SYNTHESIS OF 4(5)-(5'-AMINO-5'-DEOXY-α-L-ARABINOFURANOSYL)IMIDAZOLE AND ITS 5'-DERIVATIVES USING MODIFIED MITSUNOBU CYCLIZATION: SYNTHETIC STUDIES TOWARD NOVEL HISTAMINE H_3-LIGANDS

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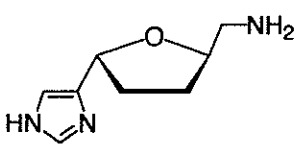
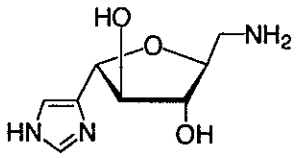
Abstract - The modified Mitsunobu cyclization of 4-(2',3',5'-tri-*O*-benzyl-L-arabinosyl)imidazole (**11*RS***) using *N*,*N*,*N*',*N*'-tetramethylazodicarboxamide and Bu_3P followed by ethoxycarbonylation produced a mixture (α / β = 20 / 1) of ethyl 4-(2',3',5'-tri-*O*-benzyl-L-arabinofuranosyl)-imidazole-1-carboxylate (**13**). The compound (**13**) was converted into ethyl 4-(5'-deoxy-5'-phthaloylamino-L-arabinofuranosyl)imidazole-1-carboxylate (**15**), which was subsequently led to 4-(5'-amino-5'-deoxy-α-L-arabinofuranosyl)imidazole (**2α**). The 4(5)-{5-[*N*-(4-chlorophenyl)thio-ureido]-α-L-arabinofuranosyl}imidazole (**18**), 4(5)-{5-[*N*-(4-chlorophenyl)-ureido]-α-L-arabinofuranosyl}imidazole (**19**), and 1-cyano-2-methyl-3-{5-deoxy–1-[1*H*-imidazol-4(5)-yl]-α-L-arabinofuranosyl}guanidine (**20**) were efficiently synthesized from **2α**.

Introduction

The histamine H_3(H_3) receptors[1] exist on histaminergic fibers in the brain and modulate the synthesis and release of histamine as an autoreceptor.[2] Moreover, H_3-receptors have been shown to be heteroreceptors[3] which modulate the release of a number of different neurotransmitters.[3,4] This type of receptor can be also found in many peripheral tissues.[1] *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.[3,4] H_3-Agonists are regarded as a target for new therapeutics of bronchial asthma,[5] and H_3-antagonists are now expected to be potential drugs for memory degenerative disorders like Alzheimer's disease.[3,4]



1 (Imifuramine)



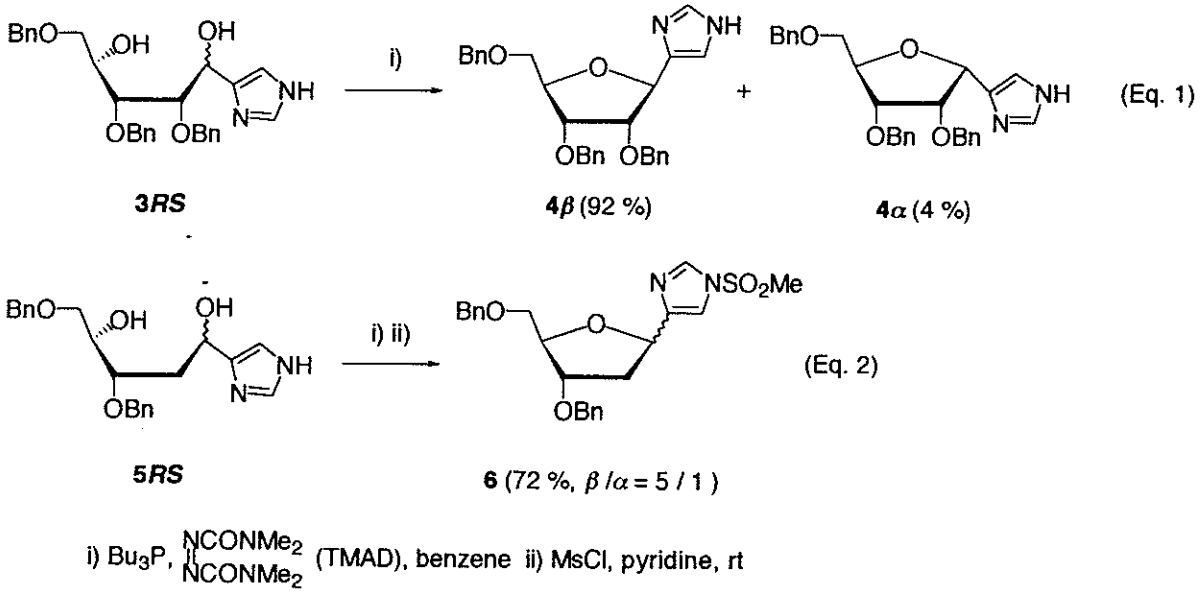
2α

Figure 1

We recently communicated[6] the synthesis of novel *cis*- and *trans*-imidazole *C*-nucleoside derivatives using an unprecedented synthetic method characterized by efficient use of a PhSe group for the formation of the tetrahydrofuran ring. Of particular interest, the results of an *in vivo* brain microdialysis[7] indicated that, among them, only (+)-4(5)-[5-(aminomethyl)tetrahydrofuran-2-yl]imidazole (imifuramine, **1**)[6a] exhibited a clear H_3-agonistic activity. The activity of imifuramine measured by microdialysis was approximately equal to that of immepip.[8] To the contrary, imifuramine exhibited a weak H_3-agonistic activity ($pD_2 = 4$) in an *in vitro* test using guinea pig ileum preparation, compared to that ($pD_2 = 8$) of *R*-α-methylhistamine.[9]

The finding of imifuramine encouraged us to synthesize 4(5)-(5'-amino-5'-deoxy-α-L-arabino-furanosyl)imidazole (**2α**), the configurations of which at the C1' and C4' positions were consistent with those of imifuramine. **2α** may be used as a base compound for the synthetic study toward novel H_3-agonists and antagonists. Furthermore, little work has been done concerning the synthesis and biological evaluation of the α-L-*C*-nucleosides,[10] the sugar moiety of which has unnatural configuration.[11]

We have recently reported[12] that the modified Mitsunobu cyclization of a 1:1 anomeric mixture (**3*RS***) having an unsubstituted imidazole, using *N,N,N',N'*-tetramethylazodicarboxamide (TMAD)[13] and Bu_3P, stereoselectively afforded a benzylated β-ribofuranosylimidazole (**4β**)in 92% yield, accompanied with a small amount of the α-anomer (**4α**)(4 %) (Scheme 1, Eq.1). Importantly, the unsubstituted imidazole moiety was indispensable for the exclusive formation of β-anomers. On the other hand, Yokoyama *et al.*[14] had reported the synthesis of *C*-ribonucleosides having typical aromatic heterocycles, in which the



Scheme 1

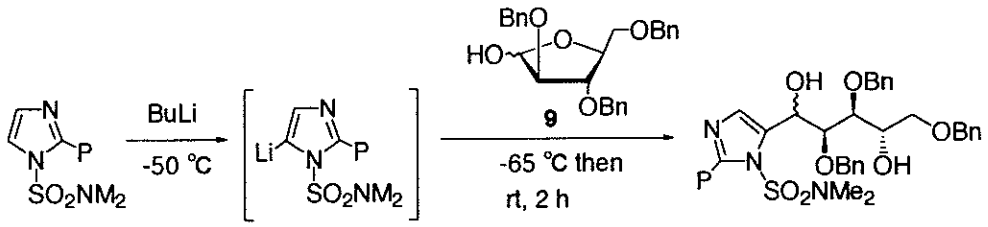
cyclization of the corresponding diols proceeds through intramolecular SN2 reaction under standard Mitsunobu conditions (DEAD, Ph_3P), and the orientation of the glycosidic linkage is controlled by the C1' configuration of the substrate: one isomer affords an α-anomer and the other, a β-anomer. In the case of 2'-deoxy compound (***5RS***),[12a,b] the modified Mitsunobu reaction produced a 5 : 1 mixture (**6**) of β- and α-anomers (Scheme 1, Eq. 2). These results suggest that the benzyloxy groups at the C2'-position may act as the directing group to control thermodynamically the stereochemistry of imidazole *C*-nucleosides. Therefore, we expected that **2**α could be selectively synthesized starting from L-arabinose having the C2β-OH group. In this paper, we report the synthesis of α-L-arabinofuranosyl-nucleosides (**2**α) as an extension of our synthetic methodology using the modified Mitsunobu cyclization. Further, in connection with this study, 5'-amino derivatives (**18**, **19** and **20**) were synthesized from **2**α.

RESULTS AND DISCUSSION

We first carried out a coupling reaction[12b] of 2,3,5-tri-*O*-benzyl-L-arabinofuranose (**9**)[15] with lithium salt (**8**) of 2-*tert*-butyldimethylsilyl-*N*,*N*-dimethylimidazole-1-sulfonamide (**7**) (Table 1). When a 1.6 M

solution of *n*-BuLi in hexane was added dropwise to a THF solution of **7** at –50℃, a white solid of **8** was precipitated in the bottom of the flask (Table 1, Run 1). Compound (**9**) in THF was then added to the resulting suspension at –65℃ and the whole was stirred at room temperature for 2 h. However, this operation afforded an epimeric mixture (**10*RS***) in only a low yield. On the other hand, use of toluene as the solvent gave **10*RS*** in 88 % yield, but its reproducibility was low and the isolated yields were variable (Table 1, Run 2). From these results, we surmised that the generation of the lithium salt (**8**) might be incomplete in toluene, since the white solid of **8** was not formed in toluene. When we used THF for the generation of the lithium salt (**8**) followed by toluene for the addition of **9**, the adduct (**10*RS***) was successfully obtained in 96% yield as a 72:28 diastereomixture of **10*R*** and **10*S*** (Table 1, Run 3). Accordingly, the lithium salt (**8**) in toluene-THF (1:1) may be stabilized by its aggregation state in contrast to **8** in THF at elevated temperature. The respective epimers (**10*R***) (polar) and (**10*S***) (less polar) were separated easily by silica gel column chromatography. The C1' stereochemical assignments of **10*R*** and **10*S***, respectively, were based on the analogy of our previous reports.[6,12] In ^{1}H-NMR, a

Table 1. Reaction of **9** with lithium salt (**8**)



Run	Solvent		Yield(%) [1]
1	i) THF	ii) THF	0 - 35
2	i) toluene	ii) toluene	8 - 88
3	i) THF	ii) toluene	96 [2]

1) Isolated Yields of **10*RS*** 2) A 72 : 28 diastereomixture of **10*R*** and **10*S***

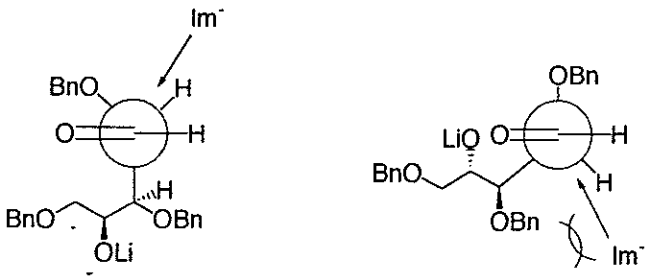
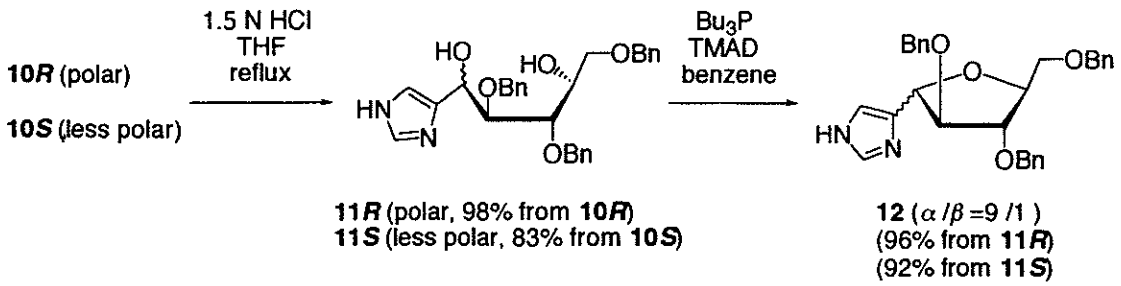


Figure 2

small $J_{1',2'}$ coupling constant (br s, $J_{1',2'} = < 2$ Hz) was observed in major isomer (**10*R***) compared to that of minor (**10*S***) (d, $J_{1',2'} = 7.3$ Hz) having a 1', 2'-*anti*-parallel orientation. The preference of **10*R*** is rationalized by applying the Felkin-Anh model[16] as illustrated in Figure 2.

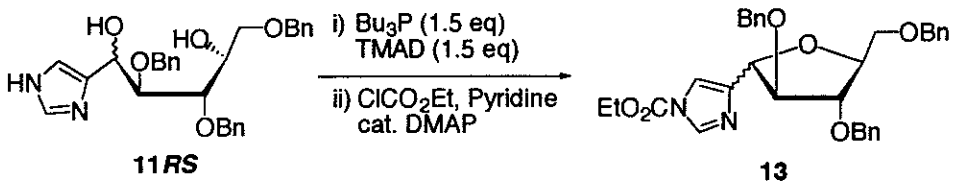
Hydrolysis of **10*R*** in refluxing 1.5N HCl afforded a diol (**11*R***) having unsubstituted imidazole in 98% yield (Scheme 2). The modified Mitsunobu cyclization of **11*R*** with TMAD and Bu_3P at room temperature in benzene, as expected, produced a 9:1 mixture (**12**) (96 %) of α- and β-anomers, the isolation of which by column chromatography was difficult. The ratio was assigned from those of methine protons at C-1' in ^{1}H-NMR (δ 5.10 for **12α** *vs* 5.18 for **12β**). The *S*-isomer (**11*S***) also afforded a 9:1 mixture (92%) of **12α** and **12β** (Scheme 2). These experiments indicated the α-anomer (**12α**) could be preferentially supplied without separation of the isomers (**11*R*** and **11*S***).

We therefore examined the modified Mitsunobu cyclization of epimeric mixture (**11*RS***) under various conditions followed by ethoxycarbonylation[12c] for the ease of isolation (Table 2). Although the reaction showed low selectivity (**13α** / 13β = 4.5 : 1) in THF (Table 2, Run 1), the α / β ratio was finally



Scheme 2

Table 2. The Modified Mitsunobu Cyclization of **11*RS***



11*RS* **13**

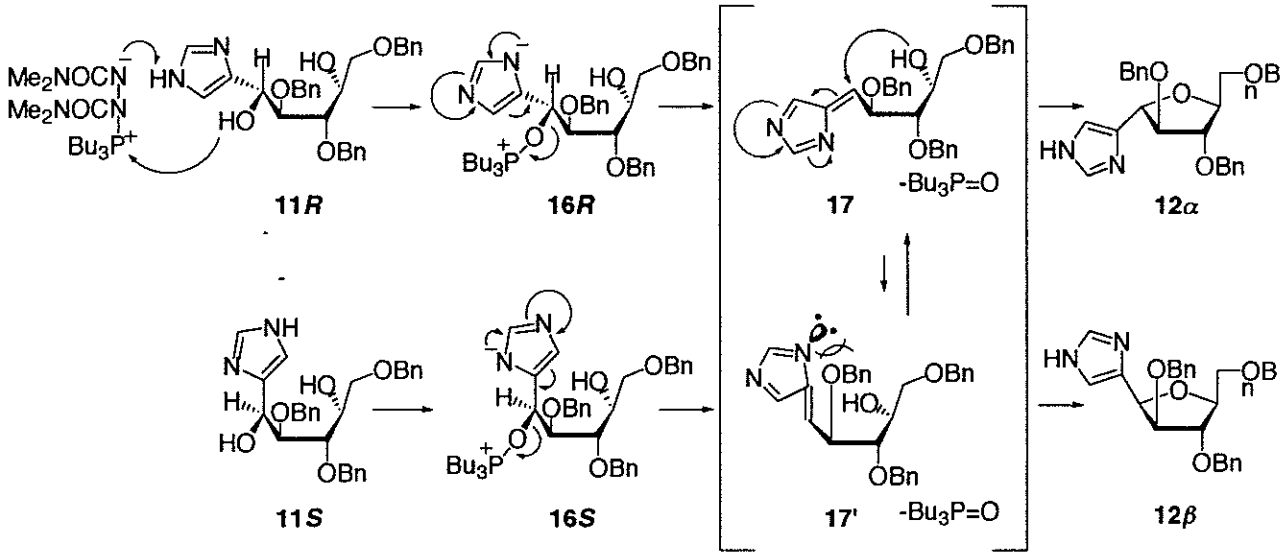
Run	Solvent	Temp. (℃)	Time (h)	Yield (%)	**13α/13β**
1	THF	rt	overnight	95	4.5 / 1
2	benzene	rt	overnight	89	9 / 1
3	toluene	0	2	82	9.5 / 1
4	CH_2Cl_2	0	2	64	15 / 1
5	CH_2Cl_2	-35	1.5	95	20 / 1

improved to give a 20:1 anomeric mixture in CH_2Cl_2 at –35℃ (Table 2, Run 5). From these results, it became clear that not only the directing group at C2' but also the solvent effect significantly influences the α / β ratio of *C*-nucleosides.

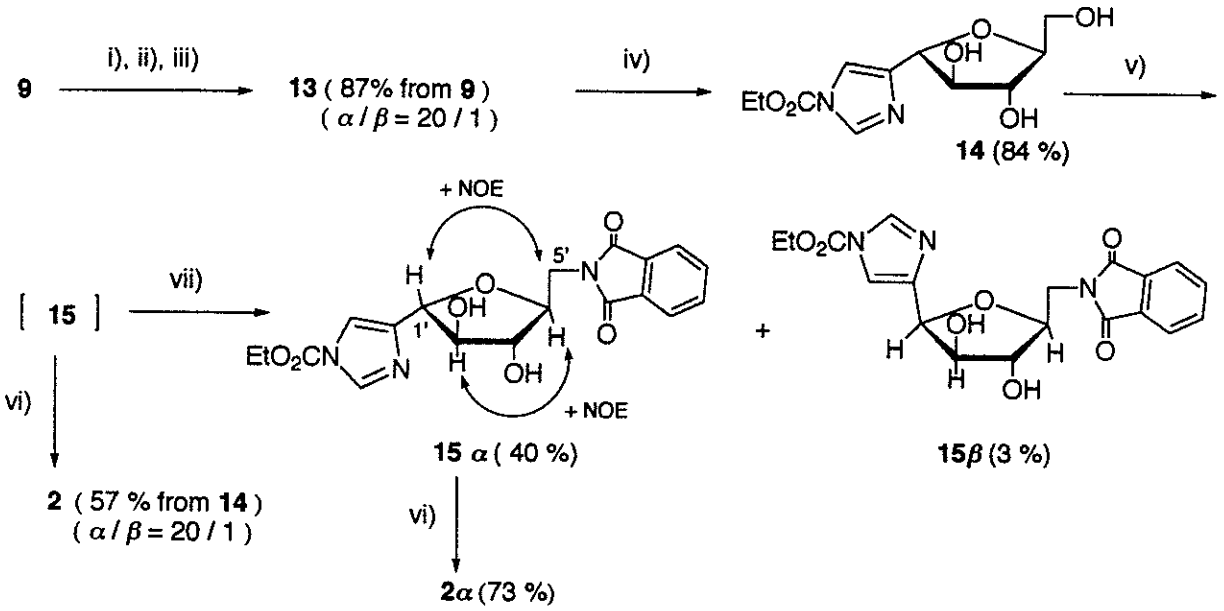
The α-selectivity in this reaction may be explained as illustrated in Scheme 3. Reaction of the TMAD-Bu_3P adduct with **11*R*** forms the zwitterion (**16*R***). Preferential elimination of Bu_3P=O from **16*R*** leads to an active form (**17**) of the imidazole ring. Spontaneous cyclization gives α-anomer (**12**α).

Although the isomer (**11*S***) similarly leads to the active species (**17'**), it exclusively supplies the α-anomer *via* rotomer (**17**) which is thermodynamically more stable. Thus, the α-stereoselectivity of the arabinofuranosylimidazole (**12**) may be facilitated by stereoelectronic repulsion in **17'**.

As results of these experiments, *N*-ethoxycarbonylcompound (**13**) (α / β = 20 / 1) could be obtained in 87 % overall yield from the starting tribenzylarabinose (**9**) without isolation of diols (**10*R***) and (**10*S***), as shown in Scheme 4. Debenzylation of **13** with $Pd(OH)_2$-C in cyclohexene afforded triol (**14**) in 84 % yield. Phthaloylimination of **14** afforded crude phthalimide (**15**), which was subjected to subsequent hydrazine degradation to give L-arabinofuranosylimidazole (**2**) (57 % from **14**) as a 20:1 mixture of **2**α



Scheme 3



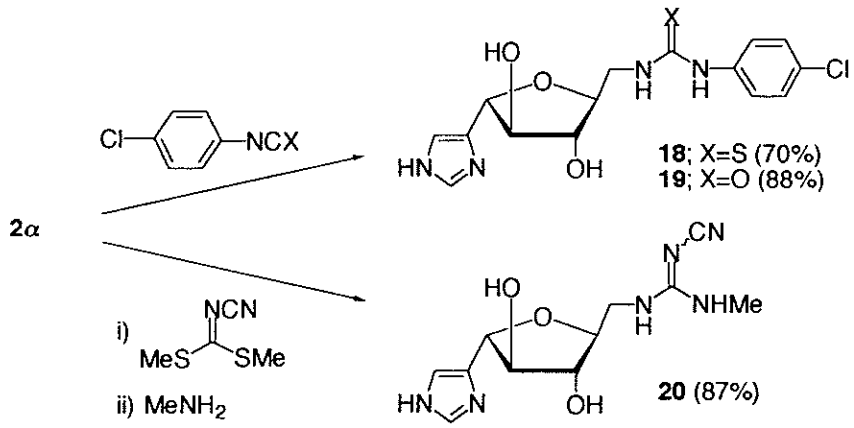
i) see Table 1, Run 3; ii) aq 1.5 N HCl - THF ; iii) see Table 2, Run 5; iv) cyclohexene, 20% $Pd(OH)_2$ - C ; v) phthalimide, Ph_3P, DEAD; vi) $NH_2NH_2 \cdot H_2O$; vii) see EXPERIMENT

Scheme 4

and **2β**. Although separation of phthalimides (**15α**) and (**15β**) was troublesome owing to the formation of a phosphorus by-product, they could be purified by either a preparative TLC to give **15α** (40%, mp 158-160℃, leaflets) and a small amount of **15β** (3%) as an oil, or a partial chromatographic

separation followed by recrystallization from ethyl acetate-hexane to give pure **15α** (*ca.*40%). The correctness of their stereochemical assignment was indicated by the observation of an NOE between the C1' and C5' protons of **15α**, although the NOE enhancement between C1' and C4' protons in **15β** was not observed. Treatment of the α-anomer (**15α**) thus obtained with hydrazine hydrate produced the single isomer (**2α**) in 73% yield.

We next directed our attention to introduction of a hydrophobic group into the 5'-amino group of **2α**, since the present H_3-antagonists exhibit three common and essential structural features: imidazole headgroup, spacer and hydrophobic tail group.[4] Treatment of **2α** with *p*-chlorophenyl isothiocyanate or *p*-chlorophenyl isocyanate afforded 5'-thiourea (**18**) or 5'-urea (**19**) in 70% and 88% yield, respectively. The amine was also converted into the cyanoguanidine (**20**) by treatment with dimethyl *N*-cyanodithioiminocarbonate followed by methylamine in 87% yield. These results indicate that α-L-arabinofuranosylimidazole (**2α**) is a versatile precursor to 5'-amino derivatives.



Scheme 5

EXPERIMENTAL

The melting points were determined on a hot-stage apparatus and are uncorrected. Optical rotations measurements were recorded with a JASCO DIP-1000 digital polarimeter. The ORD spectra were recorded with a JASCO ORD/UV-5 spectrometer. ^{1}H- and ^{13}C-NMR spectra were taken with

tetramethylsilane as an internal standard on a Varian Gemini-200, Varian Mercury-300, and Varian UNITY INOVA-500 spectrometers. 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. THF was distilled from sodium-benzophenone.

2-*tert*-Butyldimethylsilyl-5-(2',3',5'-tri-*O*-benzyl-L-arabinosyl)-*N*,*N*-dimethyl-imidazole-1-sulfonamide (10*R*, 10*S*)

A solution of **7** (1.850 g, 6.39 mmol) in THF (3 mL) was cooled to -50℃ and treated dropwise over 20 min with 1.6 M BuLi-hexane (4.0 mL, 6.39 mmol) to precipitate the white lithium salt (**8**). The resulting suspension was again cooled to -65℃, and a solution of **9** (893 mg, 2.13 mmol) in toluene (3 mL) was added slowly. The dry ice bath was removed, and the reaction mixture was stirred at rt to dissolve the salts. After 2 h, the resulting 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. The residue was purified by column chromatography to give **10*RS*** (1.445 g, 96 %) using a gradient solvent system [10% to 50% in EtOAc–hexane]. Although the separation of **10*R*** and **10*S*** was not required for the following experiment, they could be isolated by use of EtOAc-hexane (3:7) as eluent. **10*S*** (less polar): oil. $[\alpha]_D$ +1.14° (*c*=1.65, $CHCl_3$). IR (neat) cm^{-1}: 3400 (OH), 1215 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 0.40 (s, 6H, $Si(CH_3)_2$), 1.00 (s, 9H, $C(CH_3)_3$), 2.58 (s, 6H, $N(CH_3)_2$), 3.67 (m, 2H, 5'-H), 3.89 (dd, 1H, *J*=7.3, 3.4 Hz, 3'-H), 4.10 (br s, 1H, 4'-H), 4.17 (dd, 1H, *J*=7.3 Hz, 3.4 Hz, 2'-H), 4.36-4.74 (m, 6H, $CH_2Ph \times 3$), 5.28 (d, 1H, *J*=7.3 Hz, 1'-H), 7.04-7.52 (m, 16H, 5-H and Ph×3). ^{13}C-NMR ($CDCl_3$) δ: 18.5, 27.4, 37.4, 64.1, 70.1, 70.9, 73.5, 74.2, 74.6, 78.6, 81.7, 127.6–128.4 (Ph), 131.1, 135.4, 137.6, 137.7, 137.8, 155.7. SIMS *m/z*: 710 (M^++1). HRMS *m/z*: 710.3289 (Calcd for $C_{37}H_{52}N_3O_7SSi$: 710.3292). **10*R*** (more polar): pale yellow oil. $[\alpha]_D$ -27.0° (*c*=2.98, $CHCl_3$). IR (neat) cm^{-1}: 3400 (OH), 1215 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 0.41 (s,

6H, $Si(CH_3)_2$), 1.00 (s, 9H, $C(CH_3)_3$), 2.75 (s, 6H, $N(CH_3)_2$), 3.57-3.82 (m, 3H, 2'-H and 3'-H, OH), 4.03-4.12 (m, 3H, 4'-H and 5'-H), 4.23-4.69 (m, 6H, $CH_2Ph \times 3$), 5.32 (br s, 1H, 1'-H), 7.18-7.43 (m, 16H, 5-H and Ph×3). ^{13}C-NMR ($CDCl_3$) δ: 18.4, 27.3, 37.7, 65.0, 70.1, 73.4, 73.9, 75.0, 78.7, 80.8, 127.7-127.8 (Ph), 128.2-128.4 (Ph), 131.7, 135.0, 137.2, 137.7, 155.9. SIMS *m/z*: 710 (M^++1). HRMS *m/z*: 710.3289 (Calcd for $C_{37}H_{52}N_3O_7SSi$: 710.3292).

4-(2',3',5'-Tri-*O*-benzyl-L-arabinosyl)imidazole (11*R* and 11*S*)

A solution of **10*R*** (293 mg, 0.413 mmol) in THF (3 mL) and 1.5N HCl (5 mL) was refluxed for 2 h and then cooled. After neutralization by addition of 30% 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 to give an oil, which was subjected to chromatography. Elution with MeOH-EtOAc (1:19) afforded **11*R*** (197 mg, 98 %) as a pale yellow oil. **11*R***: IR (neat) cm^{-1}: 3300 (OH). ^{1}H-NMR ($CDCl_3$) δ: 3.62-3.77 (m, 3H, 4'-H and 5'-H), 4.01-4.13 (m, 2H, 2'-H and 3'-H), 4.42-4.67 (m, 6H, CH_2Ph ×3), 5.02 (d, 1H, J = 4.3 Hz, 1'-H), 6.80 (s, 1H, 4-H), 7.16-7.36 (m, 15H, Ph×3), 7.40 (s, 1H, 2-H). ^{13}C-NMR ($CDCl_3$) δ: 67.4, 71.0, 71.3, 73.4, 73.8, 74.6, 78.7, 82.4, 127.6–127.8 (Ph), 128.1–128.3 (Ph), 134.7, 137.8, 137.9. EIMS *m/z*: 489 (M^++1). HRMS *m/z*: 489.2391 (Calcd for $C_{29}H_{33}N_2O_5$: 489.2388). A solution of **10*S*** (332 mg, 0.468 mmol) in THF (8 mL) and 1.5N HCl (7.5 mL) was refluxed for 1 h to give **11*S*** (191 mg, 83 %) as described above. **11*S***: IR (neat) cm^{-1}: 3280 (OH). ^{1}H-NMR ($CDCl_3$) δ: 3.65 (m, 2H, 5'-H), 3.98 (m, 1H, 4'-H), 4.10-4.25 (m, 2H, 2'-H and 3'-H), 4.40-4.74 (m, 6H, $CH_2Ph \times 3$), 4.92 (d, 1H, J = 7.4 Hz, 1'-H), 6.70 (s, 1H, 4-H), 7.04-7.20 (m, 16H, 2-H and Ph × 3). ^{13}C-NMR ($CDCl_3$) δ: 66.9, 70.2, 71.4, 73.4, 74.0, 78.6, 81.2, 127.6–128.3 (Ph), 134.7, 137.6, 137.9. EIMS *m/z*: 489 (M^++1). HRMS *m/z*: 489.2380 (Calcd for $C_{29}H_{33}N_2O_5$: 489.2388). A solution of **10*RS*** (668 mg, 0.942 mmol) in THF (15 mL) and 1.5N HCl (15 mL) was refluxed for 1 h to give **11*RS*** (435 mg, 95 %).

4-(2',3',5'-Tri-*O*-benzyl-L-arabinofuranosyl)imidazole (12)

To a solution of **11*R*** (57 mg, 0.12 mmol) and Bu_3P (0.06 mL, 0.23 mmol) in benzene (2 mL) at 0 ℃ was added TMAD (41 mg, 0.23 mmol). The reaction mixture was stirred at rt for 2 h. The insoluble material was filtered through a Celite pad, and filtrate was condensed. The resulting crude oil was diluted with EtOAc, and the organic layer was washed with H_2O and brine, dried, and evaporated. The residual oil was chromatographed [EtOAc-hexane (8:2)] to give a 9 : 1 mixture (52 mg, 96 %) of **12**α and **12**β. **12**: pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ : 3.63 (d, 18 / 10H, J = 5.1 Hz, 5'-H_α), 3.66 (d, 2 / 10H, J = 5.1 Hz, 5'-H_β), 4.10 (t, 1 / 10H, J = 4.1 Hz, 4'-H_β), 4.15 (t, 9 / 10H, J = 4.1 Hz, 4'-H_α), 4.27-4.42 (m, 2H, 2'-H and 3'-H), 4.45-4.58 (m, 6H, $CH_2Ph\times3$), 5.10 (d, 9 / 10H, J = 4.4 Hz, 1'-H_α), 5.18 (d, 1 / 10H, J = 3.4 Hz, 1'-H_β), 6.90 (s, 1H, 5-H), 7.16-7.40 (m, 15H, Ph×3), 7.48 (s, 1H, 2-H). [This was characterized as *N*-ethoxycarbonyl derivative (**13**) as described later]. By the same procedure as above, **11*S*** (138 mg, 0.28 mmol) was treated with TMAD (97 mg, 0.57 mmol), and Bu_3P (0.15 mL, 0.57 mmol) in benzene (6 mL) to give **12** (122 mg, 92 %), whose ^{1}H-NMR was indicated the same ratio (9:1) of **12**α and **12**β.

Ethyl 4-(2',3',5'-Tri-*O*-benzyl-β-L-arabinofuranosyl)imidazole-1-carboxylate (13)

A mixture of **11*RS*** (770 mg, 1.58 mmol), TMAD (408 mg, 2.37 mmol), and Bu_3P (0.58 mL, 2.37 mmol) was treated in CH_2Cl_2 (25 mL) at -35℃ for 1.5 h to give a crude oil of **12** by the same procedure as used for the above preparation. The solution of the crude **12** in benzene (25 mL) was refluxed with ethyl chloroformate (0.30 mL, 3.10 mmol), pyridine (0.19 mL, 2.37 mmol), and a catalytic amount of 4-DMAP for 15 min. The solvent was removed under reduced pressure to give a residue, which was dissolved in EtOAc. The solution was washed with H_2O, dried, and evaporated to give a crude oil. Flash chromatography on silica gel using EtOAc–hexane (1:3) as eluent gave **13** (812 mg, 95%) as a colorless oil. IR (neat) cm^{-1}: 1760 (C=O). ^{1}H-NMR ($CDCl_3$) δ : 1.41 (t, 3H, J = 7.2 Hz, CH_3), 3.64 (d, 2H, J = 5.2 Hz, 5'-H), 4.02 (dd, 1 / 21H, J = 3.3, 1.5 Hz, 4'-H_β), 4.16 (dd, 20 / 21H, J = 4.6, 3.2 Hz, 4'-H_α), 4.30-4.66 (m, 10H, 2', 3'-H and CO_2CH_2, $CH_2Ph\times3$), 5.08 (d, 20 / 21H, J = 4.2 Hz,

1'-H $_{\alpha}$), 5.17 (dd, 1 / 10H, J = 4.1, 1.2 Hz, 1'-H $_{\beta}$), 7.08-7.20 (m, 16H, 5-H and Ph×3), 8.14 (s, 1H, 2-H). ^{13}C-NMR ($CDCl_3$) δ: 14.2, 64.4, 70.1, 71.8, 72.0, 73.3, 79.2, 81.7, 84.7, 87.6, 114.4, 127.4–128.3 (Ph), 136.9, 137.7, 138.0, 142.8, 148.3. EIMS *m/z*: 543 (M^++1). HRMS *m/z*: 543.2477 (Calcd for $C_{32}H_{35}N_2O_6$: 543.2493).

Ethyl 4-(L-Arabinofuranosyl)imidazole-1-carboxylate (14)

A mixture of **13** (197 mg, 0.36 mmol), 20% $Pd(OH)_2$-C (118 mg), and cyclohexene (1.1 mL, 10.9 mmol) in EtOH (17 mL) was refluxed for 2 h. After 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 (BW-127ZH), which was subsequently placed in a column. Chromatography using MeOH-EtOAc (1:9) to give **14** (83 mg, 84 %) as a colorless oil. IR (neat) cm^{-1}: 3350 (OH), 1760 (C=O). ^{1}H-NMR (CD_3OD) δ : 1.42 (t, 3H, J = 6.9 Hz, CH_3), 3.65 (d, 1 / 21H, J = 4.6 Hz, 5'-H $_{\beta}$), 3.69 (d, 20 / 21H, J = 4.6 Hz, 5'-H $_{\alpha}$), 3.73 (d, 20 / 21H, J = 3.5 Hz, 5'-H $_{\alpha}$), 3.77 (d, 1 / 21H, J = 3.5 Hz, 5'-H $_{\beta}$), 3.91 (m, 1 / 21H, 4'-H $_{\beta}$), 3.98 (m, 20 / 21H, 4'-H $_{\alpha}$), 4.06 (t, 20 / 21H, J = 5.9 Hz, 3'-H $_{\alpha}$), 4.12 (t, 1 / 21H, J = 5.9 Hz, 3'-H $_{\beta}$), 4.27 (t, 1H, J = 5.9 Hz, 2'-H), 4.48 (q, 2H, J = 6.9 Hz, CO_2CH_2), 4.73 (d, 20 / 21H, J = 5.9 Hz, 1'-H $_{\alpha}$), 5.04 (d, 1 / 21H, J = 3.2 Hz, 1'-H $_{\beta}$), 7.54 (s, 1H, 5-H), 8.26 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ: 14.4, 63.2, 65.9, 78.7, 79.4, 80.2, 82.1, 85.6, 116.4, 138.8, 143.2. EIMS *m/z*: 273 (M^++1). HRMS *m/z*: 273.1085 (Calcd for $C_{11}H_{17}N_2O_6$: 273.1085).

Ethyl 4-(5'-Deoxy-5'-phthaloylamino-α-L-arabinofuranosyl)imidazole-1-carboxylate (15α) and Its C-1' Epimer (15β)

Phthalimide (24 mg, 0.166 mmol) and Ph_3P (139 mg, 0.529 mmol) were dissolved in a solution of **14** (41 mg, 0.151 mmol) in THF (5 mL). DEAD (0.09 mL, 0.529 mmol) was added and the resulting mixture was stirred for 1 h at rt, then the whole was evaporated to give a residue, which was subjected to chromatography to give a crude oil **15** [EtOAc-hexane (1:1)]. This was subsequently purified on a preparative TLC with EtOAc to give **15α** (19 mg, 32 %) and **15β** (2 mg, 3 %). The crude oil (**15**) was

allowed to stand at rt for a few days to give a semi-solid, which purified by twice recrystallization (EtOAc-hexane) to give **15α** (ca. 40 %). **15α** (less polar): white leaflets, mp 158-160℃. IR (KBr) cm^{-1}: 3470 (OH), 1770 (N-CO-O), 1725 (CO-N-CO). ^{1}H-NMR ($CDCl_3$) δ : 1.42 (t, 3H, J = 7.0 Hz, CH_3), 3.90 (s, 2H, 5'-H), 4.06 (s, 1H, 2'-H or 3'-H), 4.08 (s, 1H, 2'-H or 3'-H), 4.43 (t, 1H, J = 5.2 Hz, 4'-H), 4.48 (q, 2H, J = 7.0 Hz, CO_2CH_2), 5.09 (s, 1H, 1'-H), 7.38 (s, 1H, 5-H), 7.72 (m, 2H, phthalimide), 7.86 (m, 2H, phthalimide), 8.11 (s, 1H, 2-H). ^{13}C-NMR ($CDCl_3$) δ: 14.3, 37.7, 57.0, 58.7, 64.7, 73.9, 74.6, 114.7, 123.2, 132.0, 133.8, 137.3, 141.0, 148.2, 168.0. EIMS *m/z*: 401 (M^+). HRMS *m/z*: 401.1212 (Calcd for $C_{19}H_{19}N_3O_7$: 401.1222). Handling of **15α** was troublesome as static electricity caused it to stick to the spatula or paper. **15β** (more polar): oil. ^{1}H-NMR ($CDCl_3$) δ : 1.40 (t, 3H, J = 7.2 Hz, CH_3), 3.85 (br d, 1H, J = 2.5 Hz, 2'-H or 3'-H), 3.87 (d, 1H, J = 3.5 Hz, 5'-H), 3.91 (d, 1H, J = 3.5 Hz, 5'-H), 4.10 (br d, 1H, J = 2.5 Hz, 2'-H or 3'-H), 4.46 (q, 2H, J = 7.2 Hz, CO_2CH_2), 4.58 (t, 1H, J = 6.2 Hz, 4'-H), 5.18 (s, 1H, 1'-H), 7.48 (s, 1H, 4-H), 7.74 (m, 2H, phthalimide), 7.88 (m, 2H, phthalimide), 8.21 (s, 1H, 2-H).

4-(5'-Amino-5'-deoxy-α-L-arabinofuranosyl)imidazole (2α)

A solution of **15α** (106 mg, 0.27 mmol) and 100% $NH_2NH_2 \cdot H_2O$ (0.03 mL, 0.66 mmol) in EtOH (11 mL) was refluxed for 3 h and cooled. A small amount of 10% Pd-C was then added to the solution, and the reaction mixture was further refluxed for 20 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 column (Chromatorex NH-DM 1020). Chromatography using MeOH-EtOAc (1:1) as the eluent gave (+)-**2α** (38 mg, 73 %) as a single isomer. colorless oil. $[\alpha]_D$ +39.3° (c=1.95, MeOH). ^{1}H-NMR (CD_3OD) δ : 2.91 (d, 2H, J = 6.1 Hz, 5'-H), 3.87 (d, 1H, J = 3.2 Hz, 3'-H), 3.92 (d, 1H, J = 3.2 Hz, 2'-H), 4.05 (t, 1H, J = 6.1 Hz, 4'-H), 5.06 (s, 1H, 1'-H), 7.10 (s, 1H, 4-H), 7.68 (s, 1H, 2-H). ^{13}C-NMR ($CDCl_3$) δ: 42.7, 58.0, 59.0, 75.1, 78.4, 137.0.

Conversion of 14 into 2

Phthalimide (27 mg, 0.19 mmol) and Ph_3P (155 mg, 0.59 mmol) were dissolved in a solution of **14** (46 mg, 0.17 mmol) in THF (5 mL). Then, DEAD (0.10 mL, 0.59 mmol) was added and the resulting mixture was stirred for 2.5 h at rt to give crude **15** by the same procedure as used for the preparation of **15**. A solution of crude **15** and 100% $NH_2NH_2 \cdot H_2O$ (0.02 mL, 0.42 mmol) in EtOH (7 mL) was refluxed for 40 min to give a 20:1 mixture (19 mg, 57 %) of **2α** and **2β** as an oil. The coexistence of the minor product (**2β**) was indicated in the ^{1}H-NMR spectrum [e. g. 5.03 (s, 1'H)].

4(5)-{5-[*N*-(4-Chlorophenyl)thioureido]-α-L-arabinofuranosyl} imidazole (18)

The same procedure for the preparation of **19** as described later provided **18** (80 mg, 70 %) as an oil from **2α** (62 mg) and 4-phenyl isothiocyanate (80 mg, 0.47 mmol) in MeOH (7 mL). ORD (c= 2.88, EtOH) [α] (nm) +45.9 (589), +52.2 (550), +66.8 (500), +85.6 (450); IR (nujol) cm^{-1}: 3260 (OH), 1535, 1082 [NHC(S)NH]. ^{1}H-NMR (CD_3OD) δ: 3.8–4.0 (m, 4H, 2', 3', 5'-H), 4.30 (t, 1H, J = 4.0 Hz, 4'-H), 5.08 (s, 1H, 1'-H), 7.10 (s, 1H, 4-H), 7.2–7.5 (m, 4H, Ph), 7.70 (s, 1H, 2-H). EIMS *m/z*: 242 [M^+ -(NHC_6H_4Cl)], 169 {M^+ -[$NHC(S)NHC_6H_4Cl$].

4(5)-{5-[*N*-(4-Chlorophenyl)ureido]-α-L-arabinofuranosyl}imidazole (19)

A solution of **2α** (38 mg, 0.19 mmol) and 4-chlorophenyl isocyanate (45 mg, 0.29 mmol) in THF (3 mL) was stirred at rt. After 2 h, a small amount of silica gel was added to the solution and the solvent was evaporated to give a coated silica gel, which was subsequently placed in a column. Chromatography using a gradient solvent system (0% to 30% in MeOH-EtOAc) gave **19** (60 mg, 88%) as an oil. ORD (c= 1.47, EtOH) [α] (nm) +43.7 (589), +51.7 (550), +66.8 (500), +88.3 (450). ^{1}H NMR (CD_3OD) δ : 3.4-3.6 (m, 2H, 5'-H), 3.83 (d, 1H, J = ca. 1 Hz), 3.89 (d, 1H, J = ca. 1 Hz), 4.11 (t, 1H, J = 3.6 Hz, 4'-H), 5.08 (s, 1H, 1'-H), 7.09 (s, 1H, 4-H), 7.10 (d, 1H, J =10.8 Hz, Ph), 7.35 (d, 1H, J =10.8 Hz, Ph), 7.69 (s, 1H, 2-H). SIMS *m/z*: 335 (M^+ -H_2O). HRMS *m/z*: 335.0917 (calcd for C_{15} $H_{15}N_4O_2Cl$: 335.0910).

1-Cyano-2-methyl-3-{5-deoxy-1-[1*H*-imidazol-4(5)-yl]-α-L-arabinofuranosyl}-guanidine (20)

A solution of **2α** (91 mg, 0.46 mmol) and dimethyl *N*-cyanodithioiminocarbonate (81 mg, 0.50 mmol) was stirred overnight at rt, and then 40% $MeNH_2$ in MeOH (4.0 mL) was added to the solution. The resulting mixture was stirred for 3 h at rt. The solvent was evaporated to give a residual oil, which was chromatographed [Chromatorex NH-DM 1020, MeOH-AcOEt (1:9 to 3:7)] to give **20** (87 mg, 87 %) as an oil. ORD (c= 2.38, EtOH) [α] (nm) +23.5 (589), +27.0 (550), +35.4 (500), +48.7 (450); IR (neat) cm^{-1}: 2170 (CN), 1590 (C=N). ^{1}H-NMR (CD_3OD) δ: 2.80 (s, 3H, NHMe), 3.50 (t, 2H, J = 4.0 Hz, 5'-H), 3.88 (d, 1H, J = 1.6 Hz), 3.95 (d, 1H, J =1.6 Hz), 4.20 (t, 1H, J = 4.0 Hz, 4'-H), 5.09 (s, 1H, 1'-H), 7.12 (s, 1H, 4H), 7.70 (s, 1H, 2H). SIMS *m/z*: 263 (M^+ -OH).

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