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Effective synthesis of *C*-nucleosides with 2′,4′-BNA modification

Yoshiyuki Hari,[a] Satoshi Obika,[a] Minako Sakaki,[a] Ken-ichiro Morio,[a] Yuriko Yamagata[b] and Takeshi Imanishi[a,*]

[a]*Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan*
[b]*Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto, Kumamoto 862-0973, Japan*

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Abstract—The effective synthesis of some *C*-nucleosides with 2′-*O*,4′-*C*-methylene bridged nucleic acid (2′,4′-BNA) modification was accomplished by using the coupling reaction of a tetrahydrofurancarbaldehyde **1** with the magnesium or lithium derivatives of aromatic heterocycles followed by the Mitsunobu cyclization. Moreover, it was clearly shown by ^{1}H NMR spectra and X-ray crystallography that the sugar conformation in the synthesized *C*-nucleosides, independent of the nucleobases, was fixed in N-form.

1. Introduction

C-Nucleosides are well known nucleoside analogues that contain a carbon–carbon linkage between the furanose and the heterocyclic base, instead of the carbon–nitrogen linkage in the natural *N*-nucleosides. They are very intriguing compounds as an antitumor, antibacterial or antiviral agent.[1] Recently, several research groups have also reported that some *C*-nucleosides were good substrates in DNA replication.[2] Thus, valuable applications of the *C*-nucleosides will increasingly spread in the future. Concerning the sugar puckering, the *C*-nucleosides were known to exist in S-type conformation predominantly due to lack of an anomeric effect. Therefore, restriction of the sugar puckering of *C*-nucleosides, especially in N-type conformation, is thought to contribute towards discovery of the novel biological activities of *C*-nucleosides and clarification of the structure–activity relationship.

On the other hand, nucleoside analogues with a restricted sugar conformation have attracted considerable attention in view of their property not only as a biologically active compound but also as a synthon toward development of practical antisense and/or antigene strategy.[3,4] Recently, we have accomplished the synthesis of 2′-*O*,4′-*C*-methylene bridged nucleic acids (2′,4′-BNA/LNA), which have a locked N-type sugar conformation, by methylene bridging between the 2′-oxygen and 4′-carbon atoms (Fig. 1),[5,6] and also found that oligonucleotides containing the 2′,4′-BNA monomers showed extremely high binding affinity not only to single-stranded RNA but also to double-stranded DNA.[7,8] Therefore, application of the *C*-nucleoside analogues of the 2′,4′-BNA for antisense and antigene oligonucleotides is also of great interest.

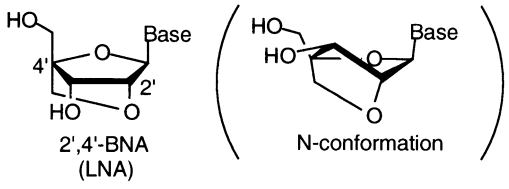

Figure 1. Chemical structure of 2′,4′-BNA/LNA.

In this paper, we describe the effective synthesis of 2′,4′-BNA modified *C*-nucleosides containing some unnatural nucleobases such as oxazole, 2-phenyloxazole, pyridine, pyrrole and imidazole, and also discuss their conformation.[9]

2. Results and discussion

To synthesize *C*-nucleosides with 2′,4′-BNA modification, we selected a coupling reaction of the aldehyde **1** with aromatic heterocycles and the following ring-closure reaction as the key steps. The synthesis of the aldehyde **1** was effectively accomplished as shown in Scheme 1. Methyl 4-hydroxymethyl-2,3-*O*-isopropylideneribofuranoside (**2**)[10] was monosilylated by a *tert*-butyldiphenylsilyl group to afford **3** (70%),[†] which was then tosylated to give **4** (98%). Acidic hydrolysis of **4** afforded diol **5** (77%). The

Keywords: nucleosides; nitrogen heterocycles; Grignard reaction; Mitsunobu reaction.

* Corresponding author. Tel.: +81-6-6879-8200; fax: +81-6-6879-8204; e-mail: imanishi@phs.osaka-u.ac.jp

[†] The stereochemistry of compounds **3**, **10** was confirmed by ^{1}H NMR and NOE measurements.

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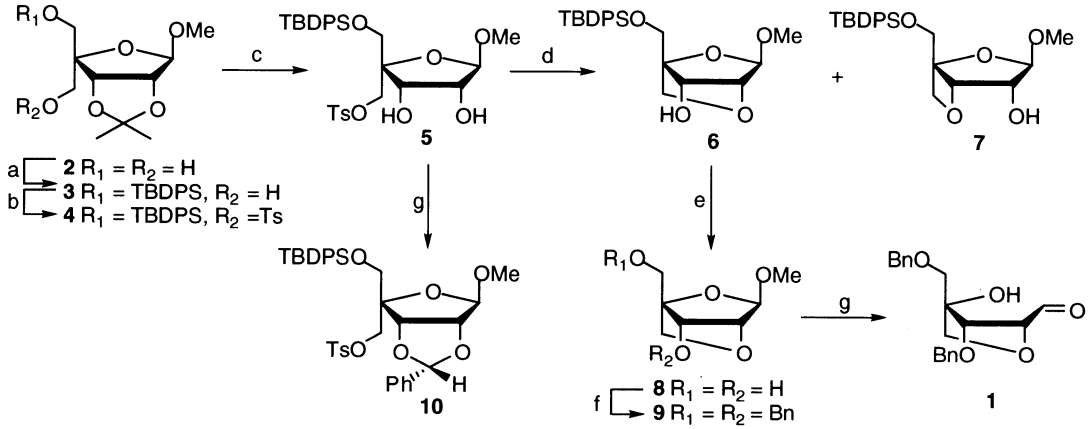
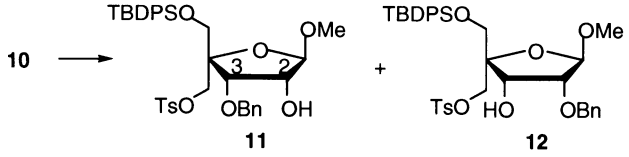


Scheme 1. *Reagents and conditions*: (a) TBDPSCl, Et_3N, CH_2Cl_2, rt, 13 h, 70%; (b) *p*-TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 17 h, 98%; (c) TFA, THF, H_2O, rt, 20 min, 77%; (d) HMDS, $NaNH_2$, benzene, rt, 30 min, then added **5**, THF, further rt, 1 h, 35% (**6**), 43% (**7**); (e) TBAF, THF, rt, 0.5 h, quant.; (f) BnBr, NaH, DMF, 0°C, 1 h, 91%; (g) 10% HCl aq., THF, rt, 2 h, quant.; (h) PhCHO, $ZnCl_2$, rt, 2 h, quant.

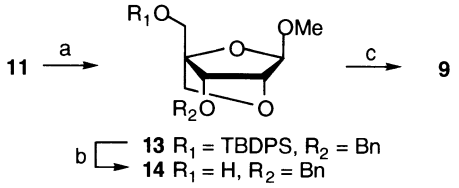
Table 1. Reductive cleavage of 2,3-*O*-benzylidene **10**



Run	Reagents (equiv.)	Solvent	Temperature	Time (h)	Yield (%)[a]	
					11	**12**
1	DIBAH (5.0)	CH_2Cl_2	0°C→rt	6	9	56
2	$NaBH_3CN$ (5.0), $SnCl_4$ (5.0)	CH_3CN	rt	5	14	40
3	$NaBH_3CN$ (5.0), $TiCl_4$ (5.0)	CH_3CN	rt	1	67	27
4	$NaBH_3CN$ (1.2), $TiCl_4$ (5.0)	CH_3CN	rt	2	16	24
5	$NaBH_3CN$ (5.0), $TiCl_4$ (1.2)	CH_3CN	rt	2	45	37

[a] Isolated yield.

reaction of diol **5** under the alkaline conditions was found to give the desired product **6** (35%) along with the oxetane product **7** (43%). After desilylation of **6** (quant.), the obtained diol **8** was protected by a benzyl group to afford dibenzyl derivative **9** (90%), which was then treated with 10% HCl aq. to give the desired compound **1** successively (quant.).[11] On the other hand, the selective protection of the C3-hydroxy group in **5** is thought to lead to convenient synthesis of **9**. The diol **5** was initially treated with PhCHO and $ZnCl_2$ to give 2,3-*O*-benzylidene **10** (quant.) as the sole diastereoisomer.[†] Reductive cleavage of the benzylidene C–O bond in **10** was examined as shown in Table 1. As a result, **10** was reduced with $NaBH_3CN$ (5 equiv.) and $TiCl_4$ (5 equiv.) to afford the desired 3-*O*-benzyl derivative **11** (67%) effectively (Table 1, run 3). A decrease in the amount of $NaBH_3CN$ or $TiCl_4$ gave lower selectivity (Table 1, runs 4, 5). Interestingly, 2-*O*-benzyl compound **12** was yielded as a major product by using DIBAL or a combination of $NaBH_3CN$ and $SnCl_4$ (Table 1, runs 1, 2). The difference in selectivity of the cleavage was likely explained as follows: $TiCl_4$ would initially coordinate with the less hindered 2-oxygen in **10** rather than 3-oxygen, and then reductive cleavage at the C2–O bond immediately proceeded owing to its high reactivity. On the other hand, DIBAL or $SnCl_4$ formed a thermodynamically stable complex with both 3-oxygen and the sulfonyl oxygen in **10**; thereby, the cleavage of the C3–O bond was observed as a main reaction. Next, on exposure of **11** to $NaN(TMS)_2$, bicyclic methyl ribofuranoside **13** was obtained (95%) as shown in Scheme 2. Deprotection at the 5-hydroxy group in **13** (**13→14**, quant.) followed by substitution by a benzyl group gave **9** (**14→9**, 92%).

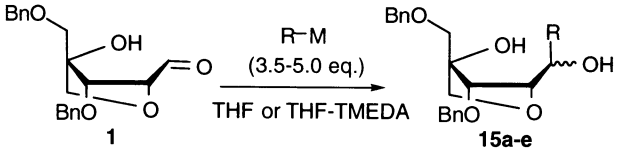


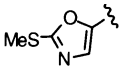
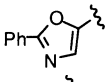
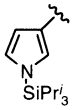
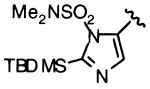
Scheme 2. *Reagents and conditions*: (a) NaHMDS, THF, rt, 3 h, 95%; (b) TBAF, THF, rt, 6 h, quant.; (c) BnBr, NaH, DMF, rt, 7 h, 92%.

The aldehyde **1** was coupled with the magnesium and the lithium derivatives of some aromatic heterocycles (Table 2). The magnesium derivatives of 2-methylthio-5-oxazole[12] and 2-phenyl-5-oxazole[13] gave *S*-**15a** and *S*-**15b** as the main product, respectively.[‡] The same stereoselectivity

[‡] The stereochemistry of *R*- and *S*-**16** was determined by NOE measurement after the Mitsunobu reaction.

Table 2. Coupling reaction of aldehyde **1** with some aromatic heterocycles



R	M	Temperature	Time (h)	Product	Yield (%)[a]	*R*/*S*[b]
	MgBr	rt	1	**15a**	61	15:85
	Li	−78°C	13		78	39:61
	MgBr	rt	18	**15b**	70	8:92
	Li	−78°C→30°C	2		82	33:67
	MgBr	rt→50°C	3	**15c**	65	85:15
	Li	−78°C	3		56	22:78
	MgBr	rt	2	**15d**	81	98:2
	Li	−78°C→rt	2		56	50:50
	MgBr	rt	2	**15e**	72	90:10
	Li	−78°C→rt	2		80	69:31

[a] Isolated yield of the mixture of *R*- and *S*-**14**.
[b] Determined by ^{1}H NMR measurements.

was observed when the magnesium derivatives of 2-pyridine,[14] *N*-triisopropylsilyl-3-pyrrole[15] and 2-*tert*-butyldiphenylsilyl-1-*N*,*N*-dimethylsulfamoyl-5-imidazole[16] were employed. This stereoselectivity would be explained by the *re*-face attack of nucleophiles on the carbonyl group of the chelation model (Fig. 2).[17] On the contrary, the lithium salts of heterocycles also gave the corresponding products; however, significant stereoselectivities were not observed.

After separation of the *R*- and *S*-epimers of **15a**–**d**, these compounds were cyclized under typical Mitsunobu conditions.[18] In the case of **15a**, the 2-methylthio group in the oxazole moiety was removed with Raney Ni (W-2) (Scheme 3), and then the corresponding oxazole derivative **15a′** was employed for the ring-closure reaction. As shown in Table 3, the β-anomer of *C*-nucleoside **16a** was obtained exclusively by the reaction of *S*-**15a′** with 1,1′-azobis(*N*,*N*-dimethylformamide) (TMAD) and *n*-tributylphosphine (TBP) in 92% yield.[§] β-Anomers of **16b** and **16c** were similarly yielded from *S*-**15b** and *R*-**15c**, respectively, by using diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP). On the contrary, *S*-**15d** gave anomeric mixtures of **16d** (α/β=29:71). This is probably due to the partial S_N1-type reaction caused by the electron-donating feature of the *N*-silylated pyrrole ring (Fig. 3). A mixture of *R*- and *S*-**15e** (*R*/*S*=90:10) was also employed for this ring-closure reaction to afford the desired product **16e** (α/β=10:90). After deprotection of the imidazole moiety in **16e** by treatment with 1.5 N HCl aq., each anomer **16e′** was separated by silica gel column chromatography (Scheme 4). α-Anomers of *C*-nucleosides **16a**–**d** were also obtained by the cyclization of *R*-**15a′**, *R*-**15b**, *S*-**15c** and *S*-**15d**.

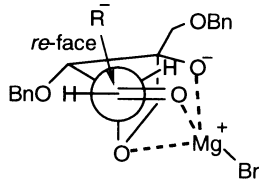
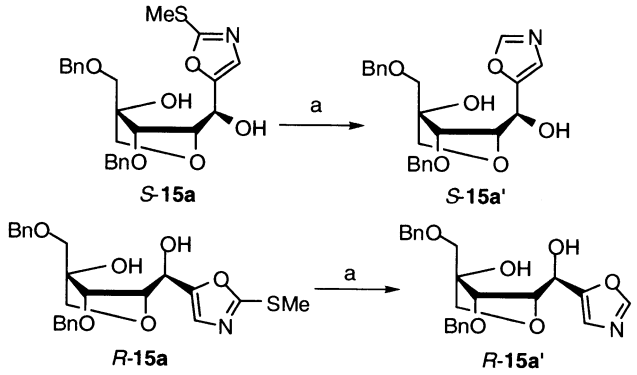


Figure 2. Plausible chelation model.



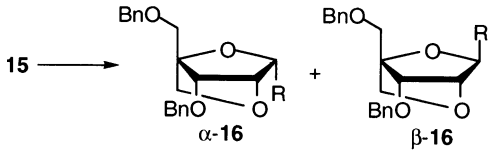
Scheme 3. *Reagents and conditions*: (a) Raney Ni (W-2), EtOH, reflux, 30 min, 69% (*S*-**15a′**), 50% (*R*-**15a′**).

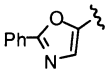
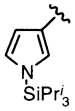
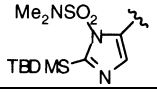
All attempts (H_2/Pd(OH)$_2$–C, cyclohexene/Pd(OH)$_2$–C, BBr_3 etc.) to remove the benzyl group in β-**16d** failed and gave only complex mixtures. Although the details are not clear, this is probably due to the unstable feature of C1′–O4′ bond in β-**16d** under the debenzylation conditions. On the other hand, a typical Pd-catalyzed hydrogenolysis of β-anomers of **16a**–**c** and **16e′** successfully proceeded to give the desired *C*-nucleosides **17** (Scheme 5).

The conformation of nucleosides in a solution is readily estimated by their ^{1}H NMR spectra. The fact that the H1′, H2′ and H3′ signals of **17a**–**c** and **17e** were observed as a

[§] The stereochemistry of α- and β-**16** was confirmed by NOE measurement.

Table 3. Cyclization of diols **15** under Mitsunobu conditions



Substrate	R	Method[a]	Temperature	Time (h)	Yield (%)	α/β
S-**15a**′		A	rt	2	92	0:100
R-**15a**′		A	rt	17	77	100:0
S-**15b**		B	0°C→rt	6	90	0:100
R-**15b**		B	0°C	2	72	100:0
R-**15c**		B	0°C	3	80	0:100
S-**15c**		B	0°C→rt	4	64	100:0
R-**15d**		B	rt	12	59[b]	29:71[c]
S-**15d**		B	rt	3	86[b]	78:22[c]
15e (*R*/*S*=90:10)		A	rt	15	90[b]	10:90[c]

[a] Method A: TMAD, TBP, benzene; Method B: DEAD, TPP, THF.
[b] Isolated yield of the anomeric mixture.
[c] Determined by ^{1}H NMR measurements.

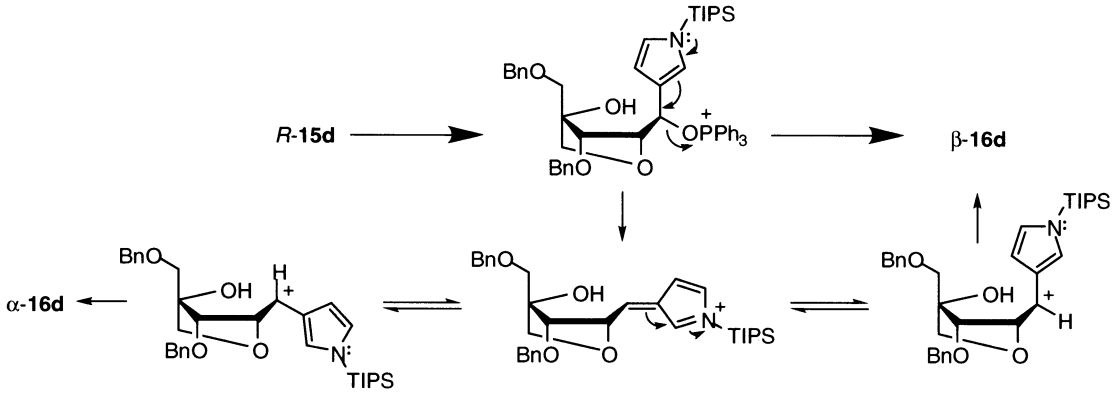
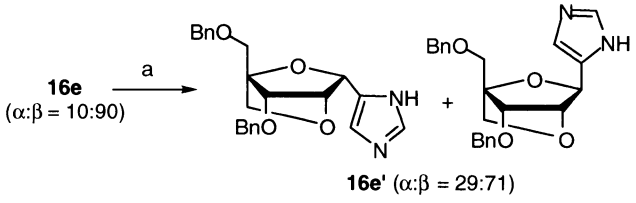
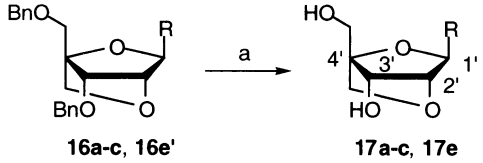


Figure 3. Cyclization of *R*-**15d**.



Scheme 4. *Reagents and conditions*: (a) 1.5N HCl aq., THF, reflux, 2.5 h, 84%.



Scheme 5. *Reagents and conditions*: (a) H_2 (1 atm), 20% $Pd(OH)_2$–C, EtOH, rt, 18 h, 82% (**17a**), 9 h, 46% (**17b**); 20% $Pd(OH)_2$–C, cyclohexene, EtOH, reflux, 2.5 h, 71% (**17c**), 5 h, 83% (**17e**).

singlet, supported that the sugar puckering of these 2′,4′-BNA modified *C*-nucleosides was strictly restrained in N-type conformation.[19] On the contrary, $J_{1'2'}$ values of the ribo-type *C*-nucleosides, 2-ribofuranosylpyridine[20] and 4-ribofuranosylimidazole[21] bearing pyridine and imidazole as a nucleobase were known to be 5.5 and 6.9 Hz,

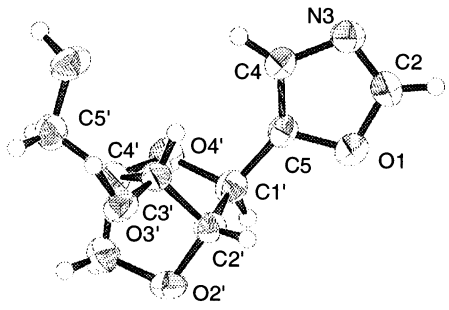
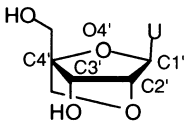


Figure 4. ORTEP drawing of **17a**.

Table 4. Torsion angles and pseudorotation phase angle (*P*) of **17a** and **18**



18

	17a	**18**
ν_0(C4′–O4′–C1′–C2′)	0.4°	0.6°
ν_1(O4′–C1′–C2′–C3′)	−37.2°	−36.5°
ν_2(C1′–C2′–C3′–C4′)	56.0°	53.9°
ν_3(C2′–C3′–C4′–O4′)	−56.9°	−54.3°
ν_4(C3′–C4′–O4′–C1′)	36.6°	34.9°
P	18.0°	17.4°

respectively. These relatively large $J_{1'2'}$ values mean that these ribo-type *C*-nucleosides predominantly existed in S-type conformation.[19] Thus, the 2′-*O*,4′-*C*-methylene bridging (2′,4′-BNA modification) is quite effective to restrict the sugar puckering in N-form not only for *N*-nucleosides but also for *C*-nucleosides.

In addition, X-ray crystallographic analysis[22] of **17a** was performed to clarify the detailed structure (Fig. 4 and Table 4). The endocyclic sugar torsion angles (ν_0–ν_4) of **17a** were almost identical to those of 2′,4′-BNA modified *N*-nucleoside, 2′-*O*,4′-*C*-methyleneuridine **18**.[5] The pseudorotation phase angle (*P*) of **17a** was calculated to be 18.0°, characteristic of the typical C3′-*endo* sugar puckering.[23]

Herein, effective synthesis of the 2′,4′-BNA modified *C*-nucleosides with N-type conformation was achieved by coupling reaction of a metal salt of heteroaromatic compounds and aldehyde **1** followed by the Mitsunobu reaction. This synthetic route should be very useful for preparing the conformationally locked *C*-nucleosides having various heteroaromatics, and we also believe that the *C*-nucleosides with 2′,4′-BNA modification will contribute to greater practical use of antisense and/or antigene strategy.

3. Experimental

3.1. General

All melting points were measured on a Yanagimoto micro melting points apparatus and are uncorrected. Optical rotations were recorded on a JASCO DIP-370 instrument. IR spectra were recorded on a JASCO FT/IR-200 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-200 (^{1}H, 200 MHz; ^{13}C, 50.3 MHz), JEOL EX-270 (^{1}H, 270 MHz; ^{13}C, 67.8 MHz) or JEOL GX-500 (^{1}H, 500 MHz; ^{13}C, 126 MHz). Mass spectra were recorded on a JEOL JMS-D300 or JMS-600 mass spectrometer. For column chromatography, Merck Kieselgel 60 (70–200 mesh) or Fuji Silysia BW-127ZH (100–200 mesh) was used. For flash column, Fuji Silysia BW-300 (200–400 mesh) was used. For almina column chromatography, Merck aluminium oxide 90 active, neutral (70–230 mesh) was used.

3.1.1. Methyl 5-*O*-(*tert*-butyldiphenylsilyl)-4-(hydroxymethyl)-2,3-*O*-isopropylidene-β-D-ribofuranoside (3). Under a nitrogen atmosphere, TBDPSCl (4.88 ml, 18.8 mmol), Et_3N (2.62 ml, 18.8 mmol) were added to a solution of compound **2**[10] (2.00 g, 8.54 mmol) in anhydrous CH_2Cl_2 (40 ml) at 0°C and the mixture was stirred at rt for 13 h. After addition of a saturated aqueous solution of $NaHCO_3$, the mixture was extracted with AcOEt. The organic phase was washed with brine and dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [*n*-hexane/AcOEt (10:1, v/v)] to give compound **3** (2.82 g, 70%) as a colorless oil. $[\alpha]_D^{17}$=−16.2 (*c* 0.52, $CHCl_3$). IR ν_{max} (KBr): 3511, 3061, 2938, 2852, 1465, 1380, 1203, 1103 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.09 (9H, s), 1.28 (3H, s), 1.49 (3H, s), 3.22 (3H, s), 3.67, 3.76 (2H, AB, *J*=11 Hz), 3.88, 3.93 (2H, AB, *J*=11 Hz), 4.49 (1H, d, *J*=6 Hz), 4.57 (1H, d, *J*=6 Hz), 4.93 (1H, s), 7.38–7.43 (6H, m), 7.67 (4H, d, *J*=7 Hz). ^{13}C NMR ($CDCl_3$) δ: 19.25, 24.35, 25.93, 26.87, 55.02, 62.86, 64.82, 82.21, 85.95, 88.70, 108.63, 112.63, 127.78, 129.87, 133.03, 135.65. Mass (EI): *m*/*z* 457 (M^+-CH_3, 5.9), 129 (100). Anal. calcd for $C_{26}H_{36}O_6Si\cdot 1/4H_2O$: C, 65.45; H, 7.71. Found: C, 65.43; H, 7.59.

3.1.2. Methyl 5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-4-(*p*-toluenesulfonyloxymethyl)-β-D-ribofuranoside (4). Under a nitrogen atmosphere, *p*-TsCl (1.34 g, 7.03 mmol), Et_3N (3.92 ml, 28.1 mmol), DMAP (90 mg, 0.74 mmol) were added to a solution of compound **3** (2.13 g, 4.51 mmol) in anhydrous CH_2Cl_2 (15 ml) at 0°C and the mixture was stirred at rt for 17 h. After addition of a saturated aqueous solution of $NaHCO_3$, the mixture was extracted with AcOEt. Usual work-up and purification by silica gel column chromatography [*n*-hexane/AcOEt (5:1, v/v)] gave compound **4** (2.76 g, 98%) as a colorless oil. $[\alpha]_D^{17}$=−3.8 (*c* 0.56, $CHCl_3$). IR ν_{max} (KBr): 2934, 2852, 1369, 1184, 1104 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.02 (9H, s), 1.20 (3H, s), 1.32 (3H, s), 2.41 (3H, s), 3.09 (3H, s), 3.51, 3.77 (2H, AB, *J*=10 Hz), 4.25, 4.39 (2H, AB, *J*=9 Hz), 4.34 (1H, d, *J*=6 Hz), 4.47 (1H, d, *J*=6 Hz), 4.77 (1H, s), 7.28 (2H, d, *J*=9 Hz), 7.39–7.46 (6H, m), 7.62–7.65 (4H, m), 7.81 (2H, d, *J*=9 Hz). ^{13}C NMR ($CDCl_3$) δ: 19.16, 21.58, 24.55, 25.81, 26.79, 54.99, 62.73, 68.81, 81.87, 85.64, 87.51, 108.70, 112.78, 127.75, 127.78, 128.21, 129.58, 129.63, 129.87, 132.92, 135.63, 144.42. Mass (EI): *m*/*z* 611 (M^+-CH_3, 6.0), 353 (100). Anal. calcd for $C_{33}H_{42}O_8SSi$: C, 62.99; H, 6.53; S, 5.13. Found: C, 63.23; H, 6.75; S, 5.11.

3.1.3. Methyl 5-*O*-(*tert*-butyldiphenylsilyl)-4-(*p*-toluenesulfonyloxymethyl)-β-D-ribofuranoside (5). TFA (14 ml) was added to a solution of compound **4** (645 mg, 1.03 mmol) in THF/H_2O (8:3, 11 ml) at rt and the mixture was stirred for 20 min. The mixture was removed under reduced pressure. The residue was purified by silica gel column chromatography [*n*-hexane/AcOEt (2:1, v/v)] to give compound **5** (464 mg, 77%) as a colorless oil. $[\alpha]_D^{17}$=−35.8 (*c* 1.90, $CHCl_3$). IR ν_{max} (KBr): 3499, 3051, 2931, 2846, 1596, 1468, 1362, 1176, 1109 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.02 (9H, s), 2.42 (3H, s), 3.16 (3H, s), 3.54, 3.70 (2H, AB, *J*=10 Hz), 3.97 (1H, d, *J*=5 Hz), 4.18 (1H, d, *J*=5 Hz), 4.26, 4.39 (2H, AB, *J*=10 Hz), 4.73 (1H, s), 7.30 (2H, d, *J*=8 Hz), 7.36–7.44 (6H, m), 7.59–7.66

(4H, m), 7.78 (2H, d, J=8 Hz). ^{13}C NMR ($CDCl_3$) δ: 19.18, 21.60, 26.70, 55.15, 66.52, 69.58, 74.04, 75.22, 84.76, 107.46, 127.75, 128.01, 129.79, 129.85, 132.56, 132.67, 132.81, 135.51, 135.58, 144.87. Mass (EI): m/z 569 (M^+-OH, 6.4), 199 (100). Anal. calcd for $C_{30}H_{38}O_8SSi\cdot 1/4H_2O$: C, 60.94; H, 6.56. Found: C, 60.94; H, 6.43.

3.1.4. Methyl 5-*O*-(*tert*-butyldiphenylsilyl)-2-*O*,4-*C*-methylene-β-D-ribofuranoside (6) and methyl 5-*O*-(*tert*-butyldiphenylsilyl)-3-*O*,4-*C*-methylene-β-D-ribofuranoside (7). Under a nitrogen atmosphere, $(TMS)_2NH$ (0.70 ml, 3.31 mmol) was added to a solution of $NaNH_2$ (129 mg, 3.31 mmol) in anhydrous benzene (1.6 ml) at rt and the mixture was stirred for 30 min. The mixture was added to a solution of compound **5** (194 mg, 0.33 mmol) in anhydrous THF (4 ml) at rt under a nitrogen atmosphere and the mixture was stirred for 1 h. After addition of a saturated aqueous solution of $NaHCO_3$, the mixture was extracted with $CHCl_3$. Usual work-up and purification by silica gel column chromatography [n-hexane/AcOEt (5:1, v/v)] gave compound **6** (48 mg, 35%) and compound **7** (59 mg, 43%) each as a colorless oil. Compound **6**: $[\alpha]_D^{21}=-57.9$ (c 1.68, $CHCl_3$). IR ν_{max} (KBr): 3438, 3064, 2934, 2852, 1468, 1103, 1036 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.08 (9H, s), 2.04 (1H, brs), 3.39 (3H, s), 3.65, 3.98 (2H, AB, J=8 Hz), 3.95, 4.02 (2H, AB, J=12 Hz), 4.02 (1H, s), 4.30 (1H, s), 4.79 (1H, s), 7.38–7.46 (6H, m), 7.65–7.69 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 19.25, 26.74, 55.04, 60.72, 71.18, 73.08, 79.88, 85.46, 104.35, 127.80, 129.88, 130.03, 132.88, 135.58, 135.62, 135.71. Mass (EI): m/z 397 (M^+-OH, 1.6), 383 (M^+-OCH_3, 1.1), 357 ($M^+-C_4H_9$, 49.7), 279 (100). Anal. calcd for $C_{23}H_{30}O_5Si\cdot 1/4H_2O$: C, 65.92; H, 7.34. Found: C, 66.07; H, 7.14. Compound **7**: $[\alpha]_D^{17}=-47.3$ (c 0.91, $CHCl_3$). IR ν_{max} (KBr): 3457, 3059, 2938, 2852, 1468, 1109 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.10 (9H, s), 3.26 (3H, s), 3.71 (2H, s), 4.02 (1H, d, J=6 Hz), 4.35, 4.95 (2H, AB, J=7 Hz), 5.01 (1H, s), 5.11 (1H, d, J=6 Hz), 7.38–7.44 (6H, m), 7.66 (4H, d, J=7 Hz). ^{13}C NMR ($CDCl_3$) δ: 19.28, 26.79, 55.40, 63.70 75.13, 77.20, 77.34, 77.86, 84.48, 86.29, 111.86, 127.78, 128.00, 129.87, 132.90, 132.96, 135.56, 135.81, 135.94. Mass (EI): m/z 357 ($M^+-C_4H_9$, 10.4), 325 (100). Anal. calcd for $C_{23}H_{30}O_5Si\cdot 1/4H_2O$: C, 65.92; H, 7.34. Found: C, 65.98; H, 7.23.

3.1.5. Methyl 2-*O*,4-*C*-methylene-β-D-ribofuranoside (8). Under a nitrogen atmosphere, TBAF (1 M in THF, 0.45 ml, 0.45 mmol) was added to a solution of compound **6** (157 mg, 0.38 mmol) in anhydrous THF (4 ml) at rt and the mixture was stirred for 0.5 h at rt. The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography [n-hexane/AcOEt (1:1, v/v)] to give compound **8** (67 mg, 100%) as a colorless oil. $[\alpha]_D^{26}=-131.0$ (c 1.31, $CHCl_3$). IR ν_{max} (KBr): 3373, 2947, 1646, 1198, 1035 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.41 (3H, s), 3.64, 3.93 (2H, AB, J=8 Hz), 3.89 (2H, s), 4.05 (1H, s), 4.31 (1H, s), 4.80 (1H, s). ^{13}C NMR ($CDCl_3$) δ: 55.63, 58.06, 70.95, 71.65, 79.65, 86.07, 104.74. Mass (FAB): m/z 177 (MH^+). Anal. calcd for $C_7H_{12}O_5\cdot 1/4H_2O$: C, 46.54; H, 6.97. Found: C, 46.62; H, 7.00.

3.1.6. Methyl 3,5-di-*O*-benzyl-2-*O*,4-*C*-methylene-β-D-ribofuranoside (9). Under a nitrogen atmosphere, a solution of compound **8** (406 mg, 2.30 mmol) in anhydrous DMF (7 ml) was added to a suspension of n-hexane-washed NaH (60% in mineral oil (w/w), 203 mg, 5.08 mmol) in anhydrous DMF (8 ml) at 0°C and the mixture was stirred for 1 h at 0°C. BnBr (0.60 ml, 5.04 mmol) was added to the reaction mixture at 0°C and the mixture was stirred for 1 h at rt. After addition of water, the mixture was extracted with Et_2O. Usual work-up and purification by silica gel column chromatography [n-hexane/AcOEt (6:1, v/v)] gave compound **9** (746 mg, 91%) as a colorless oil. $[\alpha]_D^{26}=-44.7$ (c 1.10, $CHCl_3$). IR ν_{max} (KBr): 2939, 2907, 1454, 1200, 1099, 1038 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.39 (3H, s), 3.79, 3.99 (2H, AB, J=8 Hz), 3.77 (2H, s), 4.08 (1H, s), 4.12 (1H, s), 4.56, 4.67 (2H, AB, J=12 Hz), 4.61 (2H, s), 4.81 (1H, s), 7.27–7.35 (10H, m). ^{13}C NMR ($CDCl_3$) δ: 55.28, 66.35, 71.95, 72.13, 73.48, 78.99, 84.93, 104.77, 127.41, 127.50, 127.67, 128.25, 137.47, 137.76. Mass (EI): m/z 356 (M^+, 8.8), 91 (100). Anal. calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.53; H, 6.69.

3.1.7. Methyl 2,3-*O*-benzylidene-5-*O*-(*tert*-butyldiphenylsilyl)-4-(*p*-toluenesulfonyloxymethyl)-β-D-ribofuranoside (10). Under a nitrogen atmosphere, $ZnCl_2$ (0.15 g, 1.10 mmol) was added to a solution of compound **5** (0.52 g, 0.89 mmol) in PhCHO (4 ml) at rt and the mixture was stirred for 2 h. After addition of a saturated aqueous solution of $NaHCO_3$, the mixture was extracted with $CHCl_3$. The organic phase was washed with a saturated aqueous solution of NH_4Cl and concentrated under reduced pressure. PhCHO was removed from the residue by steam distillation. The residue was extracted with AcOEt. Usual work-up and purification by silica gel column chromatography [n-hexane/AcOEt (1:1, v/v)] gave compound **10** (0.61 g, 100%) as a colorless oil. $[\alpha]_D^{24}=+17.1$ (c 1.38, $CHCl_3$). IR ν_{max} (KBr): 2933, 2864, 1463, 1365, 1179, 1110 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.04 (9H, s), 2.37 (3H, s), 3.13 (3H, s), 3.59, 3.84 (2H, AB, J=10 Hz), 4.30, 4.42 (2H, AB, J=10 Hz), 4.49 (1H, d, J=6 Hz), 4.80 (1H, d, J=6 Hz), 4.95 (1H, s), 5.67 (1H, s), 7.16–7.43 (13H, m), 7.64–7.73 (6H, m). ^{13}C NMR ($CDCl_3$) δ: 19.16, 21.60, 26.76, 55.06, 62.64, 68.73, 82.61, 86.22, 87.64, 106.29, 108.23, 126.84, 127.76, 127.82, 128.12, 128.39, 129.51, 129.85, 132.63, 132.69, 132.78, 135.29, 135.62, 144.33. Mass (EI): m/z 674 (M^+, 0.6), 353 (100). Anal. calcd for $C_{37}H_{42}O_8SSi$: C, 65.85; H, 6.27; S, 4.75. Found: C, 65.94; H, 6.40; S, 4.75.

3.1.8. Methyl 3-*O*-benzyl-5-*O*-(*tert*-butyldiphenylsilyl)-4-(*p*-toluenesulfonyloxymethyl)-β-D-ribofuranoside (11) and methyl 2-*O*-benzyl-5-*O*-(*tert*-butyldiphenylsilyl)-4-(*p*-toluenesulfonyloxymethyl)-β-D-ribofuranoside (12). Under a nitrogen atmosphere, $NaBH_3CN$ (23 mg, 0.37 mmol), $TiCl_4$ (40 μl, 0.37 mmol) were added to a solution of compound **8** (51 mg, 76 μmol) in anhydrous MeCN (1.2 ml) at 0°C and the mixture was stirred for 1 h at rt. After addition of a saturated aqueous solution of NH_4Cl, the mixture was neutralized by addition of a saturated aqueous solution of $NaHCO_3$ and filtered through Celite which was subsequently washed with $CHCl_3$. The combined filtrate was extracted with $CHCl_3$. Usual work-up and purification by silica gel column chromatography [n-hexane/AcOEt (5:1, v/v)] gave compound **11** (33 mg, 67%) and compound **12** (14 mg, 27%) each as a colorless oil. Compound **11**: $[\alpha]_D^{23}=-32.8$ (c 3.89, $CHCl_3$). IR ν_{max}

(KBr): 3545, 3068, 2932, 2859, 1457, 1362, 1178, 1114, 1042 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.03 (9H, s), 2.40 (3H, s), 2.67 (1H, d, J=5 Hz), 3.11 (3H, s), 3.51, 3.72 (2H, AB, J=10 Hz), 3.95 (1H, dd, J=5, 5 Hz), 4.10 (1H, d, J=5 Hz), 4.24, 4.36 (2H, AB, J=10 Hz), 4.52, 4.54 (2H, AB, J=10 Hz), 4.68 (1H, s), 7.21–7.44 (13H, m),7.60–7.75 (6H, m). ^{13}C NMR ($CDCl_3$) δ: 19.19, 21.58, 26.76, 54.86, 66.64, 69.75, 73.24, 73.66, 81.43, 84.14, 107.64, 127.75, 128.08, 128.20, 128.50, 129.57, 129.81, 129.87, 132.46, 132.64, 132.84, 135.45, 135.60, 136.91, 144.50. Mass (EI): m/z 619 ($M^+-C_4H_9$, 0.4), 91 (100). Anal. calcd for $C_{37}H_{44}O_8SSi$: C, 65.65; H, 6.55; S, 4.74. Found: C, 65.48; H, 6.56; S, 4.36. Compound **12**: $[\alpha]_D^{23}$=+3.2 (c 3.31, $CHCl_3$). IR ν_{max} (KBr): 3534, 3068, 2932, 2858, 1596, 1469, 1362, 1178, 1112, 1042 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.00 (9H, s), 2.39 (3H, d, J=6 Hz), 2.59 (1H, s), 3.18 (3H, s), 3.47, 3.63 (2H, AB, J=10 Hz), 3.80 (1H, dd, J=2, 6 Hz), 4.23 (1H, dd, J=6, 6 Hz), 4.26, 4.41 (2H, AB, J=10 Hz), 4.50, 4.63 (2H, AB, J=12 Hz), 4.77 (1H, d, J=2 Hz), 7.21–7.44 (13H, m), 7.62–7.76 (6H, m). ^{13}C NMR ($CDCl_3$) δ: 19.16, 21.55, 26.69, 55.39, 64.94, 69.48, 73.04, 73.15, 82.41, 85.04, 105.66, 127.72, 127.79, 128.05, 128.19, 128.58, 129.58, 129.76, 132.84, 132.93, 135.59, 136.83, 144.35. Mass (EI): m/z 619 ($M^+-C_4H_9$, 0.3), 91 (100). Anal. calcd for $C_{37}H_{44}O_8SSi$: C, 65.65; H, 6.55; S, 4.74. Found: C, 65.50; H, 6.49; S, 4.61.

3.1.9. Methyl 3-*O*-benzyl-5-*O*-(*tert*-butyldiphenylsilyl)-2-*O*,4-*C*-methylene-β-D-ribofuranoside (13). Under a nitrogen atmosphere, $NaN(TMS)_2$ (1 M in THF, 0.92 ml, 0.92 mmol) was added to a solution of compound **11** (0.31 g, 0.46 mmol) in anhydrous THF (6 ml) at 0°C and stirred for 3 h at rt. After addition of a saturated aqueous solution of sodium $NaHCO_3$, the mixture was extracted with AcOEt. Usual work-up and purification by silica gel column chromatography [n-hexane/AcOEt (5:1, v/v)] gave compound **13** (0.22 g, 95%) as a colorless oil. $[\alpha]_D^{24}$=−34.5 (c 1.90, $CHCl_3$). IR ν_{max} (KBr): 2933, 2864, 1195, 1103, 1040 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.06 (9H, s), 3.40 (3H, s), 3.67, 3.97 (2H, AB, J=7 Hz), 3.96 (2H, s), 4.13 (1H, s), 4.22 (1H, s), 4.59, 4.67 (2H, AB, J=12 Hz), 4.83 (1H, s), 7.26–7.42 (11H, m), 7.70–7.72 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 19.32, 26.68, 54.84, 60.08, 72.06, 72.15, 77.30, 78.84, 86.19, 104.47, 127.44, 127.67, 128.35, 129.67, 133.16, 133.36, 135.60, 135.65, 137.82. Mass (EI): m/z 504 (M^+, 0.2), 91 (100). Anal. calcd for $C_{30}H_{36}O_5Si$: C, 71.39; H, 7.19. Found: C, 71.48; H, 7.22.

3.1.10. Methyl 3-*O*-benzyl-2-*O*,4-*C*-methylene-β-D-ribofuranoside (14). Under a nitrogen atmosphere, TBAF (1 M in THF, 0.41 ml, 0.41 mmol) was added to a solution of compound **13** (138 mg, 0.27 mmol) in anhydrous THF (3 ml) at rt and the mixture was stirred for 6 h at rt. The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography [n-hexane/AcOEt (1:1, v/v)] to give compound **14** (72 mg, 100%) as a colorless oil. $[\alpha]_D^{24}$=−52.4 (c 1.74, $CHCl_3$). IR ν_{max} (KBr): 3442, 2942, 1455, 1197, 1141, 1099, 1037 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.92 (1H, dd, J=6, 6 Hz), 3.38 (3H, s), 3.65, 3.99 (2H, AB, J=8 Hz), 3.87–3.88 (2H, m), 4.12 (2H, d, J=6 Hz), 4.60, 4.67 (2H, AB, J=12 Hz), 7.26–7.37 (5H, m). ^{13}C NMR ($CDCl_3$) δ: 55.43, 58.65, 71.72, 72.15, 77.26, 78.47, 85.55, 105.10, 127.52, 127.84, 128.40, 137.56. Mass (FAB): m/z 267 (MH^+). Anal. calcd for $C_{14}H_{18}O_5\cdot 1/6H_2O$: C, 62.44; H, 6.86. Found: C, 62.48; H, 6.78.

3.1.11. Methyl 3,5-di-*O*-benzyl-2-*O*,4-*C*-methylene-β-D-ribofuranoside (9). Under a nitrogen atmosphere, a solution of compound **14** (46 mg, 0.17 mmol) in anhydrous DMF (1.5 ml) was added to a suspension of n-hexane-washed NaH (60% in mineral oil (w/w), 8.0 mg, 0.20 mmol) in anhydrous DMF (1.5 ml) at 0°C and the mixture was stirred for 10 min at 0°C. BnBr (24 μl, 0.21 mmol) was added to the reaction mixture at 0°C and the mixture was stirred for 7 h at rt. After addition of water, the mixture was extracted with AcOEt. Usual work-up and purification by silica gel column chromatography [n-hexane/AcOEt (6:1, v/v)] gave compound **9** (56 mg, 92%) as a colorless oil.

3.1.12. 3,5-Di-*O*-benzyl-2-*O*,4-*C*-methylene-D-ribofuranose (1). HCl (10% in water, 5 drops) was added to a solution of compound **9** (280 mg, 0.79 mmol) in THF (6 ml) at 0°C and the mixture was stirred for 2 h at rt. After addition of a saturated aqueous solution of $NaHCO_3$, the mixture was extracted with $CHCl_3$. Usual work-up and purification by silica gel column chromatography [n-hexane/AcOEt (3:2, v/v)] gave compound **1** (269 mg, 100%) as a colorless oil. $[\alpha]_D^{24}$=+55.1 (c 0.85, $CHCl_3$). IR ν_{max} (KBr): 3381, 2869, 1727, 1454, 1099 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.51, 3.83 (2H, AB, J=9 Hz), 3.93, 3.96 (2H, AB, J=9 Hz), 3.94 (1H, s), 4.37 (1H, s), 4.52, 4.67 (2H, AB, J=12 Hz), 4.54, 4.55 (2H, AB, J=12 Hz), 7.26–7.35 (10H, m), 9.65 (1H, s). ^{13}C NMR ($CDCl_3$) δ: 67.93, 71.83, 73.68, 75.01, 80.94, 87.01, 87.14, 127.71, 127.76, 127.91, 127.98, 128.43, 128.48, 137.09, 137.29. Mass (EI): m/z 342 (M^+, 1.3), 91 (100). Anal. calcd for $C_{20}H_{22}O_5\cdot 1/3H_2O$: C, 68.95; H, 6.56. Found: C, 69.09; H, 6.56.

3.1.13. 5-(3,5-Di-*O*-benzyl-2-*O*-4-*C*-methylene-D-ribitol-1-yl)-2-(methylthio)oxazole (15a). *Grignard reaction*. Under a nitrogen atmosphere, $MgBr_2$ (0.494 M in THF, 5 ml, 2.68 mmol) was added to a solution of 5-lithio-2-(methylthio)oxazole[12] [0.148 M in THF/TMEDA (7:4), 11 ml, 1.63 mmol] at rt and the mixture was stirred at rt for 15 min. A solution of compound **1** (160 mg, 0.47 mmol) in anhydrous THF (3 ml) was added to the mixture at rt and the mixture was stirred for 1 h at rt. After addition of water, the mixture was extracted with AcOEt. Usual work-up and purification by flash silica gel column chromatography [n-hexane/AcOEt (1:1, v/v)] gave a mixture of compound *R*-**15a** and compound *S*-**15a** (131 mg, 61%, *R*-**15a**/*S*-**15a**=15:85). *Reaction using organolithium reagent*. Under a nitrogen atmosphere, a solution of compound **1** (233 mg, 0.68 mmol) in anhydrous THF (4 ml) was added to a solution of 5-lithio-2-(methylthio)oxazole[12] [0.171 M in THF/TMEDA (4:3), 14 ml, 2.39 mmol] at −78°C and the mixture was stirred at −78°C for 13 h. According to the Grignard reaction, a mixture of compound *R*-**15a** and compound *S*-**15a** (244 mg, 78%, *R*-**15a**/*S*-**15a**=39:61) was given. Compound *R*-**15a**. Pale yellow oil. $[\alpha]_D^{22}$=+70.9 (c 0.72, $CHCl_3$). IR ν_{max} (KBr): 3372, 2867, 1490, 1104 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.61 (3H, s), 3.29 (2H, brs), 3.58, 3.83 (2H, AB, J=9 Hz), 3.79, 3.91 (2H, AB, J=9 Hz), 4.01 (1H, s), 4.29, 4.31 (2H, AB, J=12 Hz), 4.30 (1H, d, J=4 Hz),

4.58 (2H, s), 4.99 (1H, d, *J*=4 Hz), 7.01 (1H, s), 7.12–7.32 (10H, m). ^{13}C NMR ($CDCl_3$) δ: 14.79, 66.82, 68.86, 72.00, 73.83, 74.95, 81.38, 83.32, 87.08, 125.51, 127.39, 127.70, 127.80, 127.93, 128.28, 128.43, 137.17, 137.27, 152.18, 161.10. Mass (EI): *m/z* 457 (M^+, 6.8), 91 (100). Anal. calcd for $C_{24}H_{27}NO_6S\cdot 1/5H_2O$: C, 62.51; H, 5.99; N, 3.04; S, 6.95. Found: C, 62.54; H, 5.99; N, 2.95; S, 6.67. Compound *S*-**15a**. Pale yellow oil. $[\alpha]_D^{22}=+30.9$ (*c* 0.91, $CHCl_3$). IR ν_{max} (KBr): 3383, 2868, 1489, 1102 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.61 (3H, s), 3.01 (2H, brs), 3.57, 3.82 (2H, AB, *J*=9 Hz), 3.81 (1H, d, *J*=2 Hz), 3.85, 3.90 (2H, AB, *J*=10 Hz), 4.25 (1H, dd, *J*=2, 5 Hz), 4.46 (2H, s), 4.58 (2H, s), 4.76 (1H, d, *J*=5 Hz), 7.00 (1H, s), 7.17–7.34 (10H, m). ^{13}C NMR ($CDCl_3$) δ: 14.77, 66.67, 69.11, 72.36, 73.81, 75.21, 81.60, 84.90, 85.71, 125.86, 127.58, 127.78, 127.87, 127.94, 128.37, 128.43, 137.11, 137.18, 152.00, 161.10. Mass (EI): *m/z* 457 (M^+, 1.7), 91 (100). Anal. calcd for $C_{24}H_{27}NO_6S$: C, 63.00; H, 5.95; N, 3.06. Found: C, 62.91; H, 5.90; N, 3.10.

3.1.14. 5-(3,5-Di-*O*-benzyl-2-*O*-4-*C*-methylene-D-ribitol-1-yl)-2-phenyloxazole (15b). *Grignard reaction*. Under a nitrogen atmosphere, $MgBr_2$ (0.428 M in THF, 40 ml, 17.1 mmol) was added to a solution of 5-(2-phenyloxazolyl)lithium[13] (0.137 M in THF, 100 ml, 13.7 mmol) at 30°C and the mixture was stirred at 30°C for 15 min. A solution of compound **1** (1.17 g, 3.42 mmol) in anhydrous THF (20 ml) was added to the mixture at 30°C and the mixture was stirred for 18 h at rt. After addition of a saturated aqueous solution of NH_4Cl, the mixture was extracted with AcOEt. Usual work-up and purification by flash silica gel column chromatography [*n*-hexane/AcOEt (3:2, v/v)] gave a mixture of compound *R*-**15b** and compound *S*-**15b** (1.16 g, 70%, *R*-**15b**/*S*-**15b**=8:92). *Reaction using organolithium reagent*. Under a nitrogen atmosphere, a solution of compound **1** (198 mg, 0.58 mmol) in anhydrous THF (4 ml) was added to a solution of 5-(2-phenyloxazolyl)lithium[13] (0.191 M in THF, 14 ml, 2.67 mmol) at −78°C and the mixture was stirred at 30°C for 2 h. According to the Grignard reaction, a mixture of compound *R*-**15b** and compound *S*-**15b** (230 mg, 82%, *R*-**15b**/*S*-**15b**=33:67) was given. Compound *R*-**15b**. Pale yellow oil. $[\alpha]_D^{23}=+104.9$ (*c* 0.74, $CHCl_3$). IR ν_{max} (KBr): 3360, 2918, 2866, 1100, 1062 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.33 (1H, brs), 3.60, 3.85 (2H, AB, *J*=9 Hz), 3.84, 3.95 (2H, AB, *J*=10 Hz), 3.89 (1H, d, *J*=3 Hz), 4.05 (1H, d, *J*=2 Hz), 4.24, 4.26 (2H, AB, *J*=12 Hz), 4.43 (1H, dd, *J*=2, 4 Hz), 4.59 (2H, s), 5.14 (1H, m), 6.99–7.45 (14H, m), 8.00–8.02 (2H, m). ^{13}C NMR ($CDCl_3$) δ: 67.21, 68.86, 71.97, 73.84, 75.04, 81.41, 83.25, 87.31, 125.66, 126.18, 127.08, 127.25, 127.62, 127.81, 127.95, 128.19, 128.44, 128.69, 130.31, 137.06, 137.18, 150.82, 161.45. Mass (EI): *m/z* 487 (M^+, 5.5), 91 (100). Anal. calcd for $C_{29}H_{29}NO_6$: C, 71.44; H, 6.00; N, 2.87. Found: C, 71.36; H, 6.14; N, 2.93. Compound *S*-**15b**. Pale yellow oil. $[\alpha]_D^{21}=+40.0$ (*c* 1.24, $CHCl_3$). IR ν_{max} (KBr): 3340, 3063, 3031, 2928, 2866, 1452, 1097 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.30 (1H, brs), 3.59, 3.84 (2H, AB, *J*=9 Hz), 3.66 (1H, brs), 3.87 (1H, d, *J*=2 Hz), 3.88, 3.93 (2H, AB, *J*=10 Hz), 4.35 (1H, dd, *J*=2, 4 Hz), 4.46 (2H, s), 4.59 (2H, s), 4.88 (1H, m), 7.12–7.43 (14H, m), 8.00–8.02 (2H, m). ^{13}C NMR ($CDCl_3$) δ: 66.81, 69.13, 72.40, 73.80, 75.22, 81.65, 84.91, 85.93, 126.24, 126.34, 127.28, 127.64, 127.89, 127.92, 128.03, 128.43, 128.54, 128.70, 130.35, 137.14, 137.30, 150.66, 161.64. Mass (EI): *m/z* 487 (M^+, 2.4), 91 (100). Anal. calcd for $C_{29}H_{29}NO_6$: C, 71.44; H, 6.00; N, 2.87. Found: C, 71.12; H, 6.06; N, 2.84.

3.1.15. 2-(3,5-Di-*O*-benzyl-2-*O*-4-*C*-methylene-D-ribitol-1-yl)pyridine (15c). *Grignard reaction*. Under a nitrogen atmosphere, a solution of compound **1** (205 mg, 0.60 mmol) in anhydrous THF (2.5 ml) was added to a solution of 2-pyridylmagnesium bromide[14] (0.233 M in THF, 9.0 ml, 2.10 mmol) at rt and the mixture was stirred at rt for 2 h and stirring was continued at 50°C for 1 h. After addition of a saturated aqueous solution of NH_4Cl, the mixture was extracted with AcOEt. Usual work-up and purification by flash silica gel column chromatography [*n*-hexane/AcOEt (9:8, v/v)] gave a mixture of compound *R*-**15c** and compound *S*-**15c** (163 mg, 0.39 mmol, 65%, *R*-**15c**/*S*-**15c**=85:15). *Reaction using organolithium reagent*. Under a nitrogen atmosphere, *n*-BuLi (1.60 M in THF, 1.47 ml, 2.35 mmol) was added to a solution of 2-bromopyridine (0.224 ml, 2.34 mmol) in THF (10 ml) at −78°C and the mixture was stirred at −78°C for 40 min. A solution of compound **1** (161 mg, 0.47 mmol) in anhydrous THF (3 ml) was added to the mixture at −78°C and the mixture was stirred at −78°C for 3 h. According to the Grignard reaction, a mixture of compound *R*-**15c** and compound *S*-**15c** (111 mg, 0.26 mmol, 56%, *R*-**15c**/*S*-**15c**=22:78) was given. Compound *R*-**15c**. Colorless crystals. Mp 103–104°C (*n*-hexane–AcOEt). $[\alpha]_D^{25}=+50.5$ (*c* 0.53, $CHCl_3$). IR ν_{max} (KBr): 3370, 2865, 1593, 1449, 1057 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.61, 3.77 (2H, AB, *J*=10 Hz), 3.80, 3.94 (2H, AB, *J*=9 Hz), 3.86 (1H, d, *J*=2 Hz), 3.99 (2H, s), 4.15 (1H, brs),4.28 (1H, dd, *J*=2, 4 Hz), 4.58 (2H, s), 5.04 (1H, d, *J*=4 Hz), 5.13 (1H, brs), 6.94–6.99 (2H, m), 7.18–7.32 (9H, m), 7.47 (1H, d, *J*=8 Hz), 7.71 (1H, ddd, *J*=2, 8, 8 Hz), 8.56 (1H, ddd, *J*=2, 8, 8 Hz). ^{13}C NMR ($CDCl_3$) δ: 69.35, 71.48, 72.60, 73.78, 75.28, 81.46, 83.51, 89.29, 121.60, 122.86, 127.40, 127.53, 127.75, 127.80, 128.18, 128.39, 136.80, 137.66, 137.77, 148.32, 158.36. Mass (EI): *m/z* 421 (M^+, 2.9), 91 (100). Anal. calcd for $C_{25}H_{27}NO_5$: C, 71.24; H, 6.46; N, 3.32. Found: C, 71.00; H, 6.42; N, 3.26. Compound *S*-**15c**. Colorless crystals. Mp 84–85°C (*n*-hexane–AcOEt). $[\alpha]_D^{25}=+16.2$ (*c* 0.51, $CHCl_3$). IR ν_{max} (KBr): 3372, 2867, 1594, 1449, 1096 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.64, 3.83 (2H, AB, *J*=10 Hz), 3.76, 3.84 (2H, AB, *J*=9 Hz), 4.08 (1H, brs), 4.13 (1H, d, *J*=3 Hz), 4.33 (1H, dd, *J*=3, 3 Hz), 4.58, 4.59 (2H, AB, *J*=12 Hz), 4.61 (2H, s), 4.79 (1H, d, *J*=3 Hz), 4.96 (1H, brs), 7.19–7.22 (1H, m), 7.27–7.35 (11H, m), 7.70 (1H, ddd, *J*=2, 8, 8 Hz), 8.53 (1H, m). ^{13}C NMR ($CDCl_3$) δ: 69.49, 72.58, 73.10, 73.82, 75.60, 81.49, 85.41, 87.98, 120.83, 122.61, 127.75, 127.82, 128.43, 136.84, 137.83, 148.10, 158.80. Mass (EI): *m/z* 421 (M^+, 26.4), 91 (100). Anal. calcd for $C_{25}H_{27}NO_5$: C, 71.24; H, 6.46; N, 3.32. Found: C, 71.05; H, 6.41; N, 3.30.

3.1.16. 3-(3,5-Di-*O*-benzyl-2-*O*-4-*C*-methylene-D-ribitol-1-yl)-1-(triisopropylsilyl)pyrrole (15d). *Grignard reaction*. Under a nitrogen atmosphere, 3-bromo-1-(triisopropylsilyl)pyrrole (3.36 g, 11.1 mmol) was added to a solution of $MrBr_2$ (0.494 M in THF, 45 ml, 22.2 mmol) at rt and the mixture was stirred at rt for 1 h. A solution of compound **1** (952 mg, 2.78 mmol) in anhydrous THF (15 ml) was

added to the mixture at rt and the mixture was stirred at rt for 2 h. After addition of water, the mixture was extracted with AcOEt. Usual work-up and purification by flash silica gel column chromatography [*n*-hexane/AcOEt (3:1, v/v)] gave a mixture of compound *R*-**15d** and compound *S*-**15d** (1.28 g, 2.26 mmol, 81%, *R*-**15d**/*S*-**15d**=98:2). *Reaction using organolithium reagent*. Under a nitrogen atmosphere, a solution of compound **1** (195 mg, 0.57 mmol) in anhydrous THF (3 ml) was added to a solution of 3-lithio-1-(triisopropylsilyl)pyrrole[15] (0.221 M in THF, 9.0 ml, 1.99 mmol) at −78°C and the mixture was stirred at −78°C for 1 h and continued stirring at rt for 1 h. According to the Grignard reaction, a mixture of compound *R*-**15d** and compound *S*-**15d** (182 mg, 0.32 mmol, 56%, *R*-**15d**/*S*-**15d**= 50:50) was given. Compound *R*-**15d**. Pale yellow oil. $[\alpha]_D^{21}$=+19.9 (*c* 0.84, $CHCl_3$). IR ν_{max} (KBr): 3327, 2947, 2867, 1464, 1102 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.05, 1.08 (both 9H, d, *J*=7 Hz), 1.42 (3H, hept, *J*=7 Hz) 3.17 (1H, brs), 3.62, 3.80 (2H, AB, *J*=10 Hz), 3.80, 3.93 (2H, AB, *J*=9 Hz), 3.89 (1H, brs), 3.92, 3.99 (2H, AB, *J*=12 Hz), 3.97 (1H, d, *J*=2 Hz), 4.20 (1H, dd, *J*=2, 2 Hz), 4.58 (2H, s), 5.12 (1H, m), 6.29 (1H, m), 6.77 (1H, m), 6.83 (1H, m), 7.05–7.06 (2H, m), 7.23–7.29 (8H, m). ^{13}C NMR ($CDCl_3$) δ: 11.56, 17.77, 69.49, 69.63, 71.41, 73.73, 75.31, 81.19, 83.24, 90.76, 108.57, 121.10, 124.89, 125.79, 127.24, 127.39, 127.71, 128.14, 128.37, 137.88, 138.08. Mass (EI): *m*/*z* 565 (M^+, 0.7), 252 (100). Anal. calcd for $C_{33}H_{47}NO_5Si$: C, 70.05; H, 8.37; N, 2.48. Found: C, 69.99; H, 8.32; N, 2.59. Compound *S*-**15d**. Pale yellow oil. $[\alpha]_D^{25}$=+23.9 (*c* 0.80, C_6H_6). IR ν_{max} (KBr): 3434, 2867, 1461, 1096 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 1.01, 1.02 (both 9H, d, *J*=7 Hz), 1.43 (3H, hept, *J*=7 Hz), 3.53, 3.57 (2H, AB, *J*=10 Hz), 3.63 (1H, d, *J*=3 Hz), 3.70 (2H, s), 3.83 (1H, dd, *J*=3, 8 Hz), 4.00, 4.02 (2H, AB, *J*=12 Hz), 4.50 (2H, s), 4.59 (1H, dd, *J*=5, 8 Hz), 4.83 (1H, d, *J*= 5 Hz), 5.10 (1H, s), 6.26 (1H, m), 6.75–6.77 (2H, m), 7.05–7.08 (2H, m), 7.23–7.32 (8H, m). ^{13}C NMR (DMSO-d_6) δ: 10.93, 17.66, 68.52, 70.95, 71.03, 72.58, 74.22, 80.78, 86.48, 89.12, 109.92, 121.64, 123.75, 126.85, 127.03, 127.16, 127.26, 127.92, 127.99, 138.05, 138.33. Mass (EI): *m*/*z* 565 (M^+, 0.3), 252 (100). Anal. calcd for $C_{33}H_{47}NO_5Si$: C, 70.05; H, 8.37; N, 2.48. Found: C, 69.73; H, 8.31; N, 2.47.

3.1.17. 2-(*tert*-Butyldimethylsilyl)-5-(3,5-di-*O*-benzyl-2-*O*-4-*C*-methylene-D-ribitol-1-yl)-1-(*N*,*N*-dimethylsulfamoyl)imidazole (15e). *Grignard reaction*. Under a nitrogen atmosphere, $MgBr_2$ (0.521 M in THF, 30 ml, 15.6 mmol) was added to a solution of 2-(*tert*-butyldimethylsilyl)-1-*N*,*N*-dimethylsulfamoyl-5-lithio-imidazole[16] (0.396 M in THF, 30 ml, 11.9 mmol) at rt and the mixture was stirred at rt for 10 min. A solution of compound **1** (1.02 g, 2.98 mmol) in anhydrous THF (15 ml) was added to the reaction mixture at rt and the mixture was stirred for 2 h at rt. After addition of water, the mixture was extracted with AcOEt. Usual work-up and purification by flash silica gel column chromatography [*n*-hexane/AcOEt (10:7, v/v)] gave a mixture of compound *R*-**15e** and compound *S*-**15e** (1.35 g, 72%, *R*-**15e**/*S*-**15e**=90:10). *Reaction using organolithium reagent*. Under a nitrogen atmosphere, a solution of compound **1** (298 mg, 0.87 mmol) in anhydrous THF (5 ml) was added to a solution of 2-(*tert*-butyldimethylsilyl)-1-*N*,*N*-dimethylsulfamoyl-5-lithio-imidazole[16] (0.349 M in THF, 10 ml, 3.49 mmol) at −78°C and the mixture was stirred at rt for 2 h. According to the Grignard reaction, a mixture of compound *R*-**15e** and compound *S*-**15e** (448 mg, 80%, *R*-**15e**/*S*-**15e**=69:31) was given. A pale yellow oil. IR ν_{max} (KBr): 3401, 2932, 2864, 1460, 1374, 1101 cm^{-1}. Mass (EI): *m*/*z* 631 (M^+, 1.3), 91 (100). Anal. calcd for $C_{31}H_{45}N_3O_7SSi$: C, 58.93; H, 7.18; N, 6.65; S, 5.07. Found: C, 58.64; H, 7.10; N, 6.42; S, 4.98. (Compound *R*-**15e**): ^1H NMR ($CDCl_3$) δ: 0.37 (6H, s), 0.95 (9H, s), 2.84 (6H, s), 3.33 (1H, s), 3.56, 3.82 (2H, AB, *J*=9 Hz), 3.80, 3.87 (2H, AB, *J*=9 Hz), 3.92 (1H, brs), 4.05 (1H, s), 4.16, 4.24 (2H, AB, *J*=12 Hz), 4.20 (1H, d, *J*=4 Hz), 4.56 (2H, s), 5.22 (1H, dd, *J*=2, 4 Hz), 7.19–7.20 (2H, m), 7.27–7.36 (8H, m), 7.38 (1H, s). (Compound *S*-**15e**): ^1H NMR ($CDCl_3$) δ: 0.40 (3H, s), 0.41 (3H, s), 1.01 (9H, s), 2.84 (6H, s), 3.27 (1H, s), 3.50 (1H, brs), 3.57, 3.82 (2H, AB, *J*=10 Hz), 3.80 (1H, d, *J*=2 Hz), 3.86, 3.93 (2H, AB, *J*=9 Hz), 4.26 (1H, dd, *J*=2, 4 Hz), 4.42, 4.47 (2H, AB, *J*=12 Hz), 4.59 (2H, s), 5.08 (1H, dd, *J*=4, 4 Hz), 7.15–7.17 (2H, m), 7.27–7.36 (8H, m), 7.44 (1H, s).

3.1.18. 5-[(1*R*)-3,5-Di-*O*-benzyl-2-*O*-4-*C*-methylene-D-ribitol-1-yl]oxazole (*R*-15a′). Raney Ni (W-2) (ca. 1.8 g) was added to a solution of compound *R*-**15a** (304 mg, 0.66 mmol) in EtOH (8 ml) and the mixture was refluxed for 30 min. The reaction mixture was filtered and the combined filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography [*n*-hexane/AcOEt (1:1, v/v)] to give a mixture of compound *R*-**15a′** (136 mg, 0.33 mmol, 50%) as a colorless oil. $[\alpha]_D^{25}$=+45.4 (*c* 0.72, $CHCl_3$). IR ν_{max} (KBr): 3341, 2868, 1503, 1455, 1103 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.21 (2H, brs), 3.58, 3.87 (2H, AB, *J*=9 Hz), 3.80, 3.92 (2H, AB, *J*=10 Hz), 4.00 (1H, s), 4.24 (2H, s), 4.32 (1H, s), 4.58 (2H, s), 5.07 (1H, s), 7.08 (3H, m), 7.27–7.32 (8H, m), 8.00 (1H, s). ^{13}C NMR ($CDCl_3$) δ: 66.96, 68.79, 71.89, 73.85, 74.93, 81.39, 83.15, 87.22, 123.92, 127.39, 127.76, 127.81, 127.97, 128.31, 128.46, 137.13, 137.16, 150.70, 151.18. Mass (EI): *m*/*z* 411 (M^+, 13.6), 91 (100). Anal. calcd for $C_{23}H_{25}NO_6 \cdot 1/10H_2O$: C, 66.85; H, 6.15; N, 3.39. Found: C, 66.54; H, 6.20; N, 3.27.

3.1.19. 5-[(1*S*)-3,5-Di-*O*-benzyl-2-*O*-4-*C*-methylene-D-ribitol-1-yl]oxazole (*S*-15a′). Raney Ni (W-2) (ca. 2.4 g) was added to a solution of compound *S*-**15a** (360 mg, 0.79 mmol) in EtOH (8 ml) and the mixture was refluxed for 30 min. The reaction mixture was filtered and the combined filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography [*n*-hexane/AcOEt (2:3, v/v)] to give a mixture of compound *S*-**15a′** (223 mg, 0.54 mmol, 69%) as a colorless oil. $[\alpha]_D^{22}$=+13.8 (*c* 0.82, $CHCl_3$). IR ν_{max} (KBr): 3345, 2868, 1099 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.11 (2H, brs), 3.57, 3.84 (2H, AB, *J*=9 Hz), 3.84, 3.92 (2H, AB, *J*=9 Hz), 3.86 (1H, d, *J*=2 Hz), 4.26 (1H, dd, *J*=2, 4 Hz), 4.47 (2H, s), 4.59 (2H, s), 4.81 (1H, d, *J*=4 Hz), 7.05 (1H, s), 7.20–7.33 (10H, m), 7.81 (1H, s). ^{13}C NMR ($CDCl_3$) δ: 66.60, 69.04, 72.41, 73.82, 75.21, 81.60, 84.80, 86.00, 124.09, 127.62, 127.81, 127.92, 127.96, 128.41, 128.44, 137.08, 137.14, 150.73, 151.06. Mass (EI): *m*/*z* 411 (M^+, 23.3), 91 (100). Anal. calcd for $C_{23}H_{25}NO_6 \cdot 1/5H_2O$: C, 66.56; H, 6.17; N, 3.37. Found: C, 66.26; H, 6.21; N, 3.19.

3.1.20. 5-(3,5-Di-*O*-benzyl-2-*O*-4-*C*-methylene-β-D-ribofuranosyl)oxazole (β-16a). Under a nitrogen atmosphere, TBP (0.47 ml, 1.89 mmol) and TMAD (323 mg, 1.88 mmol) were added to a solution of compound *S*-**15a′** (515 mg, 1.25 mmol) in anhydrous benzene (12 ml) at 0°C and the mixture was stirred for 2 h at rt. After the solvent was filtered through Celite, the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography [*n*-hexane/AcOEt (12:5, v/v)] to give compound β-**16a** (452 mg, 92%) as a colorless oil. $[\alpha]_D^{22}=-12.2$ (*c* 0.89, $CHCl_3$). IR ν_{max} (KBr): 2951, 2878, 1501, 1456, 1102, 1030 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.80 (2H, s), 4.09, 4.12 (2H, AB, *J*=8 Hz), 4.27 (2H, s), 4.57, 4.64 (2H, AB, *J*=12 Hz), 4.60 (2H, s), 5.10 (1H, s), 6.95 (1H, s), 7.31–7.33 (10H, m), 7.81 (1H, s). ^{13}C NMR ($CDCl_3$) δ: 66.35, 72.26, 73.45, 73.69, 75.95, 78.54, 78.95, 85.85, 124.79, 127.48, 127.60, 127.66, 127.92, 128.28, 128.35, 137.14, 137.65, 148.55, 150.97. Mass (EI): *m/z* 393 (M^+, 9.1), 91 (100). Anal. calcd for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56. Found: C, 70.09; H, 5.88; N, 3.51.

3.1.21. 5-(3,5-Di-*O*-benzyl-2-*O*-4-*C*-methylene-α-D-ribofuranosyl)oxazole (α-16a). Under a nitrogen atmosphere, TBP (74 μl, 0.30 mmol) and TMAD (38 ml, 0.30 mmol) were added to a solution of compound *R*-**15a′** (81 mg, 0.20 mmol) in anhydrous benzene (3 ml) at 0°C and the mixture was stirred for 17 h at rt. After the mixture was filtered through Celite, the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography [*n*-hexane/AcOEt (2:1, v/v)] to give compound α-**16a** (60 mg, 77%) as a colorless oil. $[\alpha]_D^{24}=-27.6$ (*c* 0.71, $CHCl_3$). IR ν_{max} (KBr): 3030, 2877, 1500, 1455, 1102 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.76 (2H, s), 4.01, 4.07 (2H, AB, *J*=8 Hz), 4.23 (1H, s), 4.40 (1H, s), 4.59, 4.63 (2H, AB, *J*=12 Hz), 4.64, 4.70 (2H, AB, *J*=12 Hz), 5.11 (1H, s), 7.23 (1H, s), 7.31–7.34 (10H, m), 7.87 (1H, s). ^{13}C NMR ($CDCl_3$) δ: 65.70, 72.10, 73.75, 74.53, 77.63, 80.40, 87.37, 125.07, 127.54, 127.62, 127.68, 127.92, 128.32, 128.41, 137.18, 137.52, 149.04, 150.84. Mass (EI): *m/z* 393 (M^+, 2.0), 91 (100). Anal. calcd for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56. Found: C, 69.84; H, 6.01; N, 3.51.

3.1.22. 5-(3,5-Di-*O*-benzyl-2-*O*-4-*C*-methylene-β-D-ribofuranosyl)-2-phenyloxazole (β-16b). Under a nitrogen atmosphere, TPP (306 mg, 1.17 mmol) and DEAD (40% in toluene, 0.51 ml, 1.17 mmol) were added to a solution of compound *S*-**15b** (379 mg, 0.78 mmol) in anhydrous THF (10 ml) at 0°C and the mixture was stirred for 3 h at 0°C and stirring was continued for 3 h at rt. The solvent was concentrated under reduced pressure. The residue was purified by alumina column chromatography [*n*-hexane/AcOEt (5:1, v/v)] to give compound β-**16b** (329 mg, 90%) as a colorless oil. $[\alpha]_D^{22}=+7.2$ (*c* 1.41, $CHCl_3$). IR ν_{max} (KBr): 3031, 2943, 2879, 1484, 1451, 1364, 1112, 1028 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.86 (2H, s), 4.12, 4.16 (2H, AB, *J*=8 Hz), 4.35 (1H, s), 4.41 (1H, s), 4.62, 4.71 (2H, AB, *J*=12 Hz), 4.62 (2H, s), 5.13 (1H, s), 7.02 (1H, s), 7.31–7.32 (10H, m), 7.43–7.46 (3H, m), 7.86 (2H, d, *J*=7 Hz). ^{13}C NMR ($CDCl_3$) δ: 66.45, 72.06, 73.46, 73.73, 76.07, 78.67, 78.74, 85.90, 126.33, 126.83, 126.99, 127.57, 127.66, 127.71, 128.01, 128.37, 128.52, 128.77, 130.57, 137.27, 137.83, 148.07, 162.05. Mass (EI): *m/z* 469 (M^+, 2.9), 91 (100). Anal. calcd for $C_{29}H_{27}NO_5$: C, 74.18; H, 5.80; N, 2.98. Found: C, 73.86; H, 5.83; N, 2.98.

3.1.23. 5-(3,5-Di-*O*-benzyl-2-*O*-4-*C*-methylene-α-D-ribofuranosyl)-2-phenyloxazole (α-16b). Under a nitrogen atmosphere, TPP (71 mg, 0.27 mmol) and DEAD (40% in toluene, 0.12 ml, 0.28 mmol) were added to a solution of compound *R*-**15b** (88 mg, 0.18 mmol) in anhydrous THF (4 ml) at 0°C and the mixture was stirred for 2 h at 0°C. The solvent was concentrated under reduced pressure. The residue was purified by alumina column chromatography [*n*-hexane/AcOEt (5:1, v/v)] to give compound α-**16b** (61 mg, 72%) as a colorless oil. $[\alpha]_D^{24}=-9.4$ (*c* 0.78, $CHCl_3$). IR ν_{max} (KBr): 3033, 2939, 2876, 1454, 1362, 1119, 1062, 1005 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.78 (2H, s), 4.07, 4.11 (2H, AB, *J*=7 Hz), 4.26 (1H, s), 4.46 (1H, s), 4.61, 4.65 (2H, AB, *J*=13 Hz), 4.66, 4.72 (2H, AB, *J*=12 Hz), 5.17 (1H, s), 7.32–7.44 (14H, m), 8.01 (2H, m). ^{13}C NMR ($CDCl_3$) δ: 65.77, 72.09, 73.77, 73.99, 74.61, 77.68, 80.48, 87.39, 126.22, 126.97, 127.30, 127.56, 127.65, 127.68, 127.92, 128.32, 128.41, 128.59, 130.18, 137.23, 137.56, 148.66, 161.54. Mass (EI): *m/z* 469 (M^+, 6.6), 91 (100). Anal. calcd for $C_{29}H_{27}NO_5$: C, 74.18; H, 5.80; N, 2.98. Found: C, 74.28; H, 5.92; N, 3.00.

3.1.24. 2-(3,5-Di-*O*-benzyl-2-*O*-4-*C*-methylene-β-D-ribofuranosyl)pyridine (β-16c). Under a nitrogen atmosphere, TPP (64 mg, 0.24 mmol) and DEAD (40% in toluene, 88 μl, 0.20 mmol) were added to a solution of compound *R*-**15c** (43 mg, 0.10 mmol) in anhydrous THF (2 ml) at 0°C and the mixture was stirred for 3 h at 0°C. The solvent was concentrated under reduced pressure. The residue was purified by alumina column chromatography [*n*-hexane/AcOEt (5:1, v/v)] to give compound β-**16c** (33 mg, 80%) as a colorless oil. $[\alpha]_D^{24}=+34.5$ (*c* 0.71, $CHCl_3$). IR ν_{max} (KBr): 3030, 2939, 2878, 1589, 1455, 1148, 1096, 1037 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.85 (2H, s), 4.02 (1H, s), 4.12, 4.13 (2H, AB, *J*=8 Hz), 4.43, 4.58 (2H, AB, *J*=12 Hz), 4.61 (1H, s), 4.66 (1H, s), 5.18 (1H, s), 7.14–7.36 (11H, m), 7.51 (1H, d, *J*=8 Hz), 7.65 (1H, ddd, *J*=2, 8, 8 Hz), 8.54 (1H, m). ^{13}C NMR ($CDCl_3$) δ: 66.58, 71.88, 73.53, 73.66, 77.49, 79.82, 84.64, 86.27, 120.85, 122.30, 127.51, 127.64, 127.71, 128.27, 128.36, 136.68, 137.48, 138.08, 149.02, 158.78. Mass (EI): *m/z* 403 (M^+, 1.2), 91 (100). Anal. calcd for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.23; H, 6.34; N, 3.47.

3.1.25. 2-(3,5-Di-*O*-benzyl-2-*O*-4-*C*-methylene-α-D-ribofuranosyl)pyridine (α-16c). Under a nitrogen atmosphere, TPP (148 mg, 0.56 mmol) and DEAD (40% in toluene, 0.25 ml, 0.57 mmol) were added to a solution of compound *S*-**15c** (95 mg, 0.23 mmol) in anhydrous THF (3 ml) at 0°C and the mixture was stirred for 2 h at 0°C and stirring was continued for 2 h at rt. The solvent was concentrated under reduced pressure. The residue was purified by alumina column chromatography [*n*-hexane/AcOEt (7:2, v/v)] to give compound α-**16c** (58 mg, 64%) as a colorless oil. $[\alpha]_D^{23}=-77.6$ (*c* 1.43, $CHCl_3$). IR ν_{max} (KBr): 3028, 2939, 2877, 1584, 1462, 1099, 1056, 1010 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.85, 3.86 (2H, AB, *J*=11 Hz), 3.95, 4.05 (2H, AB, *J*=8 Hz), 4.32 (1H, s), 4.61–4.73 (5H, m), 5.22 (1H, s), 7.18–7.21 (1H, m), 7.32–7.37 (10H, m), 7.63 (1H, d, *J*=8 Hz), 7.73 (1H, ddd, *J*=2, 8, 8 Hz), 8.54 (1H, m). ^{13}C

NMR ($CDCl_3$) δ: 66.23, 71.83, 73.72, 73.77, 78.97, 80.55, 83.36, 87.61, 120.60, 122.13, 127.53, 127.58, 127.61, 127.78, 128.29, 128.35, 136.35, 137.35, 137.73, 148.74, 158.67. Mass (EI): *m/z* 403 (M^+, 0.8), 91 (100). Anal. calcd for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.10; H, 6.31; N, 3.61.

3.1.26. 3-(3,5-Di-*O*-benzyl-2-*O*-4-*C*-methylene-D-ribofuranosyl)-1-(triisopropylsilyl)pyrrole (16d). *Mitsunobu reaction of R*-**15d**. Under nitrogen atmosphere, TPP (0.79 g, 3.01 mmol) and DEAD (40% in toluene, 1.3 ml, 2.99 mmol) were added to a solution of compound *R*-**15d** (1.13 g, 2.00 mmol) in anhydrous THF (30 ml) at 0°C and the mixture was stirred for 12 h at rt. The solvent was concentrated under reduced pressure. The residue was purified by alumina column chromatography [*n*-hexane/AcOEt (10:1, v/v)] to give compounds α-**16d**, β-**16d** (0.64 g, 59%, α-**16d**/β-**16d**=29:71). *Mitsunobu reaction of S*-**15d**. Under a nitrogen atmosphere, TPP (38 mg, 0.14 mmol) and DEAD (40% in toluene, 63 μl, 0.14 mmol) were added to a solution of compound *S*-**15d** (55 mg, 0.10 mmol) in anhydrous THF (2 ml) at 0°C and the mixture was stirred for 3 h at rt. The solvent was concentrated under reduced pressure. The residue was purified by alumina column chromatography [*n*-hexane/AcOEt (10:1, v/v)] to give compounds α-**16d**, β-**16d** (46 mg, 86%, α-**16d**/β-**16d**=78:22). Compound α-**16d**. Colorless oil. $[\alpha]_D^{25}=-26.8$ (*c* 0.85, C_6H_6). IR ν_{max} (KBr): 2951, 2868, 1460, 1096, 1014 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 1.04, 1.04 (both 9H, d, *J*=7 Hz), 1.44 (3H, hept, *J*=7 Hz), 3.70 (2H, s), 3.83, 3.91 (2H, AB, *J*=7 Hz), 4.19 (1H, s), 4.36 (1H, s), 4.53 (2H, s), 4.60, 4.67 (2H, AB, *J*=12 Hz), 4.98 (1H, s), 6.28 (1H, m), 6.75 (1H, m), 6.81 (1H, m), 7.28–7.35 (10H, m). ^{13}C NMR (DMSO-d_6) δ: 10.96, 17.65, 66.55, 70.64, 72.48, 73.41, 76.47, 78.36, 80.81, 85.79, 110.36, 122.83, 123.17, 123.89, 127.29, 127.32, 127.35, 128.07, 128.10, 137.94, 138.01. Mass (EI): *m/z* 547 (M+, 22.7), 91 (100). Anal. calcd for $C_{33}H_{45}NO_4Si$: C, 72.35; H, 8.28; N, 2.56. Found: C, 72.28; H, 8.25; N, 2.64. Compound β-**16d**. Colorless oil. $[\alpha]_D^{21}=-1.3$ (*c* 1.20, C_6H_6). IR ν_{max} (KBr): 2945, 2874, 1462, 1097, 1031 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 0.96, 0.97 (both 9H, d, *J*=7 Hz), 1.35 (3H, hept, *J*=7 Hz), 3.76 (2H, s), 3.80, 3.90 (2H, AB, *J*=8 Hz), 4.11 (1H, s), 4.27 (1H, s), 4.50, 4.58 (2H, AB, *J*=12 Hz), 4.54, 4.58 (2H, AB, *J*=12 Hz), 4.90 (1H, s), 6.08 (1H, m), 6.62 (1H, m), 6.71 (1H, m), 7.29–7.31 (10H, m). ^{13}C NMR (DMSO-d_6) δ: 11.04, 17.77, 66.42, 70.84, 72.69, 77.93, 79.48, 79.77, 84.80, 108.81, 121.48, 124.48, 124.58, 127.27, 127.40, 127.54, 128.20, 128.25, 137.89, 138.35. Mass (EI): *m/z* 547 (M^+, 77.5), 91 (100). Anal. calcd for $C_{33}H_{45}NO_4Si$: C, 72.35; H, 8.28; N, 2.56. Found: C, 72.35; H, 8.27; N, 2.66.

3.1.27. 2-(*tert*-Butyldimethylsilyl)-5-(3,5-di-*O*-benzyl-2-*O*-4-*C*-methylene-D-ribofuranosyl)-1-(*N*,*N*-dimethylsulfamoyl)imidazole (16e). Under a nitrogen atmosphere, TBP (0.71 ml, 2.85 mmol) and TMAD (0.49 g, 2.85 mmol) were added to a solution of compound **15e** (1.20 g, 1.90 mmol, *R*-**15e**/*S*-**15e**=90:10) in anhydrous benzene (40 ml) at 0°C and the mixture was stirred for 15 h at rt. After the solvent was filtered through Celite, the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography [*n*-hexane/AcOEt (4:1, v/v)] to give compound α-**16e**, β-**16e** (1.05 g, 90%, α-**16e**/β-**16e**=10:90). Compound α-**16e**. Colorless oil. $[\alpha]_D^{23}=-28.3$ (*c* 0.86, $CHCl_3$). IR ν_{max} (KBr): 2934, 1459, 1370, 1254, 1187, 1144 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.38 (3H, s), 0.39 (3H, s), 0.99 (9H, s), 2.75 (6H, s), 3.75 (2H, s), 3.96, 4.04 (2H, AB, *J*=8 Hz), 4.22 (1H, s), 4.51 (1H, s), 4.59, 4.60 (2H, AB, *J*=12 Hz), 4.64, 4.71 (2H, AB, *J*=12 Hz), 5.24 (1H, s), 7.27–7.34 (10H, m), 7.56 (1H, s). ^{13}C NMR ($CDCl_3$) δ: −3.57, −3.49, 18.50, 27.27, 37.54, 65.96, 72.01, 73.61, 73.65, 74.72, 78.25, 80.69, 87.05, 127.48, 127.52, 127.65, 127.83, 128.30, 128.37, 131.41, 132.29, 137.36, 137.66, 156.10. Mass (EI): *m/z* 556 ($M^+-C_4H_9$, 100), 91 (59.6). Anal. calcd for $C_{31}H_{43}N_3O_6SSi\cdot 1/3H_2O$: C, 60.07; H, 7.10; N, 6.78; S, 5.17. Found: C, 60.06; H, 6.92; N, 6.64; S, 5.00. Compound β-**16e**. Colorless oil. $[\alpha]_D^{25}=+20.4$ (*c* 0.59, $CHCl_3$). IR ν_{max} (KBr): 2936, 2852, 1373, 1184, 1146, 1031 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.39 (6H, s), 1.01 (9H, s), 2.83 (6H, s), 3.77 (2H, s), 4.02, 4.09 (2H, AB, *J*=8 Hz), 4.13 (1H, s), 4.37 (1H, s), 4.54, 4.59 (2H, AB, *J*=12 Hz), 4.60 (2H, s), 5.20 (1H, s), 7.15 (1H, s), 7.28–7.32 (10H, m). ^{13}C NMR ($CDCl_3$) δ: −3.59, −3.48, 18.50, 27.30, 37.70, 66.21, 72.20, 73.31, 73.62, 77.15, 78.23, 79.12, 85.46, 127.48, 127.58, 127.63, 127.85, 128.33, 131.52, 131.90, 137.25, 137.68, 156.36. Mass (EI): *m/z* 556 ($M^+-C_4H_9$, 100), 91 (93.7). Anal. calcd for $C_{31}H_{43}N_3O_6SSi$: C, 60.65; H, 7.06; N, 6.85; S, 5.22. Found: C, 60.30; H, 6.84; N, 6.75; S, 5.08.

3.1.28. 4-(3,5-Di-*O*-benzyl-2-*O*-4-*C*-methylene-D-ribofuranosyl)imidazole (16e′). A solution of compounds α-**16e**, β-**16e** (1.04 g, 1.69 mmol, α-**16e**/β-**16e**=10:90) in THF (23 ml) was refluxed with HCl (1.5 N in water, 37 ml) for 2.5 h. After neutralization by addition of ammonium hydroxide (28% in water), the solvent was extracted with AcOEt. Usual work-up and purification by silica gel column chromatography [$CHCl_3$/MeOH (30:1, v/v)] gave compounds α-**16e′**, β-**16e′** (561 mg, 84%, α-**16e′**/β-**16e′**=29:71). Compound α-**16e′**. Colorless oil. $[\alpha]_D^{25}=-24.8$ (*c* 0.94, $CHCl_3$). IR ν_{max} (KBr): 3113, 2875, 1455, 1096 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.76, 3.76 (2H, AB, *J*=12 Hz), 3.98, 4.12 (2H, AB, *J*=8 Hz), 4.26 (1H, s), 4.43 (1H, s), 4.58, 4.62 (2H, AB, *J*=12 Hz), 4.64, 4.69 (2H, AB, *J*=12 Hz), 5.13 (1H, s), 5.46 (1H, brs), 7.11 (1H, s), 7.29–7.35 (10H, m), 7.64 (1H, s). ^{13}C NMR ($CDCl_3$) δ: 66.16, 72.03, 73.73, 74.18, 76.14, 78.46, 80.74, 86.79, 120.42, 127.54, 127.63, 127.85, 128.29, 128.36, 133.80, 135.24, 137.27, 137.54. Mass (EI): *m/z* 392 (M^+, 3.2), 91 (100). Anal. calcd for $C_{23}H_{24}N_2O_4\cdot 1/4H_2O$: C, 69.59; H, 6.22; N, 7.06. Found: C, 69.36; H, 6.20; N, 7.02. Compound β-**16e′**. Colorless oil. $[\alpha]_D^{25}=+3.0$ (*c* 0.76, $CHCl_3$). IR ν_{max} (KBr): 3124, 2878, 1455, 1097, 1032 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.82, 3.84 (2H, AB, *J*=11 Hz), 4.06, 4.11 (2H, AB, *J*=8 Hz), 4.33 (1H, s), 4.38 (1H, s), 4.54, 4.64 (2H, AB, *J*=12 Hz), 4.59 (2H, s), 5.13 (1H, s), 6.89 (1H, s), 7.27–7.33 (10H, m), 7.66 (1H, s). ^{13}C NMR ($CDCl_3$) δ: 66.84, 72.03, 73.44, 73.69, 79.08, 79.20, 79.45, 85.33, 115.69, 127.55, 127.66, 128.24, 128.32, 135.07, 137.16, 137.53, 137.67. Mass (EI): *m/z* 392 (M^+, 3.9), 91 (100). Anal. calcd for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.10; H, 6.22; N, 7.09.

3.1.29. 5-(2-*O*-4-*C*-Methylene-β-D-ribofuranosyl)oxazole (17a). Under a hydrogen atmosphere, a solution of compound β-**16a** (452 mg, 1.15 mmol) and 20% $Pd(OH)_2$–C

(317 mg) in EtOH (9 ml) was stirred for 18 h at rt. After the mixture was filtered, SiO_2 (1 g) was added to the filtrate. The mixture was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography [AcOEt/MeOH (20:1, v/v)] to give compound **17a** (201 mg, 82%). One crystallization from AcOEt gave the analytical specimen, colorless crystals. Mp 148–149°C (AcOEt). $[\alpha]_D^{25}=-29.7$ (*c* 0.84, MeOH). IR ν_{max} (KBr): 3147, 1507, 1338, 1130 cm^{-1}. ^1H NMR (CD_3OD) δ: 3.86 (2H, s), 3.93, 4.04 (2H, AB, *J*=8 Hz), 4.19 (1H, s), 4.36 (1H, s), 5.04 (1H, s), 7.14 (1H, s), 8.18 (1H, s). ^{13}C NMR (CD_3OD) δ: 59.43, 73.22, 73.54, 76.89, 82.46, 88.47, 125.19, 151.05, 153.49. Mass (EI): *m/z* 213 (M^+, 4.4), 96 (100). Anal. calcd for $C_9H_{11}NO_5$: C, 50.70; H, 5.20; N, 6.57. Found: C, 50.68; H, 5.14; N, 6.59.

3.1.30. 5-(2-*O*-4-*C*-Methylene-β-D-ribofuranosyl)-2-phenyloxazole (17b). Under a hydrogen atmosphere, a solution of compound β-**16b** (39 mg, 83 μmol) and 20% $Pd(OH)_2$–C (46 mg) in EtOH (8 ml) was stirred for 9 h at rt. After the mixture was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography [$CHCl_3$/MeOH (20:1, v/v)] to give compound **17b** (11 mg, 46%). One crystallization from AcOEt gave the analytical specimen, colorless crystals. Mp 148–149°C (AcOEt). $[\alpha]_D^{24}=+21.5$ (*c* 1.16, MeOH). IR ν_{max} (KBr): 3438, 3048, 2936, 2820, 2711 cm^{-1}. ^1H NMR (CD_3OD) δ: 3.88, 3.89 (2H, AB, *J*=12 Hz), 3.95, 4.06 (2H, AB, *J*=8 Hz), 4.27 (1H, s), 4.49 (1H, s), 5.09 (1H, s), 7.23 (1H, s), 7.51 (3H, m), 8.00 (2H, m). ^{13}C NMR (CD_3OD) δ: 59.31, 73.24, 73.49, 76.90, 82.52, 88.38, 127.00, 127.20, 127.86, 129.95, 131.92, 150.56, 163.19. Mass (EI): *m/z* 289 (M^+, 73.2), 174 (100). Anal. calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 61.98; H, 5.23; N, 4.79.

3.1.31. 2-(2-*O*-4-*C*-Methylene-β-D-ribofuranosyl)pyridine (17c). A solution of compound β-**16c** (510 mg, 1.26 mmol), 20% $Pd(OH)_2$–C (230 mg) and cyclohexene (6.4 ml, 63 mmol) in EtOH (20 ml) was refluxed for 2.5 h. After the mixture was filtered, SiO_2 (1 g) was added to the filtrate. The mixture was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography [AcOEt/MeOH (20:1, v/v)] to give compound **17c** (201 mg, 71%) as a white powder. Mp 123–125°C. $[\alpha]_D^{28}=-0.5$ (*c* 1.10, MeOH). IR ν_{max} (KBr): 3363, 2930, 1043 cm^{-1}. ^1H NMR (CD_3OD) δ: 3.91, 3.92 (2H, AB, *J*=13 Hz), 3.96, 4.05 (2H, AB, *J*=8 Hz), 4.04 (1H, s), 4.28 (1H, s), 5.04 (1H, s), 7.31 (1H, dd, *J*=5, 7 Hz), 7.66 (1H, d, *J*=8 Hz), 7.86 (1H, ddd, *J*=2, 7, 8 Hz), 8.49 (1H, dd, *J*=2, 5 Hz). ^{13}C NMR (CD_3OD) δ: 59.26, 71.48, 73.56, 84.11, 85.09, 88.99, 122.14, 123.90, 138.71, 149.48, 159.78. Mass (EI): *m/z* 223 (M^+, 4.5), 108 (100). Anal. calcd for $C_{11}H_{13}NO_4 \cdot 1/2H_2O$: C, 56.89; H, 6.08; N, 6.03. Found: C, 56.67; H, 5.92; N, 5.92.

3.1.32. 4-(2-*O*-4-*C*-Methylene-β-D-ribofuranosyl)imidazole (17e). A solution of compound β-**16e** (325 mg, 0.83 mmol), 20% $Pd(OH)_2$–C (200 mg) and cyclohexene (4.2 ml, 41 mmol) in EtOH (10 ml) was refluxed for 5 h. After the mixture was filtered, SiO_2 (2 g) was added to the filtrate. The mixture was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography [$CHCl_3$/MeOH (4:1, v/v)] to give compound **17e** (145 mg, 83%). One reprecipitation from AcOEt–MeOH gave the analytical specimen. A white powder. Mp 168–170°C (AcOEt–MeOH). $[\alpha]_D^{21}=-29.2$ (*c* 0.96, MeOH). IR ν_{max} (KBr): 3165, 2951, 2885, 2744, 1033 cm^{-1}. ^1H NMR (CD_3OD) δ: 3.86, 3.87 (2H, AB, *J*=12 Hz), 3.91, 4.02 (2H, AB, *J*=8 Hz), 4.12 (1H, s), 4.26 (1H, s), 4.98 (1H, s), 7.06 (1H, s), 7.64 (1H, s). ^{13}C NMR (CD_3OD) δ: 59.59, 72.47, 73.48, 80.49, 83.57, 88.04, 116.50, 136.54. Mass (EI): *m/z* 212 (M^+, 13.1), 97 (100). HRMS (EI) calcd for $C_9H_{12}N_2O_4$ (M^+) 212.0797, found 212.0826. Anal. calcd for $C_9H_{12}N_2O_4 \cdot 1/5AcOEt$: C, 51.22; H, 5.96; N, 12.19. Found: C, 51.03; H, 5.86; N, 11.89.

3.2. X-Ray crystallographic data of 17a

$C_9H_{11}NO_5$, *M*=213.19, orthorhombic, *a*=10.9079 (6) Å, *b*=13.9320 (8) Å, *c*=6.2584 (6) Å, *V*=951.1 (1) $Å^3$, *T*=283 K, space group $P2_12_12_1$ (no. 19), *Z*=4, D_{calc}=1.489 g cm^{-3}, F_{000}=448.00, μ(Cu Kα)=10.59 cm^{-1}, 918 reflections measured. The final *R*(*F*) and *Rw*(*F*) were 0.033 and 0.031 for 816 observed reflections [$F^2>3\sigma(F^2)$] used in all calculations.

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