Synthesis and Properties of *C*-Azalyxonucleosides

Atsuya Momotake,[†] Jun Mito,[†] Kentaro Yamaguchi,[†,‡] Hideo Togo,[†,§] and Masataka Yokoyama*,[†]

Department of Chemistry, Faculty of Science, Graduate School of Science and Technology, and Chemical Analysis Center, Chiba University, Yayoi-cho 1-33, Inage-ku, Chiba city 263-8522, Japan

Received March 16, 1998

1-*β*-(4-Imidazoyl)- and 1-*β*-(5-uracilyl)-1,4-dideoxy-1,4-imino-L-lyxitols were synthesized stereoselectively *via* a sequential procedure by the addition of the corresponding metal salts of heterocycles, Swern oxidation, reductive aminocyclization, and deprotection. Their structures were determined based on X-ray crystallography. From the NMR measurements of their *N*-acyl derivatives, two rotational isomers were observed. Their bioassay is also described.

Introduction

Novel ribonucleoside analogs which would be easily handed, enable a large-scale synthesis and form a long-lived enzyme−nucleoside complex have been required to investigate a variety of RNA-related enzymes in a living cell. A major purpose of our study is to develop a convenient synthetic method for new types of RNA subunits that show a complete stability under physiological conditions and to investigate their structural properties and behavior in a living cell. First, in order to obtain stable analogs of the RNA subunit, it is required to alternate the structure of the sugar moiety and/or the base moiety in nucleosides. These ribonucleoside analogs should be able not only to act as an anti-virus drug which inhibits a reverse transcriptase but also to generate a long-lived protein-RNA complex. We have focused our attention on the synthesis of an azasugar-containing *C*-linked nucleoside, the so-called *C*-azanucleosides.[1] The azasugars have been known as effective inhibitors of glycosidase enzymes, presumably by mimicking the developing positive charge on a pyranose intermediate with the heterocyclic nitrogen protonated at physiological pH.[2] If the nucleoside has an azasuger as its sugar moiety, it would also inhibit the hydrolysis of the glycosyl bond by a base-excision DNA repair enzyme which is recognized in DNA aberrant bases.[3] Owing to the lability of the N/O or N/N acetal function which characterizes the glycosides of azasugars, most natural and unnatural piperidine azasugars lack a substituent at the anomeric position. Therefore, the *N*-protected type[4] or *C*-linked type[1] of nucleosides is required as the stable azasugar-containing nucleoside analogs. To our best knowledge, such types of nucleosides have been known in some reports, but their chemistry has not been investigated in detail. Thus, we intended to synthesize the *C*-azanucleosides in gram quantities and by a simple method.[5] Here we report the following results: (1) stereoselective synthesis of *C*-azalyxonucleosides starting from *O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribo-furanose **1** *via* a sequential procedure by the addition of metal salts of uracil or imidazole, Swern oxidation, and reductive aminocyclization using ammonium formate and $NaBH_3CN$; (2) X-ray analysis of *C*-azanucleosides including three *C*-azafuranosylnucleosides reported previously; (3) two rotational isomers of their acyl derivatives; and (4) their biological activity.

Results and Discussion

1-*β*-(Base substituted)-1,4-dideoxy-1,4-imino-L-lyxitols **5** could be obtained in four steps starting from **1**[6] which was prepared from D-ribose by the usual procedure (Scheme 1). Compound **1** was treated with 5-lithio-2-(*tert*-butyldimethylsilyl)-*N*-(dimethylaminosulfonyl)imidazole[7] in THF at −78 °C to give the corresponding diol compound **2a**. In this reaction, the yield of **2a** was improved when a THF solution of protected imidazole was allowed to warm from −78 °C to −20 °C after the addition of *n*-BuLi to complete the lithiation. Compound **2b** was prepared from 5-bromo-2,4-di(*tert*-butoxy)pyrimidine by using *n*-BuLi hexane solution which was kept at −78 °C.[8] More remarkable is the first use of 5-magnesium salt of 2,4-di(*tert*-butoxy)pyrimidine (uracil Grignard reagent) for the preparation of **2b**. Although the lithium salt of 2,4-di(*tert*-butoxy)pyrimidine was easily decomposed above −78 °C, the uracil Grignard reagent which was prepared *via* the halogen−metal exchange of

[†] Graduate School of Science and Technology.
[‡] Chemical Analysis Center.
[§] Faculty of Science.

(1) (a) Kini, G. D.; Hennen, W. J. *J. Org. Chem.* **1986**, *51*, 4436−4439. (b) Just, G.; Donnini, P. *Can. J. Chem.* **1977**, *55*, 2998−3006. (c) Horenstein, B. A.; Zabinski, R. F.; Schramm, V. L. *Tetrahedron Lett.* **1993**, *34*, 7213−7216. (d) Furneaux, R. H.; Limberg, G.; Tyler, P. C.; Schramm, V. L. *Tetrahedron* **1997**, *53*, 2915−2930. (e) Deng, L.; Scharer, O. D.; Verdine, G. L. *J. Am. Chem. Soc.* **1997**, *119*, 7865−7866.

(2) Wong, C. H.; Provencher, L.; Porco, J. A., Jr.; Jung, S. H.; Wang, Y. F.; Chen, L.; Wang, R.; Steensma, D. H. *J. Org. Chem.* **1995**, *60*, 1492−1501.

(3) Lindahl, T. *Nature* **1993**, *362*, 709−715.

(4) (a) Rassu, G.; Pinna, L.; Spanu, P.; Ulgheri, F.; Casiraghi, G.; *Tetrahedron Lett.* **1994**, *35*, 4019−4022. (b) Reist, E. J.; Gueffroy, D. E.; Blackford, R. W.; Goodman, L.; *J. Org. Chem.* **1966**, *31*, 4025−4030. (c) Reist, E. J.; Fisher, L. V.; Goodman, L. *J. Org. Chem.* **1967**, *32*, 2541−2544. (d) Huang, B.; Chen, B.; Hui, Y. *Synthesis* **1993**, 769−771. (e) Altman, K. H.; Freier, S. M.; Piels, U.; Winker, T. Angew. Chem., Int. Ed. Engl. **1994**, *33*, 1654−1656.

(5) Yokoyama, M.; Akiba, T.; Ochiai, Y.; Momotake, A.; Togo, H. *J. Org. Chem.* **1996**, *61*, 6079−6082.

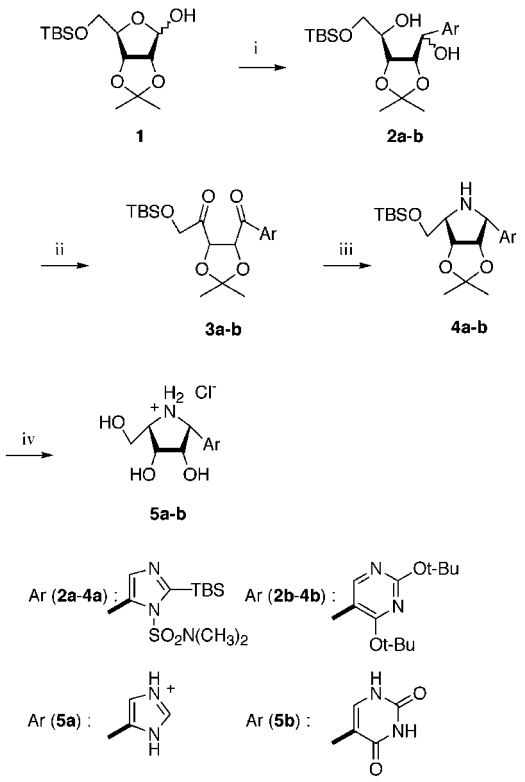
(6) Kasker, B.; Heise, G. L.; Michalak, R. S.; Vishnuvajjala, B. R. *Synthesis* **1990**, 1031−1034.

(7) (a) Chadwick, D. J.; Ngochindo, R. I. *J. Chem. Soc., Perkin Trans. 1* **1984**, 481−486. (b) Ngochindo, R. I. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1645−1648.

(8) Brown, D. M.; Burdon, M. G.; Slatcher, R. P. *J. Chem. Soc. C* **1968**, 1051−1053.

S0022-3263(98)00492-7 CCC: $15.00
Published on Web 09/30/1998

Scheme 1[a]



[a] Reagents and conditions: (i) Aryllithium, THF, rt, 1 h; (ii) DMSO, TFAA, Et_3N, CH_2Cl_2, −78 °C to rt, 4 h; (iii) (1) HCO_2NH_4, $NaBH_3CN$, MeOH, rt, 12 h, (2) $NaBH_4$, 6 h; (iv) 6 N HCl/MeOH = 3/1, rt, 0.5 h.

5-bromo-2,4-di(*tert*-butoxy)pyrimidine with *n*-BuMgCl did not decompose even at room temperature. When this reagent was allowed to react with **1**, **2b** could be obtained in 56% yield, while the use of the lithium reagent gave **2b** in 35% yield.

The thus-obtained **2a** and **2b** were oxidized by Swern oxidation (DMSO, trifluoroacetic anhydride, and Et_3N) to give the corresponding diketones **3a** and **3b** in good yields. Following reductive aminocyclization with ammonium formate and $NaBH_3CN$ afforded the *C*-azanucleosides **4a** and **4b**. In order to increase the yield of the aminocyclization, some reductive conditions were examined. The best condition was a successive addition with HCO_2NH_4−$NaBH_3CN$ and $NaBH_4$ as shown in entry 3 of Table 1. Deprotection of **4a** and **4b** was achieved in HCl−MeOH to give the corresponding HCl salts **5a** and **5b** in nearly quantitative yields.

From ^{1}H NMR data of **5b** in D_2O at room temperature, differential NOE's were observed between the following protons: uracil H6′−H1, uracil H6′−H2, H1−H2, H1−H4, H3−H4, and H4−H5a. The structure of **5b** was determined unequivocally by X-ray crystallography, and its ORTEP representation is shown in Figure 1a.[9] The azasugar pucker is in the C1-*exo* conformation (pseudorotation angle $P = 146.0°$). Glycosidic torsion angle χ (C2−C1−C′5−C′4) and torsion angle γ (C3−C4−C5−C6) are 171.2° and 73.8°, respectively.

(9) (a) Crystal of **5b** were obtained from EtOH/H_2O solution. The space group was $P2_1$ (no. 4) and the cell constants were $a = 5.378$ (2) Å, $b = 12.495(1)$ Å, $c = 8.638(9)$ Å, $\beta = 103.20(1)°$. (b) Crystals of **6a** were obtained from EtOH. The space group was $R3$, and the cell constants were $a = 24.840(3)$ Å, $c = 10.915(2)$ Å.

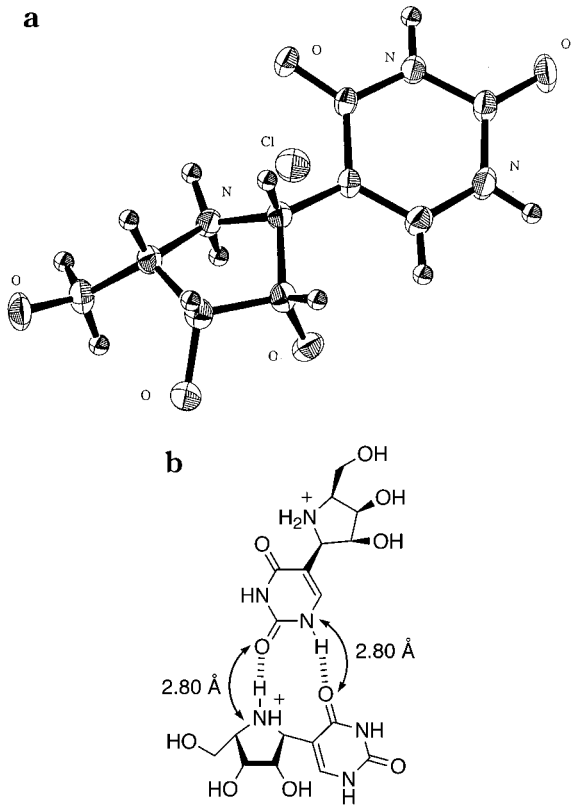


Figure 1. (a) X-ray crystal structure of **5b**. (b) Intermolecular hydrogen-bonding interaction.

Table 1. Various Conditions of Reductive Aminocyclization

3a → (reductive conditions: MeOH, MS-3A, rt) → **4a**

Entry	Conditions	Time (h)	Yield (%)
1	HCO_2NH_4 (10 eq) $NaBH_3CN$ (10 eq)	12	40
2	$AcONH_4$ (10eq) $NaBH_3CN$ (10 eq)	12	14
3	1) HCO_2NH_4 (10 eq) $NaBH_3CN$ (6 eq), 12 h 2) $NaBH_4$ (4 eq), 6 h	18	68
4	1) HCO_2NH_4 (10 eq), $NaBH_3CN$ (6 eq), KOH (2 eq), 12 h 2) $NaBH_4$ (4 eq), 6 h	18	53

The X-ray data show the intermolecular hydrogen-bonding interaction both at N1′−H1′···O4′ and O2′···H4a−N4 as shown in Figure 1b. The intermolecular distances of N1′−O4′ and O2′−N4 are 2.80 Å in each case.

With the above results in hand, we reinvestigated the structures of *C*-azanucleosides which were reported by us previously.[5] The *C*-azanucleoside bearing a 2-benzofuryl group as the base moiety was acetylated to give **6a** as good crystals. Its X-ray crystallography is shown in Figure 2.[9]

The sugar skeleton of **6a** was not D-azaribose as we tentatively showed in the previous report, but L-azalyx-

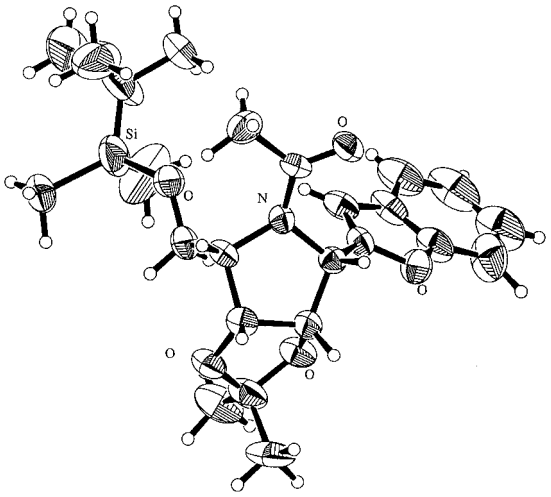
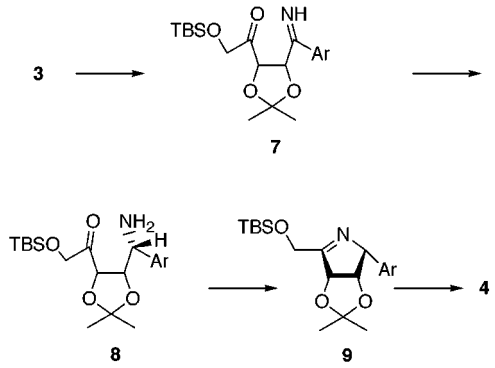


Figure 2. X-ray crystal structure of **6a**.

Scheme 2. Plausible Mechanism of Reductive Aminocyclization

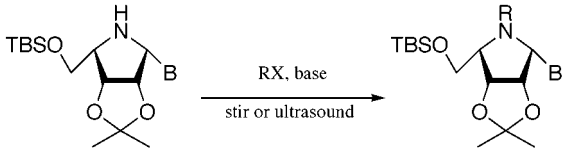


ose. Thus, the structures of the three reported *C*-azanucleosides bearing thiophene, benzofuran, and indole as the base moiety are corrected to 1-β-(base substituted)-1,4-dideoxy-1,4-imino-L-lyxitols.

The appearance of stereoselectivity in this reaction can be explained as follows: A C-1 is more electrophilic than C-4 to give an imino intermediate **7** easily. Next, the hydride attacks the *Si*-plane of C-1 in **7** to give an (*R*)-1-amino intermediate **8** due to the steric hindrance of the acetonide moiety. The following cyclization and dehydration *via* the nucleophilic attack of the amino group on the 4-carbonyl group afford an iminopyrrolidine derivative **9**, whose *Re*-plane is attacked by the hydride in a nucleophilic manner to afford the L-azalyxose skeleton due to the steric hindrance of the acetonide moiety (Scheme 2). When 2,3,5-*O*-tribenzylribose was used in this reaction, many stereoisomers were produced. The same trend of stereoselectivity has been recently reported in the reductive aminocyclization of pyrrolidine aminosugars.[10]

As a study on the chemical behavior of the amino group in the azasugar moiety, acylation and alkylation reactions were examined by using 1-β-(2-benzofuranyl)-5-*O*-(*tert*-butyldimethylsilyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-L-lyxitol **4c**[5] as a model compound. Compound **4c** could be acylated easily, while its alkylation could not be achieved successfully. Generally, the amino group in

Table 2. Functionalization of *C*-azanucleoside



4c **6**

B : 2-Benzofuranyl

RX	Conditions	Products	Yield (%)
CH_3COCl	Et_3N, stir	**6a**	99
PhCOCl	Et_3N, stir	**6b**	98
CH_3SO_2Cl	Et_3N, stir	**6c**	36
CH_3I	NaH, stir	**6d**	19
	neat, ultrasound		85
C_2H_5I	NaH, stir	**6e**	0
	neat, ultrasound		80
BnBr	NaH, stir	**6f**	0
	neat, ultrasound		85

β-homonojirimycin derivative has been known to show high resistance against the alkylation reaction due to its steric hindrance.[11] Surprisingly, **4c** could be alkylated smoothly under ultrasound conditions even though its application to the homogeneous reaction solution has generally been known to be slight (Table 2).

In ^{1}H NMR of **6a**, the protons of sugar skeleton and benzofuran were observed as broadening signals at room temperature. This fact indicates that the reorientation rate of two rotational isomers of the *N*-acetamido moiety is higher than that of normal acetamides which have no intramolecular distortion like *N*,*N*-dimethylacetamide (DMA).[12] In the case of **6a**, the band at the 3-position of benzofuran appeared as a broad singlet at room temperature. At −55 °C, this band changed to two singlets with a relative intensity of 2:1 (ΔG = 1.26 kJ/mol). When the NMR measurement was run at 5 °C, the two singlets coalesced into one broad singlet. Then, a benzoyl derivative **6b** was prepared to investigate whether the reorientation for this type of compound is generally fast. Judging from T_c value of **6b**, this type of compound has a relatively higher rate of reorientation than does DMA without distortion. The difference in ΔG and $\Delta G^{\ddagger}$ for **6a** and **6b** can be considered by the fact that the C−N double bond character of **6b** is decreased by R-effect of the phenyl group. In order to examine the effect of protecting groups, **6b** was deprotected with HCl−MeOH to give **6b′**. The T_c and $\Delta G^{\ddagger}$ values of **6b′** were higher than those of **6b**. The reason may be attributed to the hydrogen bonding between the oxygen of the *N*-benzoyl group and free 5-OH so that the interconversion between two rotational isomers is hindered. The values of ΔG, T_c, and $\Delta G^{\ddagger}$ of **6a**, **6b**, **6b′**, and DMA are summarized in Table 3.

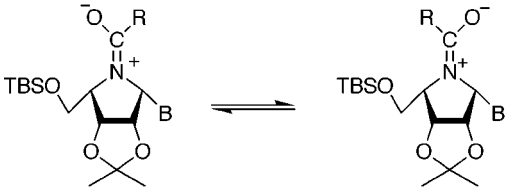
Next, the anti-HIV activity of **5b** was examined. The result did not show activity [**5b**; EC_{50} = none; CC_{50} = 53.7 μM; SI (CC_{50}/EC_{50}) = none][13] like that of a typical

(10) Reitz, A. B.; Baxter, E. W. *Tetrahedron Lett.* **1990**, *31*, 6777−6780.

(11) Saavedra, O. M.; Martin, O. R. *J. Org. Chem.* **1996**, *61*, 6987−6993.

(12) Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228−1234.

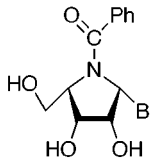
Table 3. The Rotational Isomers of 6



B : 2-benzofuryl

compounds	temp. (°C)	ΔG (kJ/mol)[a]	Tc (°C)[b]	$\Delta G^{\neq}$ (kJ/mol)[c]
6a (R = Me)	-55	1.26	5	56.8
6b (R = Ph)	-80	1.05	-30	47.4
6b'	-30	3.56	20	57.0
DMA[d]	-	-	52	50.2

a) ΔG values were calculated by $N_A/N_B=\exp(-\Delta G/RT)$
b) The temperature at which the two singlets coalesces to a single line.
c) $\Delta G^{\neq}$ values were calculated by $\Delta G^{\neq}=19.14Tc(9.97+\log T_c/\delta\nu)$
d) Ref. (12)



6b'

anti-HIV drug, 3′-azido-2′,3′-dideoxythimidine [AZT; EC_{50} = 0.162 μM; CC_{50} = 38.7 μM; SI (CC_{50}/EC_{50}) = 238].[13]

Experimental Section

All reactions were conducted in oven-dried (120 °C) glassware under dry argon. THF was distilled from sodium benzophenone ketyl. Pyridine was distilled from CaH_2. Microanalyses were performed at the Chemical Analysis Center of Chiba University. ^{1}H and ^{13}C NMR spectra were recorded respectively at 400 or 500 and 100 or 125 MHz [$CDCl_3$ and D_2O as solvents using tetramethylsilane (TMS) and sodium 2,2,3,3-tetradeuterio-4,4-dimethyl-4-silapentanesulfonate (TSP-d_4) as internal references]. Mass spectra were recorded using the fast-atom bomberment (FAB) method. For FAB mass spectra, NBA refers to *m*-nitrobenzyl alcohol matrix. Purification was carried out by column chromatography and preparative TLC (pTLC).

Preparation of 5 from 1. Typical example was described in the case of uracil (**2b**, **3b**, **4b**, and **5b**).

5-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-1-[5-(2′-*tert*-butyldimethylsilyl)-*N*-(dimethylaminosulfonyl)-imidazolyl]-D-ribitol (2a): yield 81%; foam; IR (KBr) 840, 1255, 1375, 1460, 1470, 2900, 3400 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12 (6H, s, TBDMS Si-Me), 0.40 (6H, s, TBDMS Si-Me), 0.93 (9H, s, TBDMS Si-*t*-Bu), 1.02 (9H s, TBDMS Si-*t*-Bu), 1.33 (6H, s, isopropylidene Me), 2.89 (6H, s, SO_2NMe_2), 3.83 (1H, dd, 5a-H, $J_{4,5a}$ = 6.4 Hz, J_{gem} = 10.2 Hz), 3.85-3.93 (2H, m, 4-, 5-H), 4.17 (1H, dd, 3-H, $J_{2,3}$ = 5.3 Hz, $J_{3,4}$ = 9.5 Hz), 4.56 (1H, dd, 2-H, $J_{2,3}$ = 5.3 Hz, $J_{1,2}$ = 9.5 Hz), 5.27 (1H, d, 1-H, $J_{1,2}$ = 9.5 Hz), 7.42 (1H, s, imidazole 4′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.40, −5.37, −3.64, −3.55, 18.33, 18.47, 25.30, 25.87, 27.00, 27.23, 27.88, 37.52, 62.07, 64.08, 69.41, 76.69, 79.24, 109.00, 131.27, 133.80, 156.03. HRMS (FAB) calcd for $C_{25}H_{52}N_3O_7SSi_2$ (M + H) 594.3062, found 594.3041.

5-*O*-(*tert*-Butyldimethylsilyl)-1-[5-[2′,4′-di(*tert*-butoxy)-pyrimidinyl]]-2,3-*O*-isopropylidene-D-ribitol (2b). Lithium Salt of Uracil method.[8] A solution of *n*-butyllithium in hexane (4.1 mL, 6.6 mmol) which was cooled at −78 °C was added dropwise to a solution of 5-bromo-2,4-di(*tert*-butoxy)-pyrimidine (6.0 mmol) in THF (40 mL) using a cannula. After stirring at the same temperature for 5 min, a THF solution of **1** (2.5 mL, 2.0 mmol) which was dried over MS-3A was added to the above solution. The resulting solution was stirred at the same temperature for 1 h, quenched with aqueous NH_4Cl solution, and extracted with AcOEt. The extract was dried over Na_2SO_4 and purified by a column chromatography (eluent: hexane/AcOEt = 3/1) to give **2b** in 35% yield (*R* or *S* = 2/1); oil; IR (KBr) 840, 940, 1050, 1160, 1260, 1360, 1400, 1440, 1560, 1600, 2940, 2980 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.10 (6H, s, TBDMS Si-Me), 0.92 (9H, s, TBDMS Si-*t*-Bu), 1.33 (3H, s, isopropylidene Me), 1.60 (3H, s, isopropylidene Me), 1.60 (9H, s, 4-O-*t*-Bu), 1.61 (9H, s, 2-O-*t*-Bu), 2.75 (1H, bs, 4-OH), 2.98 (1H, bs, 1-OH), 3.72 (1H, dd, 5-Ha, J_{gem} = 10.0 Hz, $J_{4,5a}$ = 5.2 Hz), 3.86 (1H, dd, 5-Hb, J_{gem} = 10.0 Hz, $J_{4,5b}$ = 3.0 Hz), 4.10-4.20 (2H, m, 3-H, 4-H), 4.34 (1H, dd, 2-H, *J* = 6.1 Hz, *J* = 1.6 Hz), 5.25 (1H, bs, 1-H), 8.27 (1H, s, 6′-H); ***another isomer***: δ 0.12 (6H, s, TBDMS Si-Me), 0.93 (9H, s, TBDMS Si-*t*-Bu), 1.30 (3H, s, isopropylidene Me), 1.34 (3H, s, isopropylidene Me), 1.61 (9H, s, O-*t*-Bu), 1.63 (9H, s, O-*t*-Bu), 3.70-3.76 (2H, m, 5-Ha, Hb), 3.93 (1H, m, 4-H), 4.17 (1H, dd, 3-H, $J_{3,4}$ = 9.8 Hz, $J_{2,3}$ = 5.5 Hz), 4.45 (1H, dd, 2-H, $J_{1,2}$ = 9.5 Hz, $J_{2,3}$ = 5.5 Hz), 4.96 (1H, d, 1-H, $J_{1,2}$ = 9.5 Hz), 8.23 (1H, s, 6′-H). HRMS (FAB) calcd for $C_{26}H_{49}N_2O_7Si$ (M + H) 529.3306, found 529.3326.

Uracil Grignard Reagent Method. A 1.0 M THF solution of *n*-butylmagnesium chloride (1.5 mL, 1.5 mmol) was added dropwise to a mixture of 5-bromo-2,4-di(*tert*-butoxy)pyrimidine (460 mg, 1.5 mmol), MS-4A (500 mg), and THF (1.5 mL) under ultrasound at room temperature for 2 h. To the uracil Grignard reagent thus obtained was added a THF solution of **1** (150 mg, 0.5 mmol). The resulting mixture was allowed to react under ultrasound for an additional 2 h at room temperature and then stirred at the same temperature overnight. The reaction mixture was quenched with 0.1 N HCl (10 mL) and extracted with ethyl acetate. The extract was evaporated to give a yellow oil, which was purified in the usual way by pTLC (eluent: hexane/AcOEt = 3/1; R_f = 0.35) to give **2b** in 56% yield (*R* or *S* = 2/1).

(2*R*,3*S*)-5-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-1-[5-(2′-*tert*-butyldimethylsilyl)-*N*-(dimethylaminosulfonyl)imidazolyl]-1,4-pentanedione (3a): yield 98%; oil; IR (neat) 1380, 1695, 1735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, TBDMS Si-Me), 0.09 (3H, s, TBDMS Si-Me), 0.43 (6H, s, TBDMS Si-Me), 0.89 (9H, s, TBDMS Si-*t*-Bu), 1.06 (9H, s,TBDMS Si-*t*-Bu), 1.47 (3H, s, isopropylidene Me), 1.50 (3H, s, isopropylidene Me), 2.91 (6H, s, SO_2NMe_2), 4.39 (1H, d, 5-Ha, J_{gem} = 18.0 Hz), 4.55 (1H, d, 5-Hb, J_{gem} = 18.0 Hz), 4.91 (1H, d, *J* = 6.9 Hz), 5.46 (1H, d, *J* = 6.9 Hz), 8.12 (1H, s, imidazole 4′−H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.55, −5.51, −3.31, 18.42, 18.69, 25.53, 25.84, 27.03, 27.37, 38.32, 68.24, 80.60, 80.87, 111.92, 130.53, 142.75, 164.48, 183.53, 204.90. HRMS (FAB) calcd for $C_{25}H_{48}O_7N_3SSi_2$ (M + H) 590.2752, found 590.2748.

(2*R*,3*S*)-5-*O*-(*tert*-Butyldimethylsilyl)-1-[5-[2′,4′-di(*tert*-butyloxy)pyrimidinyl]]-2,3-*O*-isopropylidene-1,4-pentanedione (3b). A solution of TFAA (2.53 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a solution of DMSO (2.86 mmol) in CH_2Cl_2 (6.0 mL) at −78 °C and stirred for 1 h at the same temperature. To the stirring mixture was added a solution of **2b** (0.46 mmol) in CH_2Cl_2 (3.0 mL) at −78 °C, and then the reaction mixture was stirred for an additional 2 h at the same temperature. A solution of Et_3N (3.86 mmol) in CH_2Cl_2 (2.0 mL) was added dropwise to the above solution, and the stirring was continued for 0.5 h at −78 °C. The reaction mixture was removed from the cooling bath, allowed to warm to room temperature with stirring for 0.5 h, and extracted with AcOEt. After dried over Na_2SO_4, the extract was condensed to give

(13) These values were then translated into percentage cytotoxicity and percentage antiviral protection, from which the 50% cytotoxic concentration (CC50), the 50 % effective concentration (EC_{50}), and the selectivity indexes (SI) were calculated according to the literature: Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; De Clercq, E. J. Virol. Meth. **1988**, *20*, 309−321.

an oil, which was then purified by pTLC (eluent: hexane/AcOEt, 3/1) to give **3b** in 80% yield: oil; IR (neat) 840, 1160, 1420, 1540, 1580, 1680, 1740, 2940 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, TBDMS Si-Me), 0.07 (3H, s, TBDMS Si-Me), 0.88 (9H, s, TBDMS Si-*t*-Bu), 1.39 (3H, s, isopropylidene Me), 1.41 (3H, s, isopropylidene Me), 1.64 (9H, s, O-*t*-Bu), 1.70 (9H, s, O-*t*-Bu), 4.38 (1H, d, 5-Ha, J_{gem} = 17.7 Hz), 4.52 (1H, d, 5-Hb, J_{gem} = 17.7 Hz), 4.87 (1H, d, $J_{2,3}$ = 6.7 Hz), 5.74 (1H, d, $J_{2,3}$ = 6.7 Hz), 8.67 (1H, s, 6′-H); HRMS (FAB) $C_{26}H_{45}O_7N_2Si$ calcd for 525.2993 (M + H), found 525.3010.

5-*O*-(*tert*-Butyldimethylsilyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-1-β-[5-(2′-*tert*-butyldimethylsilyl)-*N*-(dimethylaminosulfonyl)imidazolyl]-L-lyxitol (4a): yield 68%; foam; IR (KBr) 810, 1010, 1210, 1480, 2860, 2950 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (6H, s, TBDMS Si-Me), 0.39 (6H, s, TBDMS Si-Me), 0.90 (9H, s, TBDMS Si-*t*-Bu), 1.01 (9H, s, TBDMS Si-*t*-Bu), 1.28 (3H, s, isopropylidene Me), 1.45 (3H, s, isopropylidene Me), 2.82 (6H, s, SO_2NMe_2), 2.92 (1H, ddd, 4-H, $J_{4,5a}$ = 7.0 Hz, $J_{4,5b}$ = 5.5 Hz, $J_{3,4}$ = 4.2 Hz), 3.78 (1H, dd, 5-Ha, J_{gem} = 10.4 Hz, $J_{4,5a}$ = 7.0 Hz), 3.92 (1H, dd, 5-Hb, J_{gem} = 10.4 Hz, $J_{4,5b}$ = 5.5 Hz), 4.41 (1H, d, 1-H, $J_{1,2}$ = 4.0 Hz), 4.66 (1H, dd, 3-H, $J_{2,3}$ = 5.5 Hz, $J_{3,4}$ = 4.2 Hz), 4.69 (1H, dd, 2-H, $J_{2,3}$ = 5.5 Hz, $J_{1,2}$ = 4.0 Hz), 7.42 (1H, s, imidazole 4′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.30, −5.23, −3.54, −3.49, 18.44, 18.51, 24.66, 25.82, 25.99, 27.31, 37.55, 56.95, 62.04, 63.58, 80.87, 81.48, 111.56, 130.71, 133.19, 155.59; HRMS (FAB) calcd for $C_{25}H_{51}N_4O_5SSi_2$ (M + H) 575.3115, found 575.3109. Anal. Calcd for $C_{25}H_{50}N_4O_5SSi_2$: C, 52.26; H, 8.70; N, 9.75. Found: C, 52.23; H, 8.99; N, 9.79.

5-*O*-(*tert*-Butyldimethylsilyl)-1-β-[5-[2,4-di(*tert*-butoxy-)pyrimidinyl]]-1,4-dideoxy-2′,3′-*O*-isopropylidene-1,4-imino-L-lyxitol (4b). Ammonium formate (10 mmol), $NaBH_3CN$ (6.0 mmol), molecular sieves 3A (500 mg), and compound **3b** (1.0 mmol) were dissolved in MeOH (20 mL). After stirring for 18 h at room temperature, $NaBH_4$ (4.0 mmol) was added and the stirring was continued for 2 h at the same temperature. The reaction mixture was filtered through Celite (Wako hyflo super-cell), extracted with $CHCl_3$, and dried over Na_2SO_4. The solvent was removed, and the residue was purified by pTLC [eluent: hexane/ethyl acetate (3/1)] to give compound **4b** in 57% yield; foam; IR (KBr) 840, 1090, 1160, 1410, 1560, 1600, 2940, 2980, 3360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.09 (6H, s, TBDMS Si-Me), 0.90 (9H, s, TBDMS Si-*t*-Bu), 1.26 (3H, s, isopropylidene Me), 1.40 (3H, s, isopropylidene Me), 1.64 (9H, s, O-*t*-Bu), 1.66 (9H, s, O-*t*-Bu), 1.83 (1H, bs, NH), 3.01 (1H, m, 4-H), 3.84 (1H, dd, 5-Ha, J_{gem} = 10.0 Hz, $J_{4,5a}$ = 7.3 Hz), 3.92−3.98 (2H, m, 1-H, 5Hb, $J_{1,2}$ = 4.4 Hz), 4.65 (1H, dd, 3-H, $J_{2,3}$ = 5.8 Hz, $J_{3,4}$ = 4.3 Hz), 4.72 (1H, dd, 2-H, $J_{2,3}$ = 5.8 Hz, $J_{1,2}$ = 4.4 Hz), 8.23 (1H, s, 6′-H); HRMS (FAB) calcd for $C_{26}H_{48}N_3O_5Si$ (M + H) 510.3361, found 510.3365.

1,4-Dideoxy-1-β-(imidazolyl)-1,4-imino-L-lyxitol (5a): yield 96%; powder; IR (KBr) 1040, 1140, 1230, 1420, 1620, 2920, 3000, 3340, 3440 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 3.86−3.97 (2H, m, 4-H, 5-Ha), 4.03 (1H, 5-Hb, dd, J_{gem} = 11.6 Hz, $J_{4,5b}$ = 4.3 Hz), 4.60 (1H, dd, 3-H, $J_{3,4}$ = 5.6 Hz, $J_{2.3}$ = 4.4 Hz), 4.64 (1H, dd, 2-H, $J_{1,2}$ = 5.9 Hz, $J_{2,3}$ = 4.4 Hz), 4.92 (1H, d, 1-H, $J_{1,2}$ = 5.9 Hz), 7.47 (1H, s, 5′-H), 8.08 (1H, s, 2′-H); HRMS (FAB) calcd for $C_8H_{14}N_3O_3$ (M + H) 200.1034, found 200.1042.

1,4-Dideoxy-1,4-imino-1-β-(5-uracilyl)-L-lyxitol (5b). To a MeOH solution (3.0 mL) containing **4b** (50 mg) was added 6 N HCl (1.0 mL). After stirred for 30 min, the reaction solution was evaporated to give a residue, which was then dissolved in a small amount of MeOH. The resulting MeOH solution was dropped to the ether to afford **5b** as a HCl salt. **5b**: yield 95%; powder; IR (KBr) 1030, 1120, 1230, 1410, 1640, 1700, 2950, 3450 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 3.79 (1H, m, 4-H), 3.92 (1H, dd, 5-Ha, J_{gem} = 11.9 Hz, $J_{4,5a}$ = 7.5 Hz), 3.98 (1H, dd, 5-Hb, J_{gem} = 11.9 Hz, $J_{4,5b}$ = 5.1 Hz), 4.58 (3H, m, 1-, 2-, 3-H), 7.90 (1H, s, 6′-H); HRMS (FAB) calcd for $C_9H_{14}N_3O_5$ (M + H) 244.0932, found 244.0921.

Acylation of 1-β-(2-Benzofuranyl)-5-*O*-(*tert*-butyldimethylsilyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-L-lyxitol (4c) To Give 6a, 6b, and 6c. Typical Procedure. To a mixture of **4c** (0.10 mmol), Et_3N (0.20 mmol), and dry THF (2.0 mL) was added dropwise acetyl chloride (0.15 mmol) at room temperature under stirring. After stirring at the same temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and then extracted with ether. The extract was dried over Na_2SO_4 and condensed to give an oil, which was purified by pTLC (eluent: hexane/AcOEt, 3/1) to give *N*-acetyl-1-β-(2-benzofuranyl)-5-*O*-(*tert*-butyldimethylsilyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-L-lyxitol **6a**.

6a: foam; IR (KBr) 840, 1080, 1260, 1380, 1400, 1460, 1660, 2940 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.12 (3H, s, TBDMS Si-Me), 0.13 (3H, s, TBDMS Si-Me), 0.95 (12H, s, isopropylidene Me, TBDMS Si-*t*-Bu), 1.30 (3H, s, isopropylidene Me), 2.12 (3H, bs, acetyl-Me), 4.04 (2H, m, 5-Ha, 5-Hb), 4.11 (1H, bs, 4-H), 4.38 (1H, bs, 1-H), 4.96 (1H, dd, 3-H, J = 6.7 Hz, J = 6.6 Hz), 5.06 (1H, dd, 2-H, J = 7.8 Hz, J = 7.4 Hz), 6.65 (1H, s, benzofuran 3′-H), 7.17−7.26 (2H, m, benzofuran 5′-, 6′-H), 7.44−7.51 (2H, m, benzofuran 4′-, 7′-H); HRMS (FAB) calcd for $C_{24}H_{36}NO_5Si$ (M + H) 446.2361, found 446.2349. Anal. Calcd for $C_{24}H_{35}NO_5Si$: C, 64.69; H, 7.92; N, 3.14. Found: C, 64.93; H, 8.21; N, 3.20.

1-β-(2-Benzofuranyl)-*N*-benzoyl-5-*O*-(*tert*-butyldimethylsilyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-L-lyxitol (6b): foam; IR (KBr) 840, 1100, 1120, 1260, 1410, 1640, 2930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.12 (3H, s, TBDMS Si-Me), 0.14 (3H, s, TBDMS Si-Me), 0.89 (3H, s, isopropylidene Me), 0.93 (9H, s, TBDMS Si-*t*-Bu), 1.28 (3H, s, isopropylidene Me), 4.15 (1H, dd, 5-Ha, J_{gem} = 9.1 Hz, $J_{4,5a}$ = 6.1 Hz), 4.26 (1H, dd, 5-Hb, J_{gem} = 9.1 Hz, $J_{4,5b}$ = 9.0 Hz), 4.76 (1H, m, 4-H), 4.95−5.04 (2H, m, 2-, 3-H), 5.20 (1H, d, 1-H, $J_{1,2}$ = 5.8 Hz), 6.66 (1H, s, benzofuran 3′-H), 7.20−7.37 (7H, m, phenyl, benzofuran 5′-, 6′-H), 7.45−7.55 (2H, m, benzofuran 4′-, 7′-H); HRMS (FAB) calcd for $C_{29}H_{38}NO_5Si$ (M + H) 508.2517, found 508.2519.

1-β-(2-Benzofuranyl)-5-*O*-(*tert*-butyldimethylsilyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-*N*-methanesulfonyl-L-lyxitol (6c): foam; IR (KBr) 840, 1180, 1260, 1320, 1460, 2940 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.14 (6H, s, TBDMS Si-Me), 0.95 (9H, s, TBDMS Si-*t*-Bu), 1.17 (3H, s, isopropylidene Me), 1.28 (3H, s, isopropylidene Me), 2.91 (3H, s, SO_2Me), 4.04 (1H, dd, 5-Ha, J_{gem} = 10.2 Hz, $J_{4,5a}$ = 5.9 Hz), 4.13 (1H, dd, 5-Hb, J_{gem} = 10.2, $J_{4,5b}$ = 8.3 Hz), 4.37 (1H, ddd, 4-H, $J_{4.5b}$ = 8.3 Hz, $J_{3,4}$ = 6.8 Hz, $J_{4,5a}$ = 5.9 Hz), 4.99 (1H, dd, 3-H, $J_{3,4}$ = 6.8 Hz, $J_{2,3}$ = 6.5 Hz), 5.07 (1H, dd, 2-H, $J_{1,2}$ = 7.8 Hz, $J_{2,3}$ = 6.5 Hz), 5.47 (1H, d, 1-H, $J_{1,2}$ = 7.8 Hz), 6.76 (1H, s, benzofuran 3′-H), 7.20−7.31 (2H, m, benzofuran 5′-, 6′-H), 7.45−7.56 (2H, m, benzofuran 4′-, 7′-H); HRMS (FAB) calcd for $C_{23}H_{36}NO_6SSi$ (M + H) 482.2030, found 482.2026. Anal. Calcd for $C_{23}H_{35}NO_6SSi$: C, 57.35; H, 7.32; N, 2.91. Found: C, 57.31; H, 7.37; N, 2.85.

Alkylation of 4c To Give 6d, 6e, and 6f. Typical Procedure. A mixture of **4c** (0.11 mmol), CH_3I (2.0 mL), and molecular sieves 3A (1.0 g) was radiated with ultrasonic probe at frequency of 45 kHz for 1 h. The reaction mixture was filtered, washed with 1 N HCl and then H_2O, and extracted with AcOEt. The organic extract was dried over Na_2SO_4 and then purified by pTLC (eluent: hexane/AcOEt, 3/1) to give 1-β-(2-benzofuranyl)-5-*O*-(*tert*-butyldimethylsilyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-*N*-methyl-L-lyxitol **6d** in 85% yield.

6d: foam; IR (KBr) 840, 1100, 1260, 1460, 2930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.10 (6H, s, TBDMS Si-Me), 0.92 (9H, s, TBDMS Si-*t*-Bu), 1.28 (3H, s, isopropylidene Me), 1.51 (3H s, isopropylidene Me), 2.32 (3H, s, NMe), 2.36 (1H, m, 4-H), 3.37 (1H, d, 1-H, $J_{1,2}$ = 4.6 Hz), 3.87 (1H, dd, 5-Ha, J_{gem} = 10.1 Hz, $J_{4,5a}$ = 5.1 Hz), 4.05 (1H, dd, 5-Hb, J_{gem} = 10.1 Hz, $J_{4,5b}$ = 6.6 Hz), 4.74 (2H, m, 2-, 3-H), 6.74 (1H, s, benzofuran 3′-H), 7.16−7.24 (2H, m, benzofuran 5′-, 6′-H), 7.45 (1H, d, benzofuran, J = 6.9 Hz), 7.53 (1H, d, benzofuran, J = 6.9 Hz); HRMS (FAB) calcd for $C_{23}H_{36}NO_4Si$ (M + H) 418.2392, found 418.2411.

1-β-(2-Benzofuranyl)-5-*O*-(*tert*-butyldimethylsilyl)-1,4-dideoxy-*N*-ethyl-1,4-imino-2,3-*O*-isopropylidene-L-lyxitol (6e): foam; IR (KBr) 840, 1100, 1160, 1210, 1260, 1380, 1460, 2860, 2930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.10 (6H, s, TBDMS Si-Me), 0.88 (3H, t, Et-CH_3, J = 7.3 Hz), 0.92 (9H, s, TBDMS Si-*t*-Bu), 1.28 (3H, s, isopropylidene Me), 1.51 (3H, s, isopropylidene Me), 2.77 (1H, ddd, 4-H, $J_{4,5b}$ = 6.1 Hz, $J_{4,5a}$

= 5.6 Hz, $J_{3,4}$ = 5.1 Hz), 2.86 (2H, m, Et-CH_2), 3.81 (1H, d, 1-H, $J_{1,2}$ = 4.7 Hz), 3.86 (1H, dd, 5-Ha, J_{gem} = 10.1 Hz, $J_{4,5a}$ = 5.6 Hz), 4.02 (1H, dd, 5-Hb, J_{gem} = 10.1 Hz, $J_{4,5b}$ = 6.1 Hz), 4.69 (1H, dd, 3-H, $J_{2,3}$ = 6.3 Hz, $J_{3,4}$ = 5.1 Hz), 4.73 (1H, dd, 2-H, $J_{2,3}$ = 6.3 Hz, $J_{1,2}$ = 4.7 Hz), 6.74 (1H, s, benzofuran 3′-H), 7.16−7.23 (2H, m, benzofuran 5′-, 6′-H), 7.43−7.55 (2H, m, benzofuran 4′-, 7′-H); HRMS (FAB) calcd for $C_{24}H_{38}NO_4Si$ (M − H) 432.2568, found 432.2569.

1-*β*-(2-Benzofuranyl)-*N*-benzyl-5-*O*-(*tert*-butyldimethylsilyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-L-lyxitol (6f): neat, IR (KBr) 840, 1100, 1160, 1210, 1260, 1380, 1460, 2860, 2930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (6H, s, TBDMS Si-Me), 0.84 (9H, s, TBDMS Si-*t*-Bu), 1.22 (3H, s, isopropylidene Me), 1.51 (3H, s, isopropylidene Me), 2.72 (1H, ddd, 4-H, $J_{4,5b}$ = 6.9 Hz, $J_{4,5a}$ = 5.1 Hz, $J_{3,4}$ = 4.6 Hz), 3.67 (1H, d, benzyl, J_{gem} = 14.8 Hz), 3.68 (1H, d, 1-H, $J_{1,2}$ = 5.1 Hz), 3.76 (1H, dd, 5-Ha, J_{gem} = 10.0 Hz, $J_{4,5a}$ = 5.1 Hz), 3.87 (1H, dd, 5-Hb, J_{gem} = 10.0 Hz, $J_{4,5b}$ = 7.0 Hz), 4.05 (1H, d, benzyl, J_{gem} = 14.8 Hz), 4.64 (1H, dd, $J_{2,3}$ = 6.4 Hz, $J_{1,2}$ = 5.1 Hz), 4.69 (1H, dd, $J_{2,3}$ = 6.4 Hz, $J_{3,4}$ = 4.6 Hz), 6.73 (1H, s, benzofuran 3′-H), 7.12−7.24 (7H, m, Ph, benzofuran 5′-, 6′-H), 7.45 (1H, d, benzofuran, J = 6.9 Hz), 7.53 (1H, d, benzofuran, J = 6.9 Hz); HRMS (FAB) calcd for $C_{29}H_{38}NO_4Si$ (M − H) 492.2568, found 492.2578. Anal. Calcd for $C_{29}H_{37}NO_4Si$: C, 70.55; H, 7.96; N, 2.84; Found: C, 70.32; H, 8.10; N, 2.69.

1-*β*-(2-Benzofuranyl)-*N*-benzoyl-1,4-dideoxy-1,4-imino-L-lyxitol (6b′): oil, IR (neat) 850, 1120, 1160, 1260, 1390, 1420, 1620, 3400 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.43 (1H, bs, 3-OH), 3.63 (1H, bs, 2-OH), 3.90 (1H, bs, 5-OH), 4.10 (1H, bs, 5-Ha), 4.24 (1H, bs, 5-Hb), 4.31 (1H, bs, 2-H), 4.41 (2H, bs, 3, 4-H), 5.06 (1H, bs, 1-H), 6.74 (1H, s, 3′-H), 7.16−7.30 (8H, m, benzofuran 5′-, 6′-H, phenyl), 7.38 (1H, d, benzofuran, J = 8.2 Hz), 7.46 (1H, m, benzofuran, J = 7.0 Hz); HRMS (FAB, NBA + KI) calcd for $C_{20}H_{19}KNO_5Si$ (M + K) 392.0899, found 392.0889.

Acknowledgment. We thank Professor Hiroshi Takaku (Chiba Institute of Technology) for assay test of HIV and Dr. Hiroko Seki and Miss. Ritsuko Hara (Chemical Analysis Center of Chiba University) for measurements of EA and mass spectra. This work was supported by a Grant-in-Aid No. 07554085 for Scientific Research from the Ministry of Education, Science and Culture, Japan and Found for Researching Assistant of Chiba University (A.M).

Supporting Information Available: NMR spectra and an X-ray structure report (35 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS; see any current masthead page for ordering information.

JO980492M