NMR ($CDCl_3$) δ 3.79 (dd, 1H, J = 2.7, 10.8 Hz), 3.97 (dd, 1H, J = 3.0, 10.8 Hz), 4.59 (dd, 2H, J = 10.2 Hz, 29.1 Hz), 5.11 (br s, 1H), 5.81−6.01 (m, 3H), 6.85 (s, 1H), 6.90 (s, 1H), 7.40 (s, 5H); EIMS m/z 256 (M^+); HRMS m/z 256.1208 (calcd for $C_{15}H_{16}N_2O_2$ 256.1211).

4(5)-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-imidazole (27). Sodium naphthalenide (1 M in DME) (8 mL, 8.0 mmol) was added dropwise over 10 min to a solution of **26** (136 mg, 0.53 mmol) in DME (6 mL) at room temperature. The reaction mixture was stirred at room temperature for 10 min. The reaction was quenched with MeOH (3 mL), and a small amount of silica gel was added to the solution. The solvent was evaporated to give a coated silica gel, which was subsequently placed in a column. Chromatography first with EtOAc and then 5% MeOH in EtOAc as the eluent gave **27** (82 mg, 93%) as an oil: ^{1}H NMR ($CDCl_3$) δ 3.77 (d, 1H, J = 12.0 Hz), 3.98 (d, 1H, J = 12.0 Hz), 5.06 (s, 1H), 5.78−5.96 (m, 3H), 6.91 (s, 1H), 7.47 (s, 1H); EIMS m/z 166 (M^+); HRMS m/z 166.0749 (calcd for $C_8H_{10}N_2O_2$ 166.0742).

Ethyl 4-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-imidazole-1-carboxylate (28). A solution of ethyl chloroformate (26 mg, 0.24 mmol) in THF (5 mL) was added dropwise over 20 min to a stirred solution of **27** (39 mg, 0.24 mmol) and 4-DMAP (32 mg, 0.26 mM) in THF (13 mL) at room temperature. After 10 min, the solvent was evaporated to give a residual oil, which was subsequently dissolved in brine (15 mL). The aqueous solution was extracted five times with EtOAc (50 mL × 5). The extract was dried and evaporated to give a crude oil, which was purified by column chromatography using EtOAc to give **28** (39 mg, 70%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.41 (t, 3H, J = 7.5 Hz), 3.72 (dd, 1H, J = 1.5, 12.3 Hz), 3.97 (dd, 1H, J = 1.2, 12.3 Hz), 4.46 (q, 2H, J = 7.5 Hz), 5.07 (s, 1H), 5.75 (s, 1H), 5.81 (d, 1H, J = 6.0 Hz), 5.98 (d, 1H, J = 6.0 Hz), 7.35 (s, 1H), 8.09 (s, 1H); EIMS m/z 239 (M^+ + H); HRMS m/z 239.1026 (calcd for $C_{11}H_{15}N_2O_4$ 239.1031).

4(5)-(5-Amino-2,3,5-trideoxy-β-D-*glycero*-pent-2-enofuranosyl)imidazole (3). Phthalimde (49 mg, 0.33 mmol) and Ph_3P (116 mg, 0.44 mmol) were dissolved in a solution of **28** (53 mg, 0.22 mmol) in THF (10 mL). To this mixture was added DEAD (0.08 mL, 0.44 mmol) slowly with stirring at 0 °C. The reaction mixture was stirred for 19 h at room temperature and then quenched with two drops of MeOH. The whole was evaporated to give a residue, which was chromatographed [EtOAc−hexane (50% to 70%)] to give a mixture of the desirable phthalimide compound [EIMS m/z 367 (M^+); HRMS m/z 367.1174 (calcd for $C_{19}H_{17}N_3O_5$ 367.1167)] and Ph_3P═O. The mixture was dissolved in MeOH (10 mL), and 40% $MeNH_2$ in MeOH (1.7 mL, 22.1 mmol) was added to the solution. The reaction mixture was refluxed for 0.5 h, and then a small amount of silica gel was added to the cooled solution. The solvent was evaporated to give a coated silica gel, which was subsequently placed in a column (Chromatorex NH-DM 1020). Chromatography using a gradient solvent system (5% to 20% in MeOH−EtOAc) gave (+)-**3** (31 mg, 84%) as an oil: ORD (c 1.69, EtOH) [α] (nm) +38.6 (589), +50.4 (550), +62.3 (500), +90.2 (450), +121.7 (400); ^{1}H NMR (CD_3OD) δ 2.81 (m, 2H), 4.90 (overlapped with H_2O in CD_3OD, 4′-H), 5.81 (d, 1H, J = 2.1 Hz), 6.01 (m, 2H), 7.02 (s, 1H), 7.64 (s, 1H); EIMS m/z 165 (M^+); HRMS m/z 165.0897 (calcd for $C_8H_{11}N_3O$ 165.0901).

4(5)-(5-*O*-Benzyl-2,3-dideoxy-α-D-*glycero*-pent-2-enofuranosyl)imidazole (29). A mixture of **16** (341 mg, 0.83 mmol), 35% H_2O_2 (0.43 mL), and pyridine (1 drop) in CH_2Cl_2 (30 mL) was stirred for 3 h at room temperature to give **29** (198 mg, 94%) by the same procedure for the preparation of **26**: ^{1}H NMR ($CDCl_3$) δ 3.59 (d, 2H, J = 5.0 Hz), 4.61 (s, 2H), 5.13 (m, 1H), 5.95 (m, 3H), 6.90 (s, 1H), 7.36 (s, 5H), 7.53 (s, 1H); EIMS m/z 256 (M^+); HRMS m/z 256.1218 (calcd for $C_{15}H_{16}N_2O_2$ 256.1211).

4(5)-(2,3-Dideoxy-α-D-*glycero*-pent-2-enofuranosyl)-imidazole (30). Sodium naphthalenide (1 M, 5.0 mL, 5.0 mmol) in DME was added slowly over 10 min to a solution of **29** (213 mg, 0.83 mmol) in DME (12 mL) at room temperature. The mixture was stirred at the same temperature for 0.5 h. The same workup and purification as used for the preparation of **27** gave **30** (127 mg, 92%) as an oil: ^{1}H NMR (CD_3OD) δ 3.77 (dd, 1H, J = 4.8, 11.4 Hz), 3.83 (dd, 1H, J = 3.9 Hz, 11.4 Hz), 5.20 (overlapped with H_2O in CD_3OD, 4′-H), 6.07 (d, 1H, J = 5.7 Hz), 6.21 (m, 2H), 7.25 (s, 1H), 8.01 (s, 1H); EIMS m/z 166 (M^+); HRMS m/z 166.0747 (calcd for $C_8H_{10}N_2O_2$ 166.0742).

Ethyl 4-(2,3-Dideoxy-α-D-*glycero*-pent-2-enofuranosyl)-imidazole-1-carboxylate (31). A solution of ethyl chloroformate (43 mg, 0.40 mmol) in dioxane (0.5 mL) was added dropwise over 5 min to a stirred solution of **30** (60 mg, 0.36 mmol) and 4-DMAP (44 mg, 0.36 mmol) in dioxane (20 mL) at room temperature. The mixture was stirred for 0.5 h to give **31** (73 mg, 84%) by the same procedure as used for the preparation of **28**: oil; ^{1}H NMR ($CDCl_3$) δ 1.42 (t, 3H, J = 7.4 Hz), 2.40 (brs, 1H), 3.64 (dd, 1H, J = 5.0, 11.6 Hz), 3.80 (dd, 1H, J = 3.2, 11.6 Hz), 4.46 (q, 2H, J = 7.4 Hz), 5.12 (brs, 1H), 5.88 (d, 1H, J = 5.4 Hz), 5.96 (d, 1H, J = 6.0 Hz), 6.09 (d, 1H, J = 6.0 Hz), 7.35 (s, 1H), 8.09 (s, 1H); EIMS m/z 238 (M^+); HRMS m/z 238.0956 (calcd for $C_{11}H_{14}N_2O_4$ 238.0953).

4(5)-(5-Amino-2,3,5-trideoxy-α-D-*glycero*-pent-2-enofuranosyl)imidazole (4). Phthalimide (117 mg, 0.80 mmol) and Ph_3P (279 mg, 1.1 mmol) were dissolved in a solution of **31** (127 mg, 0.53 mmol) in THF (15 mL). To this mixture was added slowly DEAD (0.18 mL, 1.06 mmol) with stirring at 0 °C. The reaction mixture was stirred for 14 h at room temperature to give a mixture of the phthalimide compound [EIMS m/z 367 (M^+); HRMS m/z 367.1174 (calcd for $C_{19}H_{17}N_3O_5$ 367.1167)] and Ph_3P═O. The mixture was then dissolved in

MeOH (15 mL), and 40% $MeNH_2$ in MeOH (4.1 mL) was added to the solution. The reaction mixture was treated by the same procedure as used for the preparation of **3** to **4** (88 mg, quant): oil; ORD (*c* 2.62, EtOH) [α] (nm) −195.0 (589), −229.5 (550), −298.3 (500), −401.5 (450), −573.6 (400), −883.4 (350); ^{1}H NMR (CD_3OD) δ 2.80 (m, 2H), 5.02 (overlapped with H_2O in CD_3OD, 4′−H), 5.92 (d, 1H, J = 5.2 Hz), 6.09 (m, 2H), 7.02 (s, 1H), 7.67 (s, 1H); ^{13}C NMR (CD_3OD) δ 40.8, 76.7, 82.2, 112.1, 123.7, 125.2, 130.9; CIMS *m*/*z* 166 (M^+ + H); HRMS *m*/*z* 166.0989 (calcd for $C_8H_{12}N_3O$ 166.0980).

1-*N*,*N*-Dimethylsulfamoyl-2-*tert*-butyldimethylsilyl-5-(5-*tert*-butyldimethylsilyloxymethylfuran-2-yl)-1*H*-imidazole (36). Carbon tetrachloride (1.31 mL, 13.6 mmol) was added to a stirred solution of **33** (2.58 g, 8.50 mmol) in THF (30 mL). After the solution was cooled to −70 °C, hexamethylphosphorus triamide (2.03 mL, 11.2 mmol) was added dropwise over 5 min, and the mixture was stirred at the same temperature for 5 min. Then the resulting gelatinoid was allowed to warm to room temperature and further stirred for 2 h. The solvent was evaporated to give a residue, which was dissolved in diethyl ether−petroleum ether (1:1). The resulting insoluble material was removed by decantation, and the organic layer was evaporated to give crude **34** as an orange oil. On the other hand, a solution of 1.6 M BuLi in hexane (10.6 mL, 17 mmol) was added slowly over 10 min to a solution of 1-*N*,*N*-dimethylsulfamoyl-2-*tert*-butyldimethylsilylimidazole (4.90 g, 17 mmol) in THF (20 mL) to give white precipitates of **11** at −70 °C. After the suspension was stirred at the same temperature for 0.5 h, a solution of **34** in THF (15 mL) was added over 10 min to the mixture, and the dry ice bath was removed. The resulting mixture was stirred for 0.5 h at room temperature and then refluxed for 1 h. Then a small amount of water was added to the reaction mixture and the solvent was removed by evaporation under reduced pressure. The residue was dissolved in EtOAc, and the solution was washed with H_2O and brine and dried. Evaporation of the solvent gave crude glycal **35** as a brown oil. Silica gel (BW127ZH) (5.2 g) was added to a solution of **35** in CH_2Cl_2 (50 mL), and the resulting suspension was stirred at room temperature for 3 days. The silica gel was removed by filtration, washed with EtOAc, and the filtrate was diluted with EtOAc. The solution was washed with H_2O and brine, dried, and evaporated. The residue was purified by column chromatography using EtOAc−hexane (1:19) to give **36** (1.51 g, 36% overall yield from **33**) as white powder, which was recrystallized from hexane to give colorless needles: mp 92.5−93.0 °C; IR (Nujol, cm^{-1}) 1630, 1580 (C=C), 1160 (SO_2); ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 6H), 0.42 (s, 6H), 0.90 (s, 9H), 1.06 (s, 9H), 2.57 (s, 6H), 4.65 (s, 2H), 6.32 and 6.62 (each d, each 1H, J = 3.4 Hz), 7.29 (s, 1H); EIMS *m*/*z* 499 (M^+). Anal. Calcd for $C_{22}H_{41}N_3O_4SSi_2$: C, 52.87; H, 8.27; N, 8.41. Found: C, 52.74; H, 8.28; N, 8.31.

1-*N*,*N*-Dimethylsulfamoyl-5-(5-hydroxymethylfuran-2-yl)-1*H*-imidazole (37). A 1 M THF solution of TBAF (3.0 mL, 3.0 mmol) was added to a solution of **36** (504 mg, 1.01 mmol) in THF (10 mL) at 0 °C. After the reaction mixture was stirred for 1 h at this temperature, the solvent was removed by evaporation under reduced pressure to give a residue. It was then dissolved in EtOAc−hexane (3:1), and the solution was washed with H_2O and brine and dried. Evaporation of the solvent gave a crude oil, which was purified by column chromatography using EtOAc to give **37** (264 mg, 96%) as an oil: IR (neat, cm^{-1}) 3300 (OH), 1630, 1580 (C=C), 1390, 1170 (SO_2); ^{1}H NMR ($CDCl_3$) δ 2.72 (s, 6H), 4.63 (s, 2H), 6.38 and 6.70 (each d, each 1H, J = 3.3 Hz), 7.26 and 8.01 (each s, each 1H); EIMS *m*/*z* 271 (M^+); HRMS *m*/*z* 271.0619 (calcd for $C_{10}H_{13}N_3O_4S$ 271.0626).

1-*N*,*N*-Dimethylsulfamoyl-5-(5-aminomethylfuran-2-yl)-1*H*-imidazole (38). Phthalimide (74 mg, 0.50 mmol) and Ph_3P (354 mg, 1.35 mmol) were dissolved in a solution of **37** (122 mg, 0.45 mmol) in THF (15 mL). To this mixture was added DEAD (0.23 mL, 1.35 mmol) at 0 °C and the resulting mixture stirred for 0.5 h at room temperature. The reaction was quenched with two drops of H_2O, and the whole was evaporated to give crude phthalimide (yellow powder). A solution of the phthalimide and $NH_2NH_2 \cdot H_2O$ (0.11 mL, 2.25 mmol) in EtOH (15 mL) was then refluxed for 1 h to give **38** (53 mg, 44% from **37**) as an oil by the same procedure as used for the preparation of **1**: IR (neat, cm^{-1}) 1390, 1170 (SO_2); ^{1}H NMR ($CDCl_3$) δ 2.70 (s, 6H), 3.85 (s, 2H), 6.22 and 6.65 (each d, each 1H, J = 3.3 Hz), 7.22 and 7.99 (each s, each 1H); EIMS *m*/*z* 270 (M^+); HRMS *m*/*z* 270.0786 (calcd for $C_{10}H_{14}N_4O_3S$ 270.0793).

4(5)-(5-Aminomethylfuran-2-yl)-1*H*-imidazole (5). A solution of **38** (7 mg, 0.03 mmol) in THF (5 mL) was refluxed with 1.5 N HCl (1 mL) for 1 h and then cooled. The solution was neutralized by addition of 30% NH_4OH, and a small amount of Chromatorex NH-DM 1020 was added to the 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 (1:9) as the eluent gave **5** (4 mg, 91%) as an oil: ^{1}H NMR (CD_3OD) δ 3.83 (s, 2H), 6.30 and 6.51 (each d, each 1H, J = 3.3 Hz), 7.30 and 7.71 (each s, each 1H); EIMS *m*/*z* 163 (M^+); HRMS *m*/*z* 163.0736 (calcd for $C_8H_9N_3O$ 163.0745).

The configuration counterparts were synthesized by the present method. The ORD values of main compounds are described below.

ent-**15**: ORD (*c* 1.03, EtOH) [α] (nm) +33.2° (589), +39.0° (550), +46.8° (500), +62.4° (450), +85.9° (400), +130.7° (350), +240.0 (308).

ent-**16**: mp 117.5−118.5 °C; ORD (*c* 1.52, EtOH) [α] (nm) −21.1° (589), −28.0° (550), −34.3° (500), −42.2° (450), −58.1° (400), −80.5° (350), −170.3° (308).

ent-**21**: mp 98−98.5 °C; ORD (*c* 0.95, EtOH) [α] (nm) −102.1° (589), −120.6° (550), −146.0° (500), −190.5° (450), −266.7° (400), −390.5° (350), −535.2° (374).

ent-**25**: ORD (*c* 2.21, EtOH) [α] (nm) −40.7° (589), −48.9° (550), −62.4° (500), −81.4° (450), −122.2° (400), −198.2° (350).

ent-**1**: ORD (*c* 0.53, EtOH) [α] (nm) −22.9° (589), −22.9° (550), −28.6° (500), −45.7° (450), −57.2° (400), −91.4° (350), −131.4° (300), −262.9° (250).

ent-**2** (imifuramine): ORD (*c* 1.41, EtOH) [α] (nm) +5.7° (589), +5.7° (550), +18.5° (500), +15.5° (450), +25.5° (400), +48.2° (350), +102.1° (300).

ent-**3**: ORD (*c* 1.60, EtOH) [α] (nm) −37.6° (589), −43.9° (550), −60.2° (500), −84.0° (450), −115.4° (400).

ent-**4**: ORD (*c* 2.24, EtOH) [α] (nm) +193.3° (589), +225.5° (550), +289.9° (500), +386.6° (450), +547.7° (400).

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Supporting Information Available: Copies of ^{1}H NMR spectra for the following compounds: **1**−**5**, **7**−**10**, **12**−**16**, **18**−**31**, and **36**−**38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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