

**SYNTHESIS OF 4(5)-(5'-AMINO-5'-DEOXY- $\alpha$ -L-ARABINOFURANOSYL)IMIDAZOLE AND ITS 5'-DERIVATIVES USING MODIFIED MITSUNOBU CYCLIZATION: SYNTHETIC STUDIES TOWARD NOVEL HISTAMINE H<sub>3</sub>-LIGANDS**

Lisa Araki, Shinya Harusawa, Hirokazu Suzuki, and Takushi Kurihara\*  
Osaka University of Pharmaceutical Sciences, 4-20-1 Nasahara, Takatsuki,  
Osaka 569-1094, Japan

**Abstract** - The modified Mitsunobu cyclization of 4-(2',3',5'-tri-*O*-benzyl-L-arabinosyl)imidazole (**11RS**) using *N,N,N',N'*-tetramethylazodicarboxamide and Bu<sub>3</sub>P followed by ethoxycarbonylation produced a mixture ( $\alpha / \beta = 20 / 1$ ) 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- $\alpha$ -L-arabinofuranosyl)imidazole (**2 $\alpha$** ). The 4(5)-{5-[*N*-(4-chlorophenyl)thio-ureido]- $\alpha$ -L-arabinofuranosyl}imidazole (**18**), 4(5)-{5-[*N*-(4-chlorophenyl)-ureido]- $\alpha$ -L-arabinofuranosyl}imidazole (**19**), and 1-cyano-2-methyl-3-{5-deoxy-1-[1*H*-imidazol-4(5)-yl]- $\alpha$ -L-arabinofuranosyl}guanidine (**20**) were efficiently synthesized from **2 $\alpha$** .

## Introduction

The histamine H<sub>3</sub>(H<sub>3</sub>) receptors<sup>1</sup> exist on histaminergic fibers in the brain and modulate the synthesis and release of histamine as an autoreceptor.<sup>2</sup> Moreover, H<sub>3</sub>-receptors have been shown to be heteroreceptors<sup>3</sup> which modulate the release of a number of different neurotransmitters.<sup>3,4</sup> This type of receptor can be also found in many peripheral tissues.<sup>1</sup> *R*- $\alpha$ -Methylhistamine, imetit and imnepip, which are potent and selective agonists for the H<sub>3</sub>-receptors, have been extensively used as a pharmacological tool.<sup>3,4</sup> H<sub>3</sub>-Agonists are regarded as a target for new therapeutics of bronchial asthma,<sup>5</sup> and H<sub>3</sub>-antagonists are now expected to be potential drugs for memory degenerative disorders like Alzheimer's disease.<sup>3,4</sup>

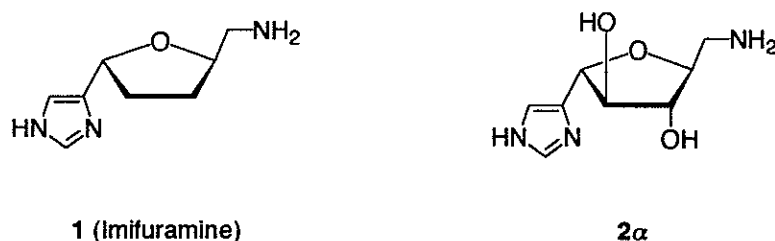
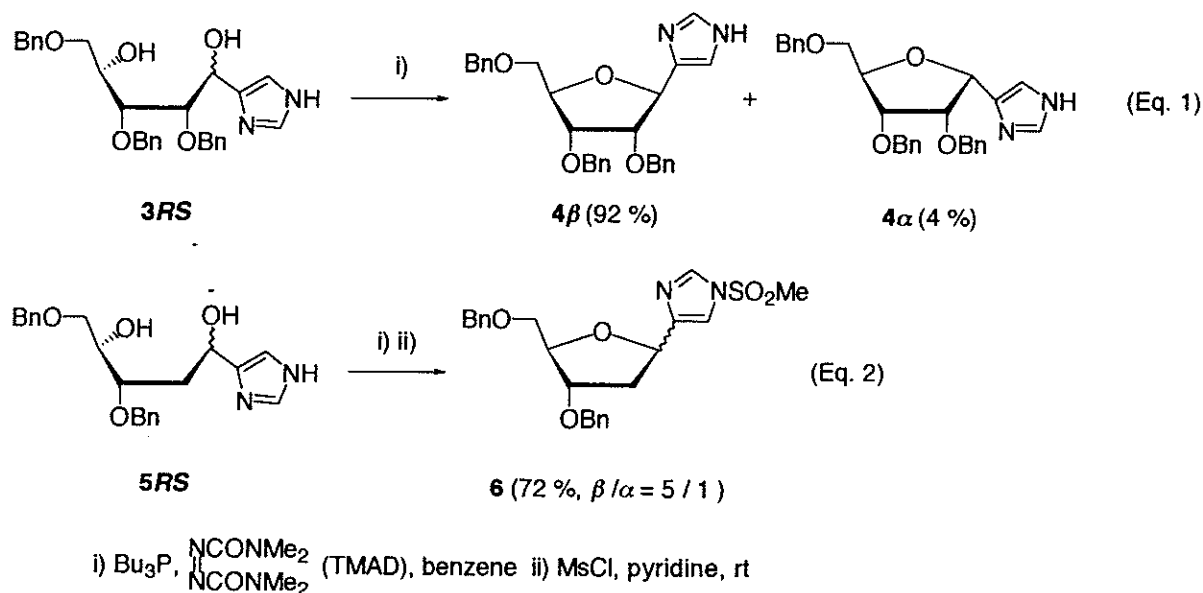


Figure 1

We recently communicated<sup>6</sup> 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<sup>7</sup> indicated that, among them, only (+)-4(5)-[5-(aminomethyl)tetrahydrofuran-2-yl]imidazole (imifuramine, **1**)<sup>6a</sup> exhibited a clear H<sub>3</sub>-agonistic activity. The activity of imifuramine measured by microdialysis was approximately equal to that of imnepip.<sup>8</sup> To the contrary, imifuramine exhibited a weak H<sub>3</sub>-agonistic activity (pD<sub>2</sub> = 4) in an *in vitro* test using guinea pig ileum preparation, compared to that (pD<sub>2</sub> = 8) of *R*- $\alpha$ -methylhistamine.<sup>9</sup>

The finding of imifuramine encouraged us to synthesize 4(5)-(5'-amino-5'-deoxy- $\alpha$ -L-arabinofuranosyl)imidazole (**2 $\alpha$** ), the configurations of which at the C1' and C4' positions were consistent with those of imifuramine. **2 $\alpha$**  may be used as a base compound for the synthetic study toward novel H<sub>3</sub>-agonists and antagonists. Furthermore, little work has been done concerning the synthesis and biological evaluation of the  $\alpha$ -L-*C*-nucleosides,<sup>10</sup> the sugar moiety of which has unnatural configuration.<sup>11</sup>

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



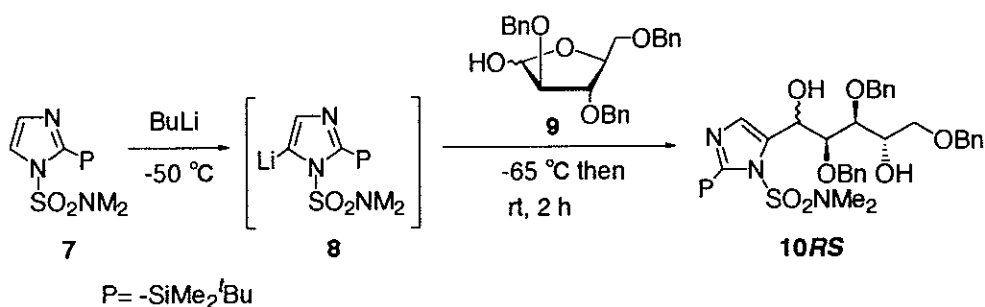
Scheme 1

cyclization of the corresponding diols proceeds through intramolecular  $\text{S}_{\text{N}}2$  reaction under standard Mitsunobu conditions (DEAD,  $\text{Ph}_3\text{P}$ ), and the orientation of the glycosidic linkage is controlled by the  $\text{C}1'$  configuration of the substrate: one isomer affords an  $\alpha$ -anomer and the other, a  $\beta$ -anomer. In the case of 2'-deoxy compound (**5RS**),<sup>12a,b</sup> the modified Mitsunobu reaction produced a 5 : 1 mixture (**6**) of  $\beta$ - and  $\alpha$ -anomers (Scheme 1, Eq. 2). These results suggest that the benzyloxy groups at the  $\text{C}2'$ -position may act as the directing group to control thermodynamically the stereochemistry of imidazole  $\text{C}$ -nucleosides. Therefore, we expected that **2α** could be selectively synthesized starting from L-arabinose having the  $\text{C}2\beta$ -OH group. In this paper, we report the synthesis of  $\alpha$ -L-arabinofuranosyl-nucleosides (**2α**) 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 **2α**.

## RESULTS AND DISCUSSION

We first carried out a coupling reaction<sup>12b</sup> of 2,3,5-tri-*O*-benzyl-L-arabinofuranose (**9**)<sup>15</sup> 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  $-50^{\circ}\text{C}$ , 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  $-65^{\circ}\text{C}$  and the whole was stirred at room temperature for 2 h. However, this operation afforded an epimeric mixture (**10RS**) in only a low yield. On the other hand, use of toluene as the solvent gave **10RS** 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 (**10RS**) was successfully obtained in 96% yield as a 72:28 diastereomixture of **10R** and **10S** (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 (**10R**) (polar) and (**10S**) (less polar) were separated easily by silica gel column chromatography. The C1' stereochemical assignments of **10R** and **10S**, respectively, were based on the analogy of our previous reports.<sup>6,12</sup> In  $^1\text{H-NMR}$ , a

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

Run	Solvent		Yield(%) <sup>1)</sup>
1	i) THF	ii) THF	0 - 35
2	i) toluene	ii) toluene	8 - 88
3	i) THF	ii) toluene	96 <sup>2)</sup>

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

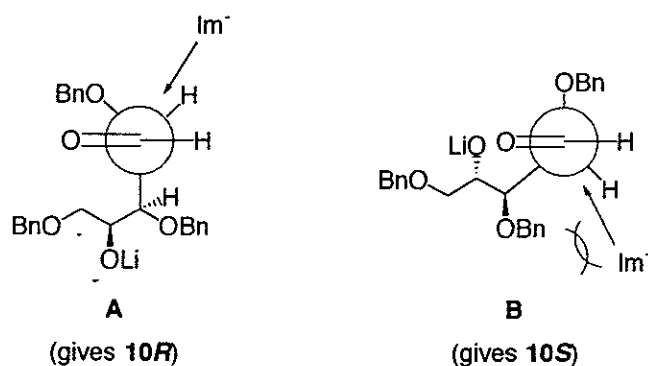
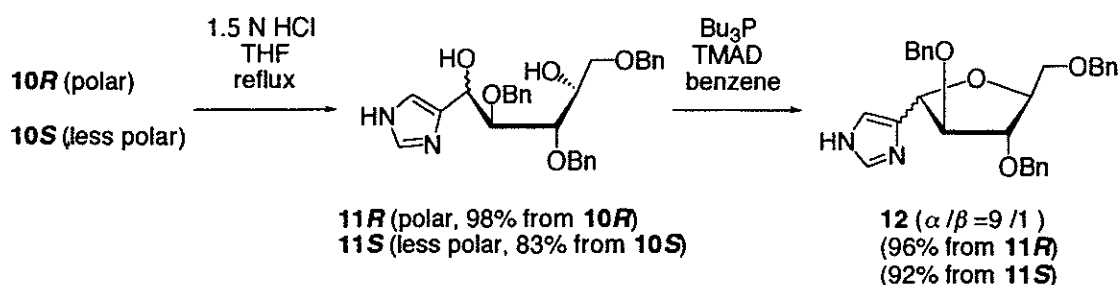


Figure 2

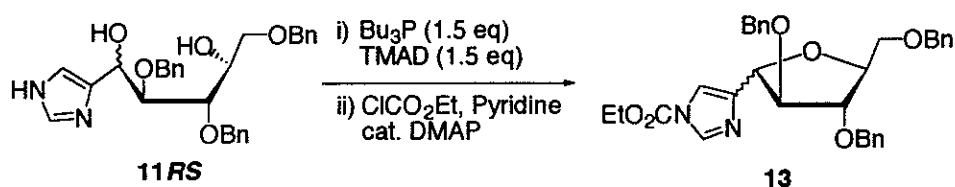
small  $J_{1',2'}$  coupling constant (br s,  $J_{1',2'} = < 2$  Hz) was observed in major isomer (**10R**) compared to that of minor (**10S**) (d,  $J_{1',2'} = 7.3$  Hz) having a 1', 2'-*anti*-parallel orientation. The preference of **10R** is rationalized by applying the Felkin-Anh model<sup>16</sup>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

Hydrolysis of **10R** in refluxing 1.5N HCl afforded a diol (**11R**) having unsubstituted imidazole in 98% yield (Scheme 2). The modified Mitsunobu cyclization of **11R** with TMAD and  $\text{Bu}_3\text{P}$  at room temperature in benzene, as expected, produced a 9:1 mixture (**12**) (96 %) of  $\alpha$ - and  $\beta$ -anomers, the isolation of which by column chromatography was difficult. The ratio was assigned from those of methine protons at C-1' in  $^1\text{H-NMR}$  ( $\delta$  5.10 for **12 $\alpha$**  vs 5.18 for **12 $\beta$** ). The *S*-isomer (**11S**) also afforded a 9:1 mixture (92%) of **12 $\alpha$**  and **12 $\beta$**  (Scheme 2). These experiments indicated the  $\alpha$ -anomer (**12 $\alpha$** ) could be preferentially supplied without separation of the isomers (**11R** and **11S**).

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



Scheme 2

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

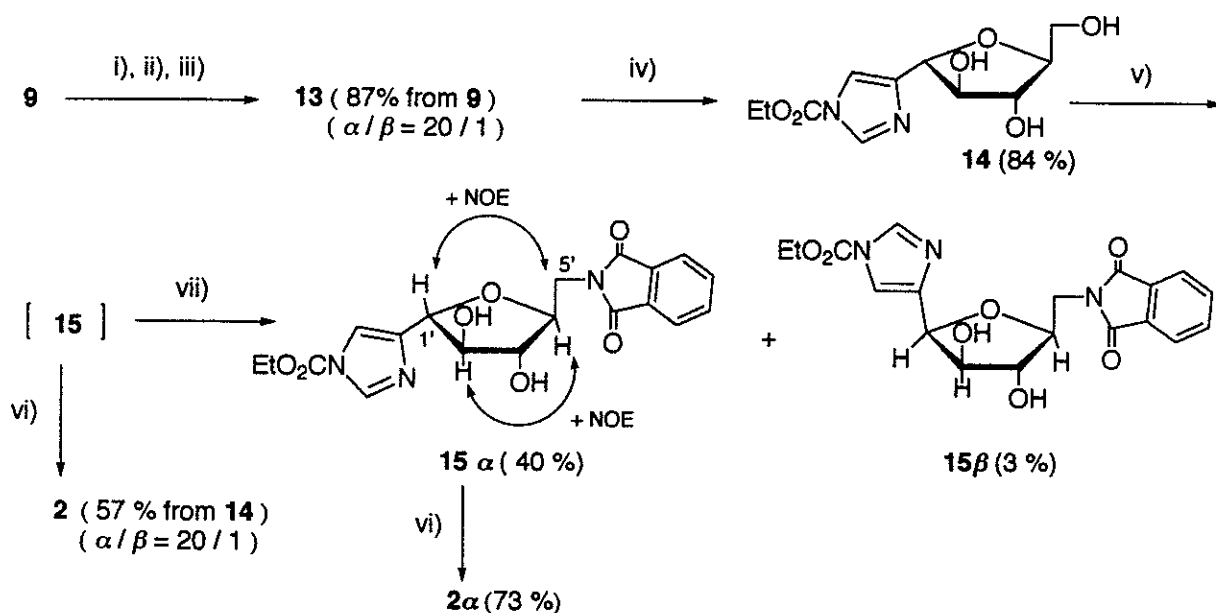
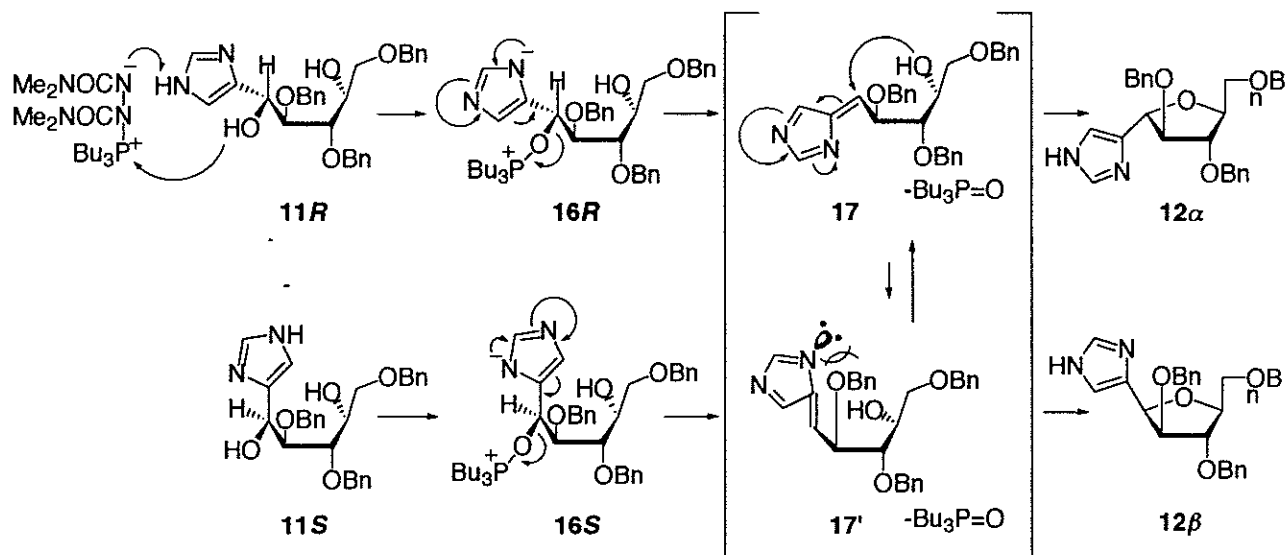
Run	Solvent	Temp. (°C)	Time (h)	Yield (%)	<b>13<math>\alpha</math></b> / <b>13<math>\beta</math></b>
1	THF	rt	overnight	95	4.5 / 1
2	benzene	rt	overnight	89	9 / 1
3	toluene	0	2	82	9.5 / 1
4	CH <sub>2</sub> Cl <sub>2</sub>	0	2	64	15 / 1
5	CH <sub>2</sub> Cl <sub>2</sub>	-35	1.5	95	20 / 1

improved to give a 20:1 anomeric mixture in CH<sub>2</sub>Cl<sub>2</sub> at -35°C (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  $\alpha$  /  $\beta$  ratio of *C*-nucleosides.

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

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

As results of these experiments, *N*-ethoxycarbonylcompound (**13**) ( $\alpha$  /  $\beta$  = 20 / 1) could be obtained in 87 % overall yield from the starting tribenzylarabinose (**9**) without isolation of diols (**10R**) and (**10S**), as shown in Scheme 4. Debenzylation of **13** with Pd(OH)<sub>2</sub>-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 $\alpha$**

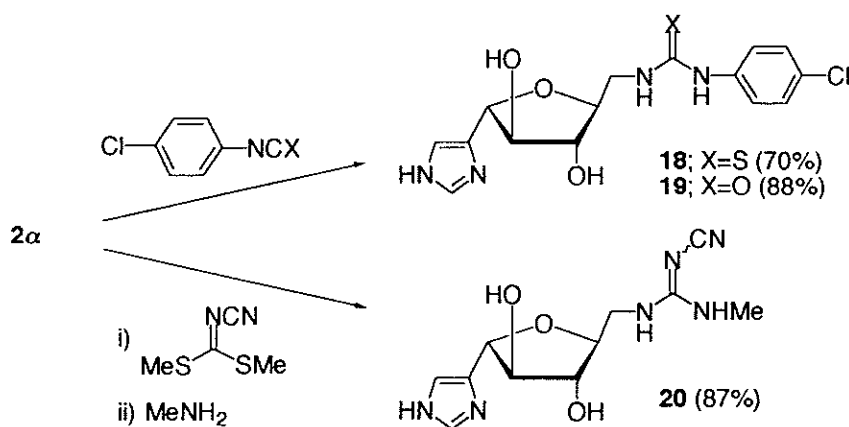


i) see Table 1, Run 3; ii) aq 1.5 N HCl - THF; iii) see Table 2, Run 5; iv) cyclohexene, 20% Pd(OH)<sub>2</sub> - C; v) phthalimide, Ph<sub>3</sub>P, DEAD; vi) NH<sub>2</sub>NH<sub>2</sub> · H<sub>2</sub>O; vii) see EXPERIMENT

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°C, 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 **15 $\alpha$**  (ca.40%). The correctness of their stereochemical assignment was indicated by the observation of an NOE between the C1' and C5' protons of **15 $\alpha$** , although the NOE enhancement between C1' and C4' protons in **15 $\beta$**  was not observed. Treatment of the  $\alpha$ -anomer (**15 $\alpha$** ) thus obtained with hydrazine hydrate produced the single isomer (**2 $\alpha$** ) in 73% yield.

We next directed our attention to introduction of a hydrophobic group into the 5'-amino group of **2 $\alpha$** , since the present H<sub>3</sub>-antagonists exhibit three common and essential structural features: imidazole headgroup, spacer and hydrophobic tail group.<sup>4</sup> Treatment of **2 $\alpha$**  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  $\alpha$ -L-arabinofuranosylimidazole (**2 $\alpha$** ) 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. <sup>1</sup>H- and <sup>13</sup>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  $\text{Na}_2\text{SO}_4$ , 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  $-50^\circ\text{C}$  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  $-65^\circ\text{C}$ , 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  $\text{H}_2\text{O}$ , and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc, and the solution was washed with  $\text{H}_2\text{O}$ , 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.  $[\alpha]_{\text{D}} +1.14^\circ$  ( $c=1.65$ ,  $\text{CHCl}_3$ ). IR (neat)  $\text{cm}^{-1}$ : 3400 (OH), 1215 ( $\text{SO}_2$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.40 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ ), 1.00 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 2.58 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 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,  $\text{CH}_2\text{Ph} \times 3$ ), 5.28 (d, 1H,  $J=7.3$  Hz, 1'-H), 7.04-7.52 (m, 16H, 5-H and  $\text{Ph} \times 3$ ).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 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 ( $\text{M}^++1$ ). HRMS  $m/z$ : 710.3289 (Calcd for  $\text{C}_{37}\text{H}_{52}\text{N}_3\text{O}_7\text{SSi}$ : 710.3292). **10*R*** (more polar): pale yellow oil.  $[\alpha]_{\text{D}} -27.0^\circ$  ( $c=2.98$ ,  $\text{CHCl}_3$ ). IR (neat)  $\text{cm}^{-1}$ : 3400 (OH), 1215 ( $\text{SO}_2$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.41 (s,

6H, Si(CH<sub>3</sub>)<sub>2</sub>), 1.00 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 2.75 (s, 6H, N(CH<sub>3</sub>)<sub>2</sub>), 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<sub>2</sub>Ph × 3), 5.32 (br s, 1H, 1'-H), 7.18-7.43 (m, 16H, 5-H and Ph × 3). <sup>13</sup>C-NMR (CDCl<sub>3</sub>) 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<sup>+</sup>+1). HRMS *m/z*: 710.3289 (Calcd for C<sub>37</sub>H<sub>52</sub>N<sub>3</sub>O<sub>7</sub>SSi: 710.3292).

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

A solution of **10R** (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<sub>4</sub>OH, the solvent was evaporated to give a residue, which was extracted with EtOAc. The extract was washed with H<sub>2</sub>O and brine, dried, and evaporated to give an oil, which was subjected to chromatography. Elution with MeOH-EtOAc (1:19) afforded **11R** (197 mg, 98 %) as a pale yellow oil. **11R**: IR (neat) cm<sup>-1</sup>: 3300 (OH). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 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<sub>2</sub>Ph × 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). <sup>13</sup>C-NMR (CDCl<sub>3</sub>) 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<sup>+</sup>+1). HRMS *m/z*: 489.2391 (Calcd for C<sub>29</sub>H<sub>33</sub>N<sub>2</sub>O<sub>5</sub>: 489.2388). A solution of **10S** (332 mg, 0.468 mmol) in THF (8 mL) and 1.5N HCl (7.5 mL) was refluxed for 1 h to give **11S** (191 mg, 83 %) as described above. **11S**: IR (neat) cm<sup>-1</sup>: 3280 (OH). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 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<sub>2</sub>Ph × 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). <sup>13</sup>C-NMR (CDCl<sub>3</sub>) 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<sup>+</sup>+1). HRMS *m/z*: 489.2380 (Calcd for C<sub>29</sub>H<sub>33</sub>N<sub>2</sub>O<sub>5</sub>: 489.2388). A solution of **10RS** (668 mg, 0.942 mmol) in THF (15 mL) and 1.5N HCl (15 mL) was refluxed for 1 h to give **11RS** (435 mg, 95 %).

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

To a solution of **11R** (57 mg, 0.12 mmol) and Bu<sub>3</sub>P (0.06 mL, 0.23 mmol) in benzene (2 mL) at 0 °C 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<sub>2</sub>O and brine, dried, and evaporated. The residual oil was chromatographed [EtOAc-hexane (8:2)] to give a 9 : 1 mixture (52 mg, 96 %) of **12α** and **12β**. **12**: pale yellow oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.63 (d, 18 / 10H, *J* = 5.1 Hz, 5'-H<sub>α</sub>), 3.66 (d, 2 / 10H, *J* = 5.1 Hz, 5'-H<sub>β</sub>), 4.10 (t, 1 / 10H, *J* = 4.1 Hz, 4'-H<sub>β</sub>), 4.15 (t, 9 / 10H, *J* = 4.1 Hz, 4'-H<sub>α</sub>), 4.27-4.42 (m, 2H, 2'-H and 3'-H), 4.45-4.58 (m, 6H, CH<sub>2</sub>Ph × 3), 5.10 (d, 9 / 10H, *J* = 4.4 Hz, 1'-H<sub>α</sub>), 5.18 (d, 1 / 10H, *J* = 3.4 Hz, 1'-H<sub>β</sub>), 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, **11S** (138 mg, 0.28 mmol) was treated with TMAD (97 mg, 0.57 mmol), and Bu<sub>3</sub>P (0.15 mL, 0.57 mmol) in benzene (6 mL) to give **12** (122 mg, 92 %), whose <sup>1</sup>H-NMR was indicated the same ratio (9:1) of **12α** and **12β**.

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

A mixture of **11RS** (770 mg, 1.58 mmol), TMAD (408 mg, 2.37 mmol), and Bu<sub>3</sub>P (0.58 mL, 2.37 mmol) was treated in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) at -35°C 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<sub>2</sub>O, 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<sup>-1</sup>: 1760 (C=O). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.41 (t, 3H, *J* = 7.2 Hz, CH<sub>3</sub>), 3.64 (d, 2H, *J* = 5.2 Hz, 5'-H), 4.02 (dd, 1 / 21H, *J* = 3.3, 1.5 Hz, 4'-H<sub>β</sub>), 4.16 (dd, 20 / 21H, *J* = 4.6, 3.2 Hz, 4'-H<sub>α</sub>), 4.30-4.66 (m, 10H, 2', 3'-H and CO<sub>2</sub>CH<sub>2</sub>, CH<sub>2</sub>Ph × 3), 5.08 (d, 20 / 21H, *J* = 4.2 Hz,

1'-H<sub>α</sub>), 5.17 (dd, 1 / 10H, *J* = 4.1, 1.2 Hz, 1'-H<sub>β</sub>), 7.08-7.20 (m, 16H, 5-H and Ph × 3), 8.14 (s, 1H, 2-H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>) 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<sup>+</sup>+1). HRMS *m/z*: 543.2477 (Calcd for C<sub>32</sub>H<sub>35</sub>N<sub>2</sub>O<sub>6</sub>: 543.2493).

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

A mixture of **13** (197 mg, 0.36 mmol), 20% Pd(OH)<sub>2</sub>-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<sup>-1</sup>: 3350 (OH), 1760 (C=O). <sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ: 1.42 (t, 3H, *J* = 6.9 Hz, CH<sub>3</sub>), 3.65 (d, 1 / 21H, *J* = 4.6 Hz, 5'-H<sub>β</sub>), 3.69 (d, 20 / 21H, *J* = 4.6 Hz, 5'-H<sub>α</sub>), 3.73 (d, 20 / 21H, *J* = 3.5 Hz, 5'-H<sub>α</sub>), 3.77 (d, 1 / 21H, *J* = 3.5 Hz, 5'-H<sub>β</sub>), 3.91 (m, 1 / 21H, 4'-H<sub>β</sub>), 3.98 (m, 20 / 21H, 4'-H<sub>α</sub>), 4.06 (t, 20 / 21H, *J* = 5.9 Hz, 3'-H<sub>α</sub>), 4.12 (t, 1 / 21H, *J* = 5.9 Hz, 3'-H<sub>β</sub>), 4.27 (t, 1H, *J* = 5.9 Hz, 2'-H), 4.48 (q, 2H, *J* = 6.9 Hz, CO<sub>2</sub>CH<sub>2</sub>), 4.73 (d, 20 / 21H, *J* = 5.9 Hz, 1'-H<sub>α</sub>), 5.04 (d, 1 / 21H, *J* = 3.2 Hz, 1'-H<sub>β</sub>), 7.54 (s, 1H, 5-H), 8.26 (s, 1H, 2-H). <sup>13</sup>C-NMR (CD<sub>3</sub>OD) 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<sup>+</sup>+1). HRMS *m/z*: 273.1085 (Calcd for C<sub>11</sub>H<sub>17</sub>N<sub>2</sub>O<sub>6</sub>: 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<sub>3</sub>P (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 **15 $\alpha$**  (ca. 40 %). **15 $\alpha$**  (less polar): white leaflets, mp 158-160 °C. IR (KBr)  $\text{cm}^{-1}$ : 3470 (OH), 1770 (N-CO-O), 1725 (CO-N-CO).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.42 (t, 3H,  $J = 7.0$  Hz,  $\text{CH}_3$ ), 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,  $\text{CO}_2\text{CH}_2$ ), 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).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 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 ( $\text{M}^+$ ). HRMS  $m/z$ : 401.1212 (Calcd for  $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_7$ : 401.1222). Handling of **15 $\alpha$**  was troublesome as static electricity caused it to stick to the spatula or paper. **15 $\beta$**  (more polar): oil.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.40 (t, 3H,  $J = 7.2$  Hz,  $\text{CH}_3$ ), 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,  $\text{CO}_2\text{CH}_2$ ), 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- $\alpha$ -L-arabinofuranosyl)imidazole (**2 $\alpha$** )

A solution of **15 $\alpha$**  (106 mg, 0.27 mmol) and 100%  $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$  (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 (+)-**2 $\alpha$**  (38 mg, 73 %) as a single isomer. colorless oil.  $[\alpha]_{\text{D}} +39.3^\circ$  ( $c=1.95$ , MeOH).  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$ : 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).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 42.7, 58.0, 59.0, 75.1, 78.4, 137.0.

### Conversion of 14 into 2

Phthalimide (27 mg, 0.19 mmol) and  $\text{Ph}_3\text{P}$  (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%  $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$  (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 2 $\alpha$  and 2 $\beta$  as an oil. The coexistence of the minor product (2 $\beta$ ) was indicated in the  $^1\text{H-NMR}$  spectrum [e. g. 5.03 (s, 1'H)].

### 4(5)-{5-[N-(4-Chlorophenyl)thioureido]- $\alpha$ -L-arabinofuranosyl} imidazole (18)

The same procedure for the preparation of 19 as described later provided 18 (80 mg, 70 %) as an oil from 2 $\alpha$  (62 mg) and 4-phenyl isothiocyanate (80 mg, 0.47 mmol) in MeOH (7 mL). ORD ( $c=2.88$ , EtOH)  $[\alpha]$  (nm) +45.9 (589), +52.2 (550), +66.8 (500), +85.6 (450); IR (nujol)  $\text{cm}^{-1}$ : 3260 (OH), 1535, 1082 [NHC(S)NH].  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$ : 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 [ $\text{M}^+ - (\text{NHC}_6\text{H}_4\text{Cl})$ ], 169 [ $\text{M}^+ - [\text{NHC(S)NHC}_6\text{H}_4\text{Cl}]$ ].

### 4(5)-{5-[N-(4-Chlorophenyl)ureido]- $\alpha$ -L-arabinofuranosyl}imidazole (19)

A solution of 2 $\alpha$  (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)  $[\alpha]$  (nm) +43.7 (589), +51.7 (550), +66.8 (500), +88.3 (450).  $^1\text{H NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  : 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 ( $\text{M}^+ - \text{H}_2\text{O}$ ). HRMS  $m/z$ : 335.0917 (calcd for  $\text{C}_{15}\text{H}_{15}\text{N}_4\text{O}_2\text{Cl}$ : 335.0910).

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

A solution of **2a** (91 mg, 0.46 mmol) and dimethyl *N*-cyanodithioiminocarbonate (81 mg, 0.50 mmol) was stirred overnight at rt, and then 40% MeNH<sub>2</sub> 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) [ $\alpha$ ] (nm) +23.5 (589), +27.0 (550), +35.4 (500), +48.7 (450); IR (neat) cm<sup>-1</sup>: 2170 (CN), 1590 (C=N). <sup>1</sup>H-NMR (CD<sub>3</sub>OD)  $\delta$ : 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<sup>+</sup> -OH).

**ACKNOWLEDGEMENT**

We are grateful to Prof. A. Yamatodani, Dr. Y. Yamamoto, and Mr. T. Hashimoto at School of Allied Health Science, Faculty of Medicine, Osaka University for biological evaluation of related compounds and encouraging us in this study. The authors also thank Mr. T. Sakai and Mr. K. Miyoshi for assistance with some of these experiments. Financial support of this work by the Ministry of Education, Science, and Culture of Japan [Grant No. 09877421 (S.H.) and 90067281 (T.K.)] is gratefully acknowledged.

**REFERENCES**

1. J. -M. Arrang, M. Garbarg, and J. -C. Schwartz, *Nature (London)*, 1983, **302**, 837.
2. J. -M. Arrang, M. Garbarg, J. -C. Lancelot, J. -M. Lecomte, H. Pollard, M. Robba, W. Schunack, and J. -C. Schwartz, *Nature (London)*, 1987, **327**, 117.
3. E. Schlicker, B. Malinowska, M. Kathmann, and M. Göthert, *Fundam Clin Pharmacol.*,

- 1994, **8**, 128.
4. For recent reviews on the medicinal chemistry and therapeutic potentials of ligands of the  $\alpha_1$  and histamine  $H_3$  receptor, see: (a) W. Schunack, *Actual. Chim. Ther.*, 1993, **20**, 9. (b) W. Schunack, Stark, *Eur. J. Drug Metab. Pharmacokinet.*, 1994, **19**, 173. (c) R. Leurs, R. C. Vollinga, and H. Timmerman, *Prog. Drug Res.*, 1995, **45**, 107. (d) H. Stark, E. Schlicker, and W. Schunack, *Drugs Future*, 1996, **21**, 507. (e) R. Leurs, P. Blandina, C. Tedford, and H. Timmerman, *TiPS* 1998, **19**, 177.
  5. N. -Y. Shin, A. T. Lupo Jr, R. Aslanian, S. Orlando, J. J. Piwinski, M. J. Green, A. K. Ganguly, M. A. Clark, S. Tozzi, W. Kreutner, and J. A. Hey, *J. Med. Chem.*, 1995, **38**, 1593
  6. (a) S. Harusawa, T. Imazu, S. Takashima, L. Araki, H. Ohishi, T. Kurihara, Y. Yamamoto, and A. Yamatodani, *Tetrahedron Lett.*, 1999, **40**, 2561. (b) S. Harusawa, T. Imazu, S. Takashima, L. Araki, H. Ohishi, T. Kurihara, Y. Sakamoto, Y. Yamamoto, and A. Yamatodani, *J. Org. Chem.*, 1999, **64**, 8608.
  7. T. Mochizuki, A. Yamatodani, K. Okakura, M. Takemura, N. Inagaki, and H. Wada, *Naunyn Schmiedebergs Arch. Pharmacol.*, 1991, **343**, 190.
  8. Y. Yamamoto, T. Mochizuki, K. Okakura-Mochizuki, A. Uno, and A. Yamatodani, *Methods Find. Exp. Clin. Pharmacol.*, 1997, **19**, 289.
  9. S. Harusawa, T. Imazu, S. Takashima, L. Araki, H. Ohishi, T. Kurihara, Y. Sakamoto, Y. Yamamoto, T. Hashimoto, and A. Yamatodani, The 8th Japan-Korea Joint Symposium on Drug and Development (Abstract, p. 37). Tokyo, April 10-12, 2000.
  10. (a) C. S. Lee, J. Du, and C. K. Chu, *Nucleosides & Nucleotides.*, 1996, **15**, 1223. (b) C. Liang, T. Ma, J. S. Cooperwood, J. Du, and C. K. Chu, *Carbohydr. Res.*, 1997, **303**, 33.
  11. For recent reviews on the chemistry, biochemistry, and synthesis of C-nucleoside analogues, see: (a) K. A. Watanabe, The Chemistry of C-Nucleosides. In *Chemistry of Nucleosides and*



- Nucleotides*; ed. by L. B. Townsend, Plenum Press, New York, 1994; Vol. 3, pp. 421-535.
- (b) M. A. E. Shaban, and A. Z. Nasr, The Chemistry of C-Nucleosides and Their Analogs I: C-Nucleosides of Hetero Monocyclic Bases. In *Advances In Heterocyclic Chemistry*; ed. by A. R. Katritzky, Academic Press, New York, 1997, Vol. 68, pp. 223-432.
- (c) D. E. Levy and C. Tang, The Chemistry of C-Glycosides. In *Tetrahedron Organic Chemistry Series*; Vol.13, ed. by J. E. Baldwin and P. D. Magnus, Pergamon, New York, 1995.
12. (a) S. Harusawa, Y. Murai, H. Moriyama, H. Ohishi, R. Yoneda, and T. Kurihara, *Tetrahedron Lett.*, 1995, **36**, 3165. (b) S. Harusawa, Y. Murai, H. Moriyama, T. Imazu, H. Ohishi, R. Yoneda, and T. Kurihara, *J. Org. Chem.*, 1996, **61**, 4405. (c) S. Harusawa, H. Moriyama, Y. Murai, T. Imazu, H. Ohishi, R. Yoneda, T. Kurihara, H. Hata, and Y. Sakamoto, *Chem. Pharm. Bull.*, 1997, **45**, 53.
13. T. Tsunoda, J. Otsuka, Y. Yamamiya, and S. Ito, *Chem. Lett.*, 1994, 539.
14. (a) M. Yokoyama, A. Toyoshima, T. Akiba, and H. Togo, *Chem. Lett.*, 1994, 265. (b) M. Yokoyama, H. Toyoshima, M. Shimizu, and H. Togo, *J. Chem. Soc., Perkin Trans. 1*, 1997, 29.
15. S. Tejima and H. G. Fletcher Jr, *J. Org. Chem.*, 1963, **28**, 2999.
16. (a) M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 1968, 2199. (b) N. T. Anh, *Top. Curr. Chem.*, 1980, **88**, 145.

Received, 25th May, 2000