SYNTHESIS OF 4(5)-(5'-AMINO-5'-DEOXY-α-L ARABINO-
FURANOSYL)IMIDAZOLE AND ITS 5'-DERIVATIVES USING MODIFIED MITSUNOBU CYCLIZATION: SYNTHETIC STUDIES TOWARD NOVEL HISTAMINE H3-LIGANDS

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Abstract - The modified Mitsunobu cyclization of 4-(2',3',5'--
tri-O-benzyl-L-arabinosyl)imidazole (11RS) using N,N,N',N'-tetramethyl-
azodicarboxamide and Bu4P 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)thio-
ureido]-α-L-arabinofuranosyl)imidazole (19), and 1-cyano-2-methyl-3-
(5-deoxy-1-1H-imidazol-4(5)-yl]-α-L-arabinofuranosyl)guanidine (20) were efficiently synthesized from 2α.

Introduction

The histamine H3(H3) receptors1 exist on histaminergic fibers in the brain and modulate the synthesis and release of histamine as an autoreceptor.2 Moreover, H3-receptors have been shown to be heteroreceptors3 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 H3-receptors, have been extensively used as a pharmacological tool.3,4 H3-Agonists are regarded as a target for new therapeutics of bronchial asthma,5 and H3-antagonists are now expected to be potential drugs for memory degenerative disorders like Alzheimer's disease.3,4
We recently communicated 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 indicated that, among them, only (+)-4(5)-[5-(aminomethyl)tetrahydrofuran-2-yl]imidazole (imifuramine, 1) exhibited a clear H₃-agonistic activity. The activity of imifuramine measured by microdialysis was approximately equal to that of immepip. To the contrary, imifuramine exhibited a weak H₃-agonistic activity (pD₂ = 4) in an in vitro test using guinea pig ileum preparation, compared to that (pD₂ = 8) of R-α-methylhistamine.

The finding of imifuramine encouraged us to synthesize 4(5)-(5'-amino-5'-deoxy-α-L-arabinofuranosyl)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 H₃-agonists and antagonists. Furthermore, little work has been done concerning the synthesis and biological evaluation of the α-L-C-nucleosides, the sugar moiety of which has unnatural configuration.

We have recently reported that the modified Mitsunobu cyclization of a 1:1 anomic mixture (3RS) having an unsubstituted imidazole, using N,N,N',N'-tetramethylazodicarboxamid (TMAD) and Bu₃P, 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. had reported the synthesis of C-ribonucleosides having typical aromatic heterocycles, in which the
cyclization of the corresponding diols proceeds through intramolecular Sn2 reaction under standard Mitsunobu conditions (DEAD, Ph3P), 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),12ab 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 2α 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 (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 reaction12b 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 $-50^\circ C$, 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 $-65^\circ C$ 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.\textsuperscript{6,12} In $^1$H-NMR, a

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

\begin{center}
\begin{tabular}{|c|c|c|}
\hline
Run & Solvent & Yield(%) \textsuperscript{1)} \\
\hline
1 & i) THF & 0 - 35 \\
2 & i) toluene & 8 - 88 \\
3 & i) THF & 96 \textsuperscript{2)} \\
\hline
\end{tabular}
\end{center}

\textsuperscript{1) Isolated Yields of 10RS 2) A 72 : 28 diastereomixture of 10R and 10S}
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\textsuperscript{16} 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 Bu$_3$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 $^1$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\textsuperscript{12c} 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](image-url)
Table 2. The Modified Mitsunobu Cyclization of 11RS

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<table>
<thead>
<tr>
<th>Run</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>13α / 13β</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>rt</td>
<td>overnight</td>
<td>95</td>
<td>4.5 / 1</td>
</tr>
<tr>
<td>2</td>
<td>benzene</td>
<td>rt</td>
<td>overnight</td>
<td>89</td>
<td>9 / 1</td>
</tr>
<tr>
<td>3</td>
<td>toluene</td>
<td>0</td>
<td>2</td>
<td>82</td>
<td>9.5 / 1</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>2</td>
<td>64</td>
<td>15 / 1</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>-35</td>
<td>1.5</td>
<td>95</td>
<td>20 / 1</td>
</tr>
</tbody>
</table>
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improved to give a 20:1 anomic mixture in CH₂Cl₂ 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 α / β ratio of C-nucleosides.

The α-selectivity in this reaction may be explained as illustrated in Scheme 3. Reaction of the TMAD-Bu₃P adduct with 11R forms the zwitterion (16R). Preferential elimination of Bu₃P=O from 16R leads to an active form (17) of the imidazole ring. Spontaneous cyclization gives α-anomer (12α).

Although the isomer (11S) 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-ethoxycarbonyl compound (13) (α / β = 20 / 1) could be obtained in 87% overall yield from the starting tribenzyllarabinose (9) without isolation of diols (10R) and (10S), as shown in Scheme 4. Debenzylation of 13 with Pd(OH)₂-C in cyclohexene afforded triol (14) in 84% yield. Phthaloylmination 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 2α.
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 15α (ca. 40%). The correctness of their stereochemical assignment was indicated by the observation of an NOE between the Cl' and C5' protons of 15α, although the NOE enhancement between Cl' 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 H1-antagonists exhibit three common and essential structural features: imidazole headgroup, spacer and hydrophobic tail group. 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.

![Reaction Scheme](image)

**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. 1H- and 13C-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 Na₂SO₄, 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 (10R, 10S)

A solution of 7 (1.850 g, 6.39 mmol) in THF (3 mL) was cooled to -50°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°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 H₂O, and the solvent was removed under
reduced pressure. The residue was dissolved in EtOAc, and the solution was washed with H₂O, dried,
and evaporated to give a crude oil. The residue was purified by column chromatography to give 10RS
(1.445 g, 96 %) using a gradient solvent system [10% to 50% in EtOAc–hexane]. Although the
separation of 10R and 10S was not required for the following experiment, they could be isolated by use
of EtOAc-hexane (3:7) as eluent. 10S (less polar): oil. [α]₀ +1.14° (c=1.65, CHCl₃). IR (neat) cm⁻¹:
3400 (OH), 1215 (SO₂). ¹H-NMR (CDCl₃) δ: 0.40 (s, 6H, Si(CH₃)₂), 1.00 (s, 9H, C(CH₃)₃), 2.58 (s,
6H, N(CH₃)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, CH₂Ph × 3), 5.28 (d, 1H, J=7.3 Hz, 1'-H),
7.04-7.52 (m, 16H, 5-H and Ph × 3). ¹³C-NMR (CDCl₃) 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 C₃₂H₃₃N₃O₇SSi: 710.3292). 10R (more polar): pale yellow
oil. [α]₀ -27.0° (c=2.98, CHCl₃). IR (neat) cm⁻¹: 3400 (OH), 1215 (SO₂). ¹H-NMR (CDCl₃) δ: 0.41 (s,
6H, Si(CH₃)_2, 1.00 (s, 9H, C(CH₃)_3), 2.75 (s, 6H, N(CH₃)_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, CH₂Ph × 3), 5.32 (br s, 1H, 1'-H), 7.18-7.43 (m, 16H, 5'-H and Ph × 3). \(^{13}\)C-NMR (CDCl₃) 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 C₉₃H₄₃N₅O₇SSi: 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% NH₄OH, the solvent was evaporated to give a residue, which was extracted with EtOAc. The extract was washed with H₂O 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⁻¹: 3300 (OH). \(^1\)H-NMR (CDCl₃) 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, CH₂Ph × 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 (CDCl₃) 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 C₉₉H₅₉N₅O₇: 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⁻¹: 3280 (OH). \(^1\)H-NMR (CDCl₃) 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, CH₂Ph × 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 (CDCl₃) 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 C₉₉H₅₉N₅O₇: 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$_3$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$_2$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. $^1$H-NMR (CDCl$_3$) $\delta$ : 3.63 (d, 18 / 10H, $J = 5.1$ Hz, 5'-H$_{a}$), 3.66 (d, 2 / 10H, $J = 5.1$ Hz, 5'-H$_{b}$), 4.10 (t, 1 / 10H, $J = 4.1$ Hz, 4'-H$_{b}$), 4.15 (t, 9 / 10H, $J = 4.1$ Hz, 4'-H$_{a}$), 4.27-4.42 (m, 2H, 2'-H and 3'-H), 4.45-4.58 (m, 6H, CH$_2$Ph $\times$ 3), 5.10 (d, 9 / 10H, $J = 4.4$ Hz, 1'-H$_{a}$), 5.18 (d, 1 / 10H, $J = 3.4$ Hz, 1'-H$_{b}$), 6.90 (s, 1H, 5-H), 7.16-7.40 (m, 15H, Ph $\times$ 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$_3$P (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 **12α** and **12β**.

**Ethyl 4-(2',3',5'-Tri-O-benzyl-$\beta$-L-arabinofuranosyl)imidazole-1-carboxylate** (13) A mixture of **11RS** (770 mg, 1.58 mmol), TMAD (408 mg, 2.37 mmol), and Bu$_3$P (0.58 mL, 2.37 mmol) was treated in CH$_2$Cl$_2$ (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$_2$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$^{-1}$: 1760 (C=O). $^1$H-NMR (CDCl$_3$) $\delta$ : 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$_{b}$), 4.16 (dd, 20 / 21H, $J = 4.6$, 3.2 Hz, 4'-H$_{a}$), 4.30-4.66 (m, 10H, 2', 3'-H and CO$_2$CH$_2$, CH$_2$Ph $\times$ 3), 5.08 (d, 20 / 21H, $J = 4.2$ Hz,
1'-H_{a}), 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). \textsuperscript{13}C-NMR (CDCl\textsubscript{3}) \delta: 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\textsuperscript{+}1). HRMS m/z: 543.2477 (Calcd for C\textsubscript{35}H\textsubscript{37}N\textsubscript{2}O\textsubscript{6}: 543.2493).

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

A mixture of 13 (197 mg, 0.36 mmol), 20% Pd(OH)\textsubscript{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\textsuperscript{-1}: 3350 (OH), 1760 (C=O). \textsuperscript{1}H-NMR (CD\textsubscript{3}OD) \delta: 1.42 (t, 3H, J = 6.9 Hz, CH\textsubscript{3}), 3.65 (d, 1 / 21H, J = 4.6 Hz, 5'-H_{\beta}), 3.69 (d, 20 / 21H, J = 4.6 Hz, 5'-H_{a}), 3.73 (d, 20 / 21H, J = 3.5 Hz, 5'-H_{a}), 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_{a}), 4.06 (t, 20 / 21H, J = 5.9 Hz, 3'-H_{a}), 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\textsubscript{2}CH\textsubscript{2}), 4.73 (d, 20 / 21H, J = 5.9 Hz, 1'-H_{\beta}), 5.04 (d, 1 / 21H, J = 3.2 Hz, 1'-H_{\beta}), 7.54 (s, 1H, 5-H), 8.26 (s, 1H, 2-H). \textsuperscript{13}C-NMR (CD\textsubscript{3}OD) \delta: 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\textsuperscript{+}1). HRMS m/z: 273.1085 (Calcd for C\textsubscript{15}H\textsubscript{17}N\textsubscript{2}O\textsubscript{6}: 273.1085).

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

Phthalimide (24 mg, 0.166 mmol) and Ph\textsubscript{3}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 15α (ca. 40 %). 15α (less polar): white leaflets, mp 158-160 °C. IR (KBr) cm⁻¹: 3470 (OH), 1770 (N-CO-O), 1725 (CO-N-CO). ¹H-NMR (CDCl₃) δ : 1.42 (t, 3H, J = 7.0 Hz, CH₃), 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, CO₂CH₂), 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). ¹³C-NMR (CDCl₃) 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. EI-MS m/z: 401 (M⁺). HRMS m/z: 401.1212 (Calcd for C₁₉H₁₆N₅O₅: 401.1222). Handling of 15α was troublesome as static electricity caused it to stick to the spatula or paper. 15β (more polar): oil. ¹H-NMR (CDCl₃) δ : 1.40 (t, 3H, J = 7.2 Hz, CH₃), 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, CO₂CH₂), 4.58 (d, 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% NH₂NH₂·H₂O (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. [α]₀ +39.3° (c=1.95, MeOH). ¹H-NMR (CD₃OD) 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). ¹³C-NMR (CDCl₃) 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 Ph₃P (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% NH₂NH₂·H₂O (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 ¹H-NMR spectrum [e.g., 5.03 (s, 1'H)].

4(5)-{5-[N-(4-Chlorophenyl)thiocarbamido]-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 thiocarbamoyl 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]. ¹H-NMR (CD₂OD) δ: 3.8–4.0 (m, 4H, 2', 3', 5'-H), 4.10 (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⁺-(NHC₆H₄Cl)], 169 [M⁺-[NHC(S)NHC₆H₄Cl]].

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). ¹H NMR (CD₂OD) 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⁺-H₂O). HRMS m/z: 335.0917 (calcd for C₁₅H₁₃N₄O₂Cl: 335.0910).
1-Cyano-2-methyl-3-[5-deoxy-1-[1H-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% MeNH₂ 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). ¹H-NMR (CD₃OD) 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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