

**SYNTHESIS OF 4(5)-(a-D-XYLOFURANOSYL)MIDAZOLE
STARTING FROM L-ARABINOSE: MITSUNOBU CYCLIZATION
VIA C4'-OXYPHOSPHONIUM INTERMEDIATE**

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Abstract - 4(5)-(a-D-Xylofuranosyl)imidazole (**3**) was synthesized using Mitsunobu cyclization *via* C4'-oxyphosphonium intermediate (**5**) starting from L-arabinose.

INTRODUCTION

Imidazoles are biologically important heterocyclic compounds.¹ We have therefore directed our attention to synthesizing *C*-nucleosides having imidazole as the base moiety.^{2,3} From these studies, we found (+)-4(5)-[(2*R*,5*R*)-5-aminomethyltetrahydrofuran-2-yl]imidazole (imifuramine, **1**)³ as a new type of H₃-agonist (Figure 1), whose activity measured by *in vivo* brain microdialysis⁴ was approximately equal to that of the current H₃-agonist, imnepip.⁵ In our study of the structure - activity relationship in imifuramine, we recently described the stereoselective synthesis of 4(5)-(5-amino-5-deoxy-*a*-L-arabinofuranosyl)-imidazole (**2**)^{2d} by using modified Mitsunobu cyclization, in which the cyclization of an epimeric mixture of a diol (**7*RS***) having an unsubstituted imidazole, using *N,N,N',N'*-tetramethylazodicarboxamide (TMAD)⁶ and Bu₃P, stereoselectively afforded an *a*-L-arabinofuranosylimidazole derivative (**9**)(Scheme 1, Eq.2).

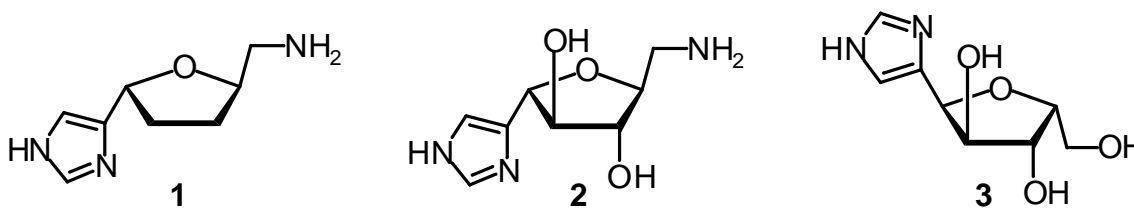
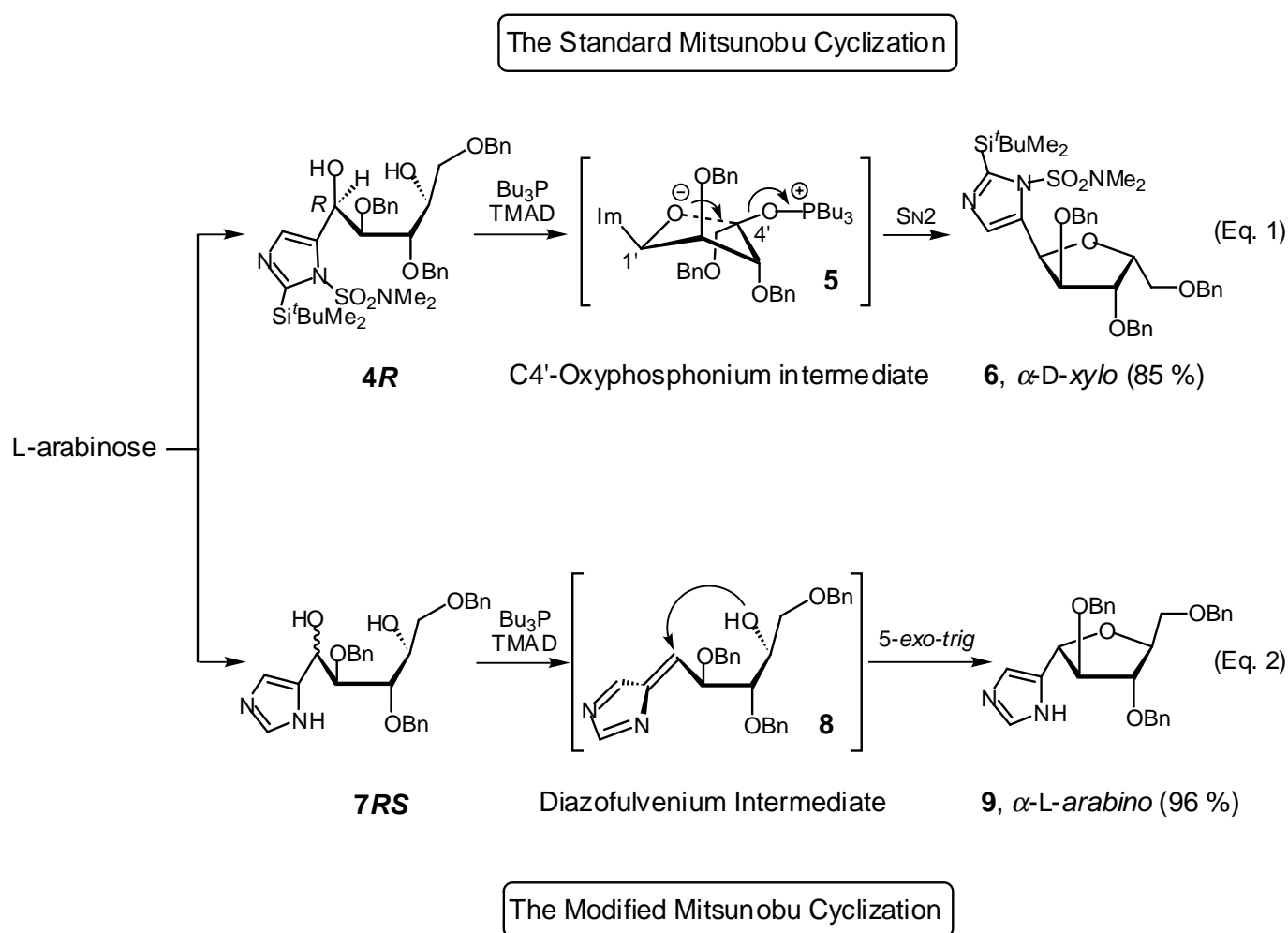


Figure 1



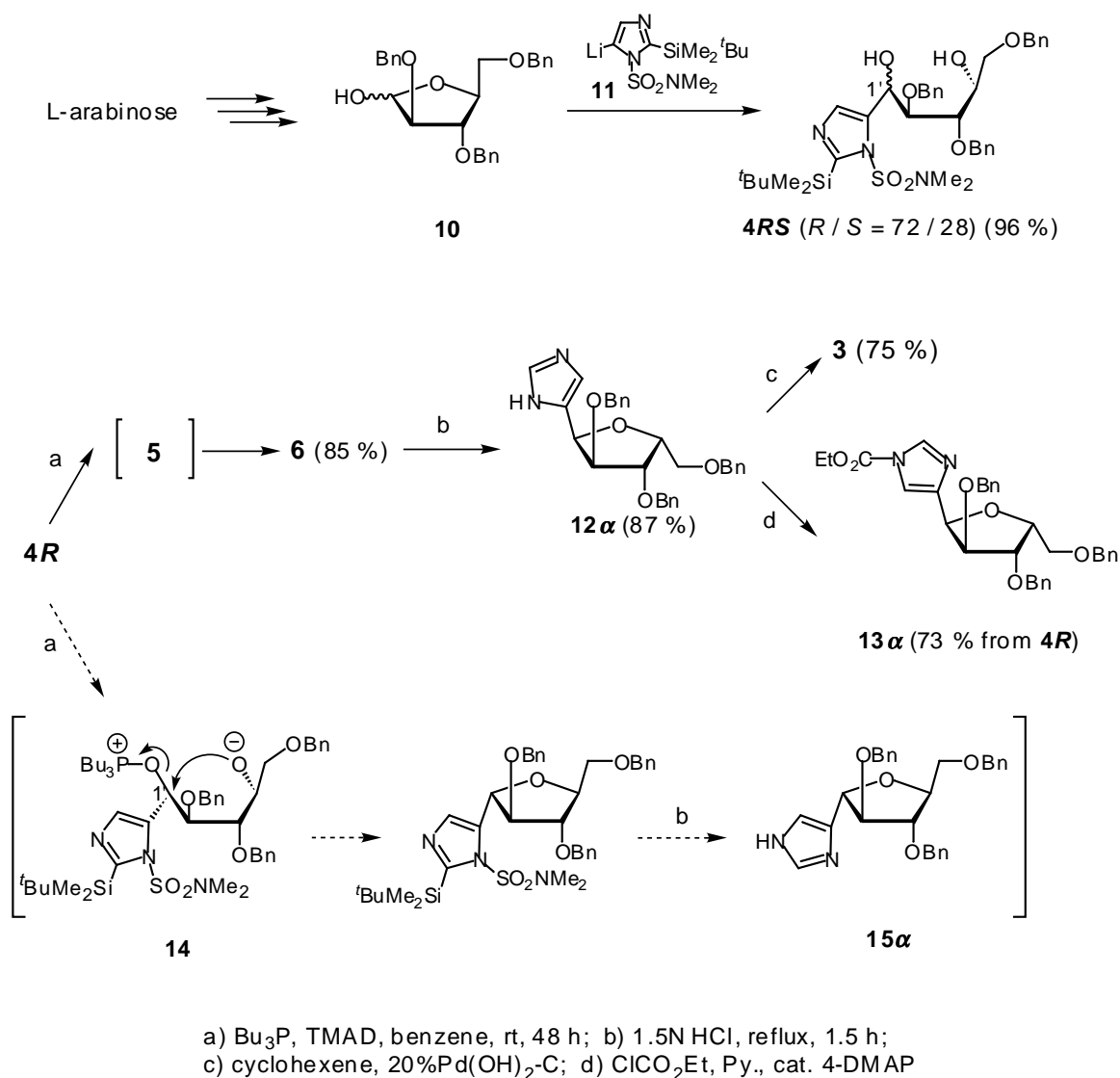
Scheme 1

The formation of the *a*-anomer (**9**) may be explained by a diazofulvene formation (**8**)^{2b,7} followed by a *5-exo-trig* process, together with action by the directing group of the C2'-benzyloxy group to control the stereochemistry of imidazole *C*-nucleosides.^{2d}

In our continuous interest in imidazole *C*-nucleosides, we found that Mitsunobu cyclization of a diol (**4R**) bearing a bis-protected imidazole proceeded through an intramolecular SN2 reaction of C4'-oxyphosphonium intermediate (**5**) to give a tribenzylated *a*-D-xylose derivative (**6**) (Scheme 1, Eq. 1). In this paper, we report the synthesis of *a*-D-xylofuranosylimidazole (**3**) starting from L-arabinose.

RESULTS AND DISCUSSION

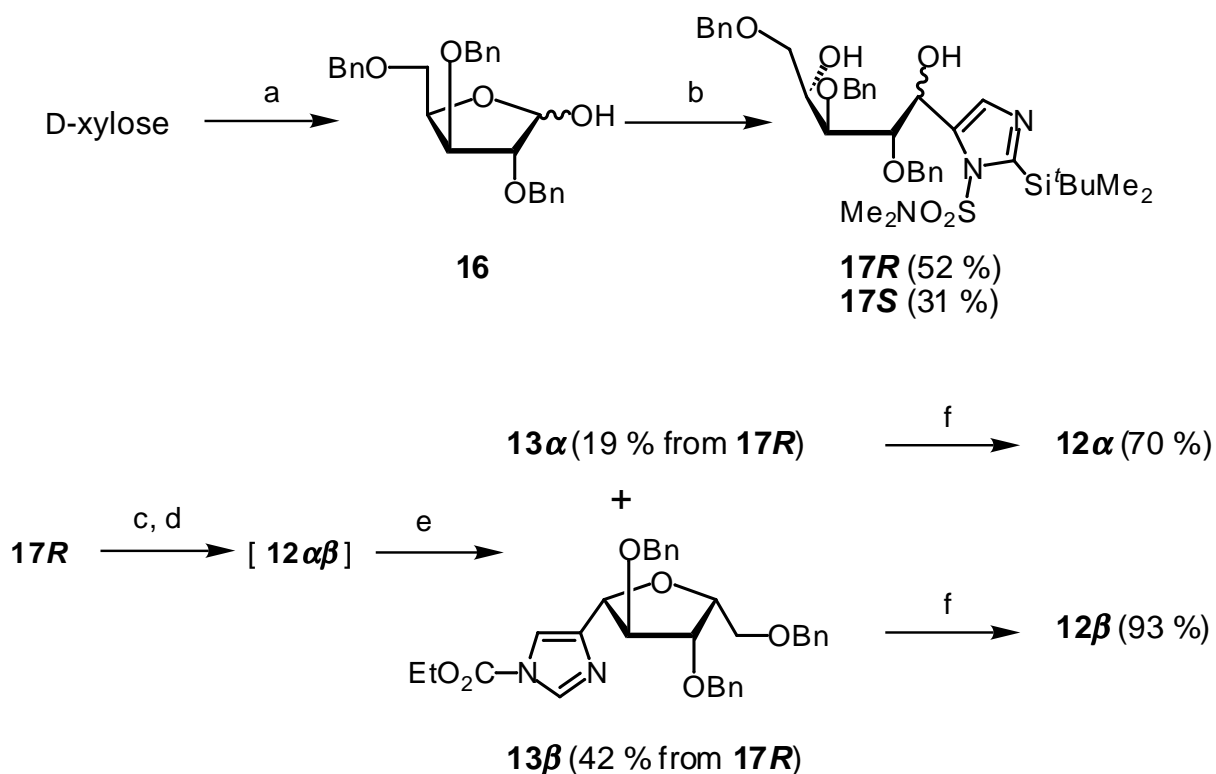
In the synthesis of *a*-L-arabinofuranosynucleoside (**2**)^{2d}, reaction of 2,3,5-tri-*O*-benzyl-L-arabinofuranose (**10**) with the lithium salt (**11**) of 2-*tert*-butyldimethylsilyl-*N,N*-dimethylimidazole-1-sulfonamide



Scheme 2

successfully affords an adduct (**4RS**) in 96% yield as a 72:28 diastereomixture, the respective epimers of which were separated easily by silica gel column chromatography (Scheme 2). Previously, Yokoyama *et al.*⁸ reported the synthesis of *C*-ribonucleosides having typical aromatic heterocycles using standard Mitsunobu conditions (DEAD , Ph_3P), in which the cyclization of the corresponding diols proceeds through an intramolecular $\text{S}_{\text{N}}2$ reaction of the C1'-oxyphosphonium intermediate, 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. We thus expected that Mitsunobu cyclization of the major isomer (**4R**) could

stereoselectively afford a tribenzylated α -L-arabinofuranosylimidazole (**15 α**) by the S_N2 reaction *via* the C1'-oxyphosphonium intermediate (**14**). However, when the Mitsunobu cyclization of **4R** was carried out with TMAD and Bu₃P at room temperature, a tetrahydrofuran derivative (**6**) was obtained in 85% yield. Hydrolysis of **6** afforded an unsubstituted imidazole (**12 α**), which was unexpectedly inconsistent with a benzylated α -L-arabinofuranosylimidazole (**15 α**) prepared previously.^{2d} The structure of **6** was corroborated as α -D-xylofuranosylimidazole by a chemical transformation from D-xylose, as described later. Debenzylation of **12 α** with Pd(OH)₂-C in cyclohexene afforded 4(5)-(α -D-xylofuranosyl)imidazole (**3**)(75%). We surmised that the compound (**6**) might be produced by the S_N2 reaction *via* the oxyphosphonium intermediate (**5**) arising from the less hindered C-4' hydroxy group. Few Mitsunobu cyclizations *via* the C4'-oxyphosphonium intermediate for the formation of C-nucleosides have been known.^{8,9} Exceptional example is the case that such an intermediate is formed due to the hydrogen bonding



Reagents and conditions : a) ref. 10 ; b) (i) **11**, -60~50 ; (ii) rt, 1 h; c) 1.5N HCl, reflux, 2.5 h; d) Bu₃P, TMAD, benzene, rt, 16 h; e) ClCO₂Et, Py., cat 4-DMAP; f) 1N HCl, reflux, 2 h

Scheme 3

between C1'-OH and the nitrogen atom on the pyridyl base in the cyclization of 2-(2,3-*O*-isopropylidene-5-*O*-trityl- α -L-lyxofuranosyl)pyridine, as speculated by Yokoyama *et al.*^{8a}

In order to confirm the structure of **6**, we thus intended to synthesize the 4(5)-(2,3,5-tri-*O*-benzyl- α -D-xylofuranosyl)imidazole (**12 α**) from D-xylose using the modified Mitsunobu cyclization (Scheme 3). The starting 2,3,5-tri-*O*-benzyl-D-xylose (**16**) was synthesized from D-xylose as described by Dondoni *et al.*¹⁰ Reaction of **16** with the lithium salt (**11**) gave diastereomers (**17R**) (polar, 52%) and (**17S**) (less polar, 31%), the configuration at C1' of which was assigned by analogy with our previous reports.^{2b} In ¹H-NMR, a small $J_{1',2'}$ coupling constant (br s, $J_{1',2'} = < 2$ Hz) was observed in **17R** compared to that of **17S** (d, $J_{1',2'} = 7.2$ Hz) having a 1',2'-anti-parallel orientation. The major isomer (**17R**) was successively transformed into **13 α** (19%) and **13 β** (42%) by deprotection of the imidazole moiety, the modified Mitsunobu cyclization, and ethoxycarbonylation of the resulting **12 $\alpha\beta$** for ease of isolation. The more polar isomer of **13 α** and **13 β** was consistent with the ethoxycarbonyl compound (**13 α**) prepared from L-arabinose. Their relative configurations were identified by NOESY experiments of the respective unsubstituted imidazoles (**12 α** and **12 β**) as illustrated in Figure 2, in which the C1'-H in **12 β** was found to have proper interaction with C4'-H, showing the β -anomer. Therefore, it was confirmed that the standard Mitsunobu cyclization of **4R** affords α -D-xylose derivative (**6**) via S_N2 reaction of the C4'-oxyphosphonium intermediate (**5**).

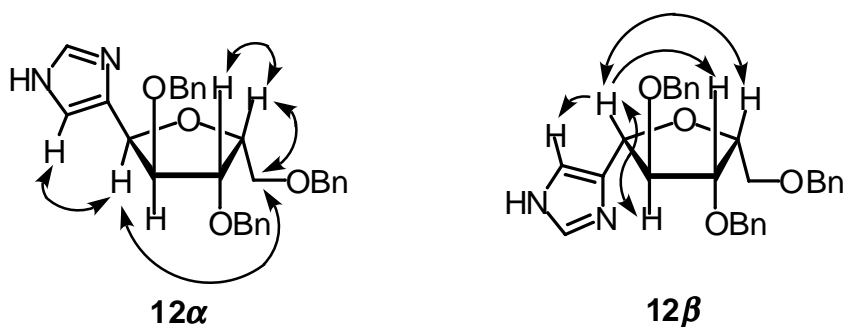


Figure 2

EXPERIMENTAL

Optical rotation measurements were recorded with a JASCO DIP-1000 digital polarimeter. ^1H - 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- α -D-xylofuranosyl)-*N,N*-dimethyl-imidazole-1-sulfonamide (6)

To a solution of **4R**^{2d} (404 mg, 0.57 mmol) and Bu_3P (0.23 mL, 0.86 mmol) in benzene (10 mL) at 0 was added TMAD (148 mg, 0.86 mmol). The reaction mixture was stirred at rt for 48 h. The insoluble material was filtered through a Celite pad, and the 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 [10% EtOAc in hexane] to give **6** (333 mg, 85 %). **6**: oil. $[\alpha]_{\text{D}} -36.6^\circ$ ($c=2.57$, CHCl_3). ^1H -NMR (CDCl_3) δ : 0.39 [s, 3H, SiCH_3], 0.41 [s, 3H, SiCH_3], 0.97 [s, 9H, $\text{C}(\text{CH}_3)_3$], 2.78 [s, 6H, $\text{N}(\text{CH}_3)_2$], 3.73 (d, 2H, $J = 6.0$ Hz, 5'-H), 4.06 (d, 1H, $J = 4.4$ Hz), 4.20 (1H, s, 4'-H), 4.24 (d, 1H, $J = 4.4$ Hz), 4.37-4.64 (m, 6H, $\text{CH}_2\text{Ph} \times 3$), 5.46 (d, 1H, $J = 4.4$ Hz, 1'-H), 7.08-7.43 (m, 16H, 5-H and $\text{Ph} \times 3$). ^{13}C -NMR (CDCl_3) δ : 18.4, 27.3, 37.7, 68.3, 72.1, 72.3, 73.4, 75.0, 79.2, 82.0, 82.3, 127.5, 127.6, 127.7, 128.2, 128.3, 130.3, 133.1, 137.4, 137.6, 138.1, 155.2. SIMS m/z : 692 ($\text{M}^+ + 1$). HRMS m/z : 692.3183 (Calcd for $\text{C}_{37}\text{H}_{50}\text{N}_3\text{O}_6\text{SSi}$: 692.3187).

4(5)-(2,3,5-Tri-*O*-benzyl- α -D-xylofuranosyl)imidazole (12 α)

A solution of **6** (333 mg, 0.48 mmol) in THF (8 mL) and 1.5N HCl (8 mL) was refluxed for 1.5 h and then cooled. After neutralization by addition of NaHCO_3 , 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 10% MeOH in EtOAc afforded **12 α** (198 mg, 87 %) as a colorless oil. $[\alpha]_D -24.7^\circ$ ($c=2.27$, CHCl_3). $^1\text{H-NMR}$ (CDCl_3) δ : 3.68-3.78 (m, 2H, 5'-H), 4.00 (dd, 1H, $J = 3.0, 1.5$ Hz, 2'-H), 4.13 (dd, 1H, $J = 4.4, 1.5$ Hz, 3'-H), 4.24 (d, 1H, $J = 11.9$ Hz, CHHPh), 4.33 (d, 1H, $J = 11.9$ Hz, CHHPh), 4.41-4.63 (m, 5H, $\text{CH}_2\text{Ph} \times 2$), 5.27 (d, 1H, $J = 3.1$ Hz, 1'-H), 7.02 (s, 1H, 5-H), 7.05-7.38 (m, 15H, $\text{Ph} \times 3$), 7.54 (s, 1H, 2-H). $^{13}\text{C-NMR}$ (CDCl_3) δ : 68.7, 72.2, 72.4, 73.5, 75.1, 79.1, 81.8, 82.8, 127.5, 127.7, 127.8, 128.2, 128.3, 135.2, 137.2, 137.4, 137.9. EIMS m/z : 470 (M^+). HRMS m/z : 470.2200 (Calcd for $\text{C}_{29}\text{H}_{30}\text{N}_2\text{O}_4$: 470.2204).

4(5)-(α -D-Xylofuranosyl)imidazole (3)

A mixture of **12 α** (198 mg, 0.42 mmol), 20% $\text{Pd}(\text{OH})_2\text{-C}$ (119 mg), and cyclohexene (1.3 mL, 12.6 mmol) in EtOH (20 mL) was refluxed for 5 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, which was subsequently placed in a column. Chromatography using 25% MeOH-EtOAc to give **3** (63 mg, 75 %) as a white amorphous product. $[\alpha]_D -36.6^\circ$ ($c=2.76$, CH_3OH). $^1\text{H-NMR}$ (CD_3OD) δ : 3.76 (dd, 1H, $J = 12.1, 6.4$ Hz, 5'-H), 3.84 (dd, 1H, $J = 12.1, 5.0$ Hz, 5'-H), 4.14 (dd, 1H, $J = 3.2, 1.6$ Hz, 2'-H), 4.27 (dd, 1H, $J = 3.8, 1.6$ Hz, 3'-H), 4.38 (ddd, $J = 6.2, 5.2$, and 3.8 Hz), 5.26 (d, 1H, $J = 3.2$ Hz, 1'-H), 7.36 (s, 1H, 5-H), 8.42 (s, 1H, 2-H). $^{13}\text{C-NMR}$ (CD_3OD) δ : 61.8, 76.3, 78.4, 79.8, 82.7, 118.9, 133.4, 135.3. EIMS m/z : 200 (M^+). HRMS m/z : 200.0782 (Calcd for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_4$: 200.0796).

Ethyl 4-(2, 3, 5-Tri-O-benzyl- α -D-xylofuranosyl)imidazole-1-carboxylate (13 α)

A solution of **6** (71 mg, 0.10 mmol) in THF (2.5 mL) was refluxed with 1.5N HCl (2.0 mL) for 1.5 h to give a crude oil (**12 α** , 59 mg) by the same procedures as above. A mixture of **12 α** , pyridine (11 mg, 0.13 mmol), ethyl chloroformate (11 mg, 0.1 mmol) and a catalytic amount of 4-DMAP was refluxed for 20 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 20% EtOAc in hexane as eluent to give **13 α** (41 mg, 73 %). **13 α** : oil. $[\alpha]_D -3.76^\circ$

($c=2.01$, CHCl_3). $^1\text{H-NMR}$ (CDCl_3) : 1.41 (t, 3H, $J = 7.1$ Hz, CH_3), 3.72 (dd, 1H, $J = 8.8, 6.2$ Hz, 5'-H), 3.77 (dd, 1H, $J = 10.7, 6.2$ Hz, 5'-H), 4.10 (dd, 1H, $J = 4.1, 1.9$ Hz), 4.22 (dd, 1H, $J = 4.1, 1.5$ Hz), 4.33 (s, 2H, CHHPh), 4.41 (d, 1H, $J = 11.8$ Hz, CHHPh), 4.43 (q, 2H, CH_2CH_3 , $J = 7.1$ Hz), 4.52 (d, 1H, CHHPh , $J = 11.8$ Hz), 4.53 (q, 1H, $J = 4.2$ Hz, 4'-H), 4.54 (d, 1H, $J = 11.8$ Hz, CHHPh), 4.63 (d, 1H, $J = 11.8$ Hz, CHHPh), 5.26 (d, 1H, $J = 4.1$ Hz, 1'-H), 7.08-7.40 (m, 15H, $\text{Ph} \times 3$), 7.48 (s, 1H, 5-H), 8.10 (s, 1H, 2-H). $^{13}\text{C-NMR}$ (CDCl_3) δ : 14.2, 64.2, 68.6, 72.2, 72.4, 73.4, 78.1, 79.3, 82.0, 82.3, 115.3, 127.4, 127.5, 126.6, 128.1, 128.2, 128.3, 136.3, 137.6, 137.7, 138.1, 140.9, 148.5. EIMS m/z : 543 ($\text{M}^+ + 1$). HRMS m/z : 543.2486 (Calcd for $\text{C}_{32}\text{H}_{35}\text{N}_2\text{O}_6$: 543.2493).

2-*tert*-Butyldimethylsilyl-5-(2,3,5-tri-*O*-benzyl-*D*-xylosyl)-*N,N*-dimethylimidazole-1-sulfonamide (17R, 17S)

A solution of 2-*tert*-butyldimethylsilyl-*N,N*-dimethylimidazole-1-sulfonamide (1.24 g, 4.29 mmol) in THF (3 mL) was cooled to -50°C and treated dropwise over 20 min with 1.6 M BuLi-hexane (2.7 mL, 4.29 mmol) to precipitate the white lithium salt (**11**). The resulting suspension was again cooled to -60°C , and a solution of **16**¹⁰ (0.60 g, 1.43 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 1 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, which was purified by column chromatography to give **17S** (309 mg, 31 %) and **17R** (525 mg, 52 %) using a gradient solvent system [30% to 85% in EtOAc-hexane]. **17S** (less polar): oil. $[\alpha]_{\text{D}} +6.03^\circ$ ($c=3.77$, CHCl_3). $^1\text{H-NMR}$ (CDCl_3) : 0.40 [s, 6H, $\text{Si}(\text{CH}_3)_2$], 1.02 [s, 9H, $\text{C}(\text{CH}_3)_3$], 2.53 (d, 1H, $J = 7.2$ Hz), 2.78 [s, 6H, $\text{N}(\text{CH}_3)_2$], 3.11 (d, 1H, $J = 7.2$ Hz), 3.30 (dd, 1H, $J = 8.0, 7.2$ Hz, 5'-H), 3.48 (dd, 1H, $J = 8.0, 7.2$ Hz, 5'-H), 3.68 (dd, 1H, $J = 6.6, 2.4$ Hz), 3.94 (m, 1H, OH), 4.10 (t, 1H, $J = 7.2$ Hz), 4.4 (s, 2H, CH_2Ph), 4.52 (d, 2H, $J = 12.0$ Hz, CH_2Ph), 4.70 (dd, 2H, $J = 12.0, 8.0$ Hz, CH_2Ph), 5.26 (t, 1H, $J = 7.2$ Hz, 1'-H), 7.1-7.45 (m, 16H, 5-H and $\text{Ph} \times 3$), 7.53 (s, 1H, 4-H). $^{13}\text{C-NMR}$ (CDCl_3) δ :

19.3, 27.4, 37.4, 64.3, 69.1, 71.2, 73.2, 74.7, 74.9, 79.1, 82.2, 127.6-128.4 (Ph), 131.6, 134.2, 137.4, 137.6, 137.9. SIMS m/z : 710 ($M^+ + 1$). HRMS m/z : 710.3280 (Calcd for $C_{37}H_{52}N_3O_7SSi$: 710.3292). **17R** (more polar): oil. $[\alpha]_D -21.2^\circ$ ($c=2.23$, $CHCl_3$). 1H -NMR ($CDCl_3$) δ : 0.40 [s, 6H, $Si(CH_3)_2$], 1.03 [s, 9H, $C(CH_3)_3$], 2.80 [s, 6H, $N(CH_3)_2$], 3.18 (m, 1H), 3.32 (dd, 1H, $J = 9.4, 7.0$ Hz), 3.48 (t, 1H, $J = 7.0$ Hz), 3.67 (d, 1H, $J = 5.9$ Hz), 3.92 (d, 1H, $J = 5.9$ Hz), 4.26-4.52 (m, 5H, $CH_2Ph \times 3$), 4.70 (d, 1H, $J = 11.8$ Hz), 5.36 (br s, 1H, 1'-H), 7.1-7.4 (m, 15H, $Ph \times 3$), 7.43 (s, 1H, 4-H). ^{13}C -NMR ($CDCl_3$) δ : 18.5, 27.4, 37.7, 63.6, 67.4, 71.0, 73.2, 73.9, 74.5, 76.1, 78.5, 127.7-128.5 (Ph), 129.1, 129.2, 131.9, 134.9, 136.0, 137.2, 137.4, 137.8, 138.6, 154.0. SIMS m/z : 710 ($M^+ + 1$). HRMS m/z : 710.3285 (Calcd for $C_{37}H_{52}N_3O_7SSi$: 710.3292).

Conversion of **17R** to **13 α** and **13 β** using the modified Mitsunobu Cyclization

A solution of **17R** (103 mg, 0.15 mmol) in THF (3 mL) and 1.5N HCl (2 mL) was refluxed for 2.5 h and then cooled. After neutralization by addition of $NaHCO_3$, the solvent was evaporated to give a residue, which was extracted with EtOAc by salting-out techniques. The extract was evaporated to give an oil (57 mg), which was then diluted with benzene (3 mL). Then, Bu_3P (0.06 mL, 0.23 mmol) and TMAD (40 mg, 0.23 mmol) were added to the solution at 0 . The reaction mixture was stirred at rt for 16 h. The insoluble material was filtered through a Celite pad, and the filtrate was condensed. The residue was diluted with EtOAc, and the organic layer was washed with H_2O and brine, dried, and evaporated to give a crude oil of **12 $\alpha\beta$** . A solution of **12 $\alpha\beta$** in benzene (2 mL) was refluxed with ethyl chloroformate (0.02 mL, 0.21 mmol), pyridine (0.03 mL, 0.37 mmol), and a catalytic amount of 4-DMAP for 3h to give **13 β** (34 mg, 42 %) and **13 α** (16 mg) by the same procedure as used for the preparation of **13 α** . **13 β** (less polar): oil. $[\alpha]_D -38.8^\circ$ ($c=2.54$, $CHCl_3$). 1H -NMR ($CDCl_3$) : 1.42 (t, 3H, $J = 8.4$ Hz, CH_3), 3.84 (m, 2H, 5'-H), 4.06 (dd, 1H, $J = 3.8, 0.8$ Hz), 4.29 (dd, 1H, $J = 3.8, 0.8$ Hz), 4.34-4.70 (m, 9H), 4.96 (d, 1H, $J = 3.1$ Hz, 1'-H), 7.08-7.40 (m, 16H, 5-H and $Ph \times 3$), 8.08 (s, 1H, 2-H). ^{13}C -NMR ($CDCl_3$) δ : 14.3, 64.3, 68.5, 71.3, 71.7, 73.4, 80.6, 80.8, 83.0, 86.5, 114.3, 127.4-128.3 (Ph), 136.7, 137.6, 137.7,

138.1, 143.2, 148.5. EIMS m/z : 542 (M^+). HRMS m/z : 542.2409 (Calcd for $C_{32}H_{34}N_2O_6$: 542.2415).

4-(2,3,5-Tri-*O*-benzyl- β -D-xylofuranosyl)imidazole (12 β)

A solution of **13 β** (78 mg, 0.14 mmol) in EtOH (1.5 mL) and 1N HCl (0.7 mL) was refluxed for 2 h and then cooled. After neutralization by addition of $NaHCO_3$, 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 10% MeOH in EtOAc afforded **12 β** (61 mg, 93 %) as a colorless oil. 1H -NMR ($CDCl_3$) δ : 3.77 (dd, 1H, $J = 9.9, 5.3$ Hz, 5'-H), 3.86 (dd, 1H, $J = 9.9, 5.3$ Hz, 5'-H), 4.14 (br m, 1H), 4.36 (dd, 1H, $J = 8.6, 5.1$ Hz, 4'-H), 4.54-4.65 (m, 6H, $J = 11.9$ Hz, $CH_2Ph \times 3$), 5.02 (d, 1H, $J = 3.2$ Hz, 1'-H), 6.94 (1H, s, 5-H), 7.26 (m, 16H, Ph $\times 3$ and 2-H). ^{13}C -NMR ($CDCl_3$) δ : 68.3, 71.9, 72.4, 73.6, 78.0, 79.8, 82.5, 86.5, 127.5, 127.8, 127.9, 128.1, 128.4, 128.5, 135.3, 137.1, 137.2, 137.6. EIMS m/z : 470 (M^+). HRMS m/z : 470.2208 (Calcd for $C_{29}H_{30}N_2O_4$: 470.2204).

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