# Efficient and β-Stereoselective Synthesis of 4(5)-(β-D-Ribofuranosyl)- and 4(5)-(2-Deoxyribofuranosyl)imidazoles[1]

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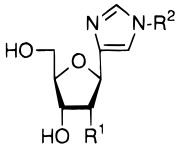
A synthetic route to 4(5)-(β-D-ribofuranosyl)imidazole (**1**), starting from 2,3,5-tri-*O*-benzyl-D-ribose (**5**), was developed *via* a Mitsunobu cyclization. Reaction of **5** with the lithium salt of bis-protected imidazole afforded the corresponding 5-ribosylimidazole **7*RS***. Hydrolysis of **7*RS*** gave a 1:1 mixture of diol isomers **8*R*** and **8*S*** having an unsubstituted imidazole. Mitsunobu cyclization of the mixture **8*RS*** using *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide and $Bu_3P$ exclusively afforded benzylated β-ribofuranosyl imidazole **9**β in 92% yield, accompanied by α-anomer **9**α, in a ratio of 26.3:1. The configuration of **9**β was established by X-ray crystallography of ethoxycarbonyl derivative **10**β. Reductive debenzylation of **9**β over Pd/C was carried out, and the synthesis of **1** was attained from starting **5** in four steps and 87% overall yield. This synthetic methodology was extended to the synthesis of 4(5)-(2-deoxy-β-D-ribofuranosyl)imidazole (**2**). Mitsunobu cyclization of a 1:1 mixture of the corresponding diol isomers **14*RS*** produced **15**β and **15**α in a ratio of 5.4:1. The synthesis of **2** was attained in a 59% overall yield from the starting 3,5-di-*O*-benzyl-2-deoxy-D-ribose (**12**). β-Stereoselective glycosylation in the key step is discussed and explained by intramolecular hydrogen bonding between an NH in the imidazole and the oxygen functional group in the sugar moiety.

## Introduction

C-Nucleosides having 5-membered nitrogen heterocycles, such as showdomycin and pyrazofurin, display remarkable antiviral and antitumor activities.[2] Imidazoles are biologically important heterocyclic compounds, and a variety of useful therapeutic agents containing the imidazole moiety have been developed.[3] Imidazole nucleotides play central roles in purine biosynthesis,[4] and thus, there should be significant potential utility for antimetabolites based on C-4 linkage rather than N-1 linkage to the sugar moiety. We thus directed our attention to synthesizing C-nucleosides having the imidazole as the base moiety. Although several imidazole C-nucleosides linked through C-2 have been synthesized,[5] the first C-4(5) linked 2′-deoxy-β-D-ribofuranosylimidazoles were recently reported by Bergstrom *et al.*[6] The synthetic methods of C-nucleosides, in general, require many steps, and the kinds of C-nucleosides that can be prepared are limited in number.[2] Since most biologically active nucleosides possess β-stereochemistry at C-1 of the sugar moiety, β-stereoselective glycosylation is the most important task in nucleoside synthesis. However, a major practical drawback in current synthetic methods is poor β-selectivity.

We report herein an efficient and stereoselective synthesis of novel 4(5)-(β-D-ribofuranosyl)imidazole (**1**) and its 2′-deoxy derivative **2**[6] using a Mitsunobu cyclization as the key step. Their *N*-(ethoxycarbonyl) compounds **3** and **4**, useful intermediates to supply related nucleosides, were also synthesized by this method. We used the hydrogen-bonding potential of imidazole in this approach to control β-stereoselective glycosylation.




**1**: $R^1$ = OH, $R^2$ = H
**2**: $R^1$ = $R^2$ = H
**3**: $R^1$ = OH, $R^2$ = $CO_2Et$
**4**: $R^1$ = H, $R^2$ = $CO_2Et$

## Results

**Synthesis of 4(5)-(β-D-Ribofuranosyl)imidazoles.** We initially attempted the direct reaction of a protected D-ribosyl chloride with 5-lithioimidazole, but it did not afford the desired glycoside due to the formation of 1-(5-

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(1) Preliminary communication: Harusawa, S.; Murai, Y.; Moriyama, H.; Ohishi, H.; Yoneda, R.; Kurihara, T. *Tetrahedron Lett.* **1995**, *36*, 3165.

(2) For recent reviews on the chemisty, biochemistry, and synthesis of C-nucleoside analogues, see: (a) Suhadolnik, R. *J. Nucleosides as Biological Probes*; Wiley-Interscience: New York, 1979. (b) Hacksell, U.; Daves, G. D. *Prog. Med. Chem.* **1985**, *22*, 1. (c) Sato, T.; Noyori, R. *Yuki Gosei Kagaku Kyokai Shi* **1980**, *38*, 862. (d) Sato, T.; Noyori, R. *Ibid.* **1980**, *38*, 947. (e) Watanabe, K. A. *Ibid.* **1987**, *45*, 212. (f) Katagiri, N. *Ibid.* **1989**, *47*, 707. (g) Postema, M. H. D. *Tetrahedron* **1992,** *48*, 8545. (h) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1. (i) Watanabe, K. A. The Chemistry of C-Nucleosides. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum Press: New York, 1994; Vol. 3, pp 421−535.

(3) Imidazole-based enzyme models: (a) Eberson, L.; Radner, F. *Acc. Chem. Res.* **1987**, *20*, 53. Imidazole-based Angiotensin II receptor antagonists: (b) Greenlee, W. J.; Siegl, P. K. S. *Annu. Rep. Med. Chem.* **1992**, *27*, 59. (c) Hodges, J. C.; Hamby, J. M.; Blankley, C. J. *Drugs Future* **1992,** *17*, 575. Imidazole-based nonprostanoid prostacyclin mimetics: (d) Meanwell, N. A.; Romine, J. L.; Seiler, S. M. *Drugs Future* **1994**, *19*, 361. Imidazole-based acyl-CoA inhibitors: (e) Kimura, T.; Watanabe, N.; Matsui, M.; Hayashi, K.; Tanaka, H.; Ohtsuka, I.; Saeki, T.; Kogushi, M.; Kabayashi, H.; Akasaka, K.; Yamagishi, Y.; Saitou, I.; Yamatsu, I. *J. Med. Chem.* **1993**, *36*, 1641. Imidazole-based $H_2$ antagonists: (f) Ganellin, R. *J. Med. Chem.* **1981**, *24*, 913. Imidazole-based $H_3$ ligands: (g) Timmerman, H. *J. Med. Chem.* **1990**, *33*, 4. Imidazole-based 5-$HT_3$ antagonists: (h) Rosen, T.; Nagel, A. A.; Rizzi, J. P. *Synlett* **1991**, 213 and references cited therein.

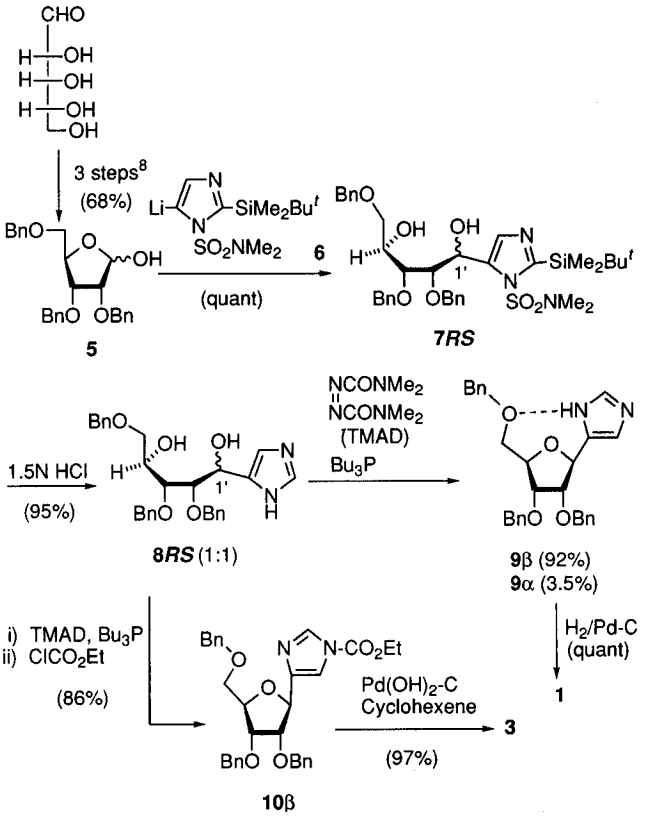
(4) Stryer, L. *Biochemistry*, 3rd ed.; Freeman: New York, 1988; pp 603−4.

(5) (a) Poonian, M. S.; Nowoswiat, E. F. *J. Org. Chem.* **1980**, *45*, 203. (b) Igolen, J.; Dinh, T. H. *J. Chem. Soc., Chem. Commun.* **1971**, 1267. (c) Kolb, A.; Gouyette, C.; Tam, H. D.; Igolen, J. *Tetrahedron Lett.* **1973,** 2971. (d) Ferris, J. P.; Hung, H. C. *J. Chem. Soc., Chem. Commun.* **1978**, 1094. (e) Ferris, J. P.; Badesha, S. S.; Ren, W. Y.; Huang, H. C.; Sorcek, R. J. *Ibid.* **1981**, 110.

(6) Bergstrom, D. E.; Zhang, P.; Zhou, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3029.

S0022-3263(95)02136-0 CCC: $12.00 

**Scheme 1**




imidazolyl)ribofuranoid glycal.[7] This failure led to another synthetic approach using the Mitsunobu cyclization.

The reaction of 2,3,5-tri-*O*-benzyl-D-ribose (**5**),[8] easily available from D-ribose, with lithium salt **6** of bis-protected imidazole[9] gave an inseparable epimeric mixture **7*RS*** of the corresponding 5-ribosylimidazole in quantitative yield, as illustrated in Scheme 1. Hydrolysis of **7*RS*** in refluxing 1.5 N HCl afforded a 1:1 mixture of diols **8*R*** and **8*S*** having an unsubstituted imidazole in 95% yield. Yokoyama *et al.*[10a] recently reported synthesis of C-ribonucleosides having typical aromatic heterocycles, in which the cyclization of the corresponding diols proceeds through intramolecular $S_N2$ reaction under Mitsunobu conditions and orientation of the glycosidic linkage is controlled by the C-1′ configuration of the substrate: one isomer affords an α-anomer and the other a *β*-anomer. When we first carried out the cyclization of the mixture **7*RS*** under standard Mitsunobu conditions [diethyl azodicarboxylate (DEAD)/$Ph_3P$], only a complex mixture was obtained. However, the same treatment of the mixture of **8*R*** and **8*S*** having the unsubstituted imidazole afforded a single crystalline compound **10***β* with an ethoxycarbonyl group at N in the imidazole moiety in only 15% yield, after partial chromatographic separation followed by recrystallization from hexane (Table 1, run 1). Although the stereochemistry at C-1′ and position of the ethoxycarbonyl group in the product could not be determined from spectral data, the structure was established as the desired *β*-anomer, ethyl 4-(2,3,5-tri-*O*-benzyl-*β*-D-ribofuranosyl)imidazole-1-carboxylate, by single-crystal X-ray diffraction analysis.[11]

**Table 1. Mitsunobu Cyclization of Diols 8**

| run | **8** | reaction condns (equiv) | products[a] (%) |
|---|---|---|---|
| 1 | **8*RS***[b] | DEAD (2.2), $Ph_3P$ (2.6), THF, rt, 3 h | **10***β* (R = $CO_2Et$, 15) |
| 2 | **8*RS***[b] | ADDP (2.0), $Bu_3P$ (2.0), benzene, rt, 22 h | **9***β*[d] (53) |
| 3 | **8*R*** | *c* | **9***β*[d] (47) |
| 4 | **8*S*** | *c* | **9***β*[d] (78) |
| 5 | **8*RS***[b] | TMAD (1.5), $Bu_3P$ (1.5), benzene, rt, 16 h | **9***β*[d] (92), **9**α[d] (3.5) |

[a] Isolated yields. [b] Referred to a 1:1 mixture of **8*R*** and **8*S***. [c] The reaction was carried out under the same conditions as in run 2. [d] R = H.

Tsunoda *et al.*[12] recently reported 1,1′-(azodicarbonyl)-dipiperidine (ADDP)−$Bu_3P$[12a] and *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD)−$Bu_3P$[12b] as new reagent systems for the Mitsunobu reaction, and we applied these to the cyclization of **8*RS***. Treatment of the mixture with ADDP−$Bu_3P$ afforded the *β*-anomer (**9***β*) having an unsubstituted imidazole in modest yield (Table 1, run 2). The structure was confirmed by conversion to **10***β* with ethyl chloroformate. This experiment interestingly suggests the *β*-anomer (**9***β*) to be produced from both isomers (**8*R*** and **8*S***), whose configurations at C-1′ were assigned by the $^1$H-NMR data and NOE experiments of their derivatives, as described in the next section. The cyclization of **8*R*** isolated by $SiO_2$ chromatography afforded **9***β* in 47% yield, and the *S*-isomer (**8*S***) also brought about **9***β* in 78% yield (Table 1, runs 3 and 4). These reactions were clear, but the isolated yields were variable and less satisfactory owing to the difficulty in product isolation from the hydrazine byproduct. The problem was solved by a water-soluble TMAD. Treatment of the mixture **8*RS*** with TMAD and $Bu_3P$ at room temperature in benzene exclusively produced the desired *β*-anomer (**9***β*) in 92% yield, together with a small amount of α-anomer (**9**α, 3.5%). The ratio of *β*- and α-isomers was 26.3:1. Importantly, it has been possible to synthesize the *β*-anomer without separation of the isomers (**8*R***, **8*S***) or stereoselective synthesis of the *R*-isomer. This is in contrast to the results of Yokoyama *et al.* mentioned above.[10a]

Patil *et al.*[13] recently reported the X-ray crystallographic analysis of a pyrrole analogue of **9***β*, 5-(2,3,5-tri-*O*-benzyl-*β*-D-ribofuranosyl)pyrrole-2-carbaldehyde, with strong hydrogen-bonding between N1-H and *O*-5′. Chemi-

(7) Harusawa, S.; Kawabata, M.; Murai, Y.; Yoneda, R.; Kurihara, T. *Chem. Pharm. Bull.* **1995**, *43*, 152.

(8) Barker, R.; Fletcher, H. G., Jr. *J. Org. Chem.* **1961**, *26*, 4605. We obtained **5** in an improved yield (68%) from D-ribose by the Barker procedure.

(9) (a) Ngochindo, R. I. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1645. (b) Kudzma, L. V.; Turbull, S. P., Jr. *Synthesis* **1991**, 1021.

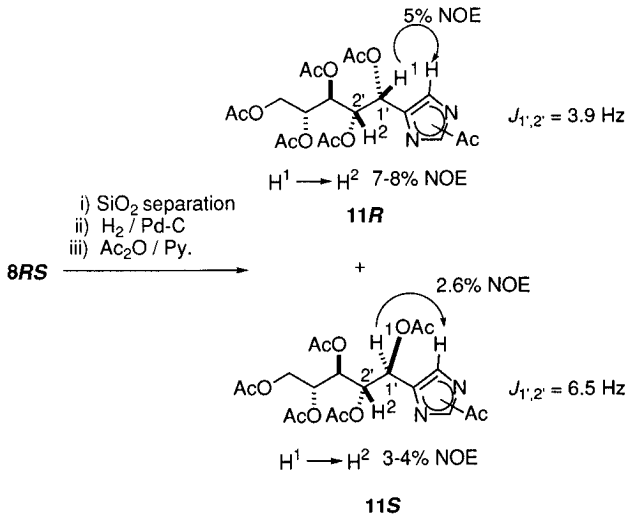
(10) (a) Yokoyama, M.; Toyoshima, A.; Akiba, T.; Togo, H. *Chem. Lett.* **1994**, 265. (b) Yokoyama, M.; Akiba, T.; Togo, H. *Synthesis* **1995**, 638. (c) Yokoyama, M.; Tanabe, T.; Toyoshima, A.; Togo, H. *Synthesis* **1993**, 517.

(11) Monoclinic, $P2_1$. More details on the crystal structure analysis (refcode: ZAPSUE) were submitted to the Cambridge Crystallographic Data Centre. The details can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(12) (a) Tsunoda, T.; Yamamiya, Y.; Itô, S. *Tetrahedron Lett.* **1993**, *34*, 1639. (b) Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Itô, S. *Chem. Lett.* **1994**, 539. (c) Tsunoda, T.; Ozaki, F.; Itô, S. *Tetrahedron Lett.* **1994**, *35*, 5081.

(13) Patil, S. A.; Otter, B. A.; Klelin, R. S. *Tetrahedron Lett.* **1994**, *35*, 5339.

**Scheme 2**




cal shifts and coupling constants of $^1$H-NMR on the sugar moiety of **9**$\beta$ are consistent with those of the pyrrole analogue. This supports the existence of hydrogen-bonding in **9**$\beta$. Debenzylation of **9**$\beta$ over Pd−C was carried out to achieve the synthesis of 4(5)-($\beta$-D-ribofuranosyl)imidazole (**1**) in four steps and an 87% overall yield from **5**. Similarly, Mitsunobu cyclization of the *RS* mixture of **8** followed by treatment with ethyl chloroformate without purification of crude **9** afforded a $\beta$-anomer (**10**$\beta$) in 86% yield (Scheme 1). Deprotection of **10**$\beta$ with $Pd(OH)_2$−cyclohexene produced an ethoxycarbonyl derivative **3** in 97% yield. The ethoxycabonyl derivative **3** was obtained from **5** in five steps and 79% overall yield.

**C-1′ Configurations in 8*R* and 8*S*.** The configurations at C-1′ of **8*R*** and **8*S*** were assigned by comparison of $J_{1',2'}$ coupling constants and NOE difference spectra of per-*O*,*N*-acetyl derivatives **11*R*** and **11*S*** at −25 °C.[14] The respective epimers of **8** were separated by column chromatography and then transformed into **11*R*** and **11*S*** by hydrogenolytic debenzylation followed by acetylation (Scheme 2). The $J_{1',2'}$ coupling constant (3.9 Hz) of **11*R*** was relatively small in comparison to **11*S*** which exhibited large $J_{1',2'}$ (6.5 Hz). By analogy with data[15] for acetyl derivatives of acyclic carbohydrates (coupling constants, <4 Hz for protons having a gauche orientation and the values >7 Hz for those having antiparallel orientation), it appears that there is a gauche relationship for **11*R*** and an antiparallel orientation for **11*S***. In the NOE experiments, mutual enhancement between $H^1$ and $H^2$ was found to be substantially greater in the case of **11*R*** (7−8%) compared to that of **11*S*** (3−4%). Respective configurations at C-1′ are thus indicated as shown in Scheme 2. C-1′ configurations in the original compounds **8*R*** and **8*S*** were tentatively assigned based on **11*R*** and **11*S***.

**Synthesis of 4(5)-(2-Deoxy-$\beta$-D-ribofuranosyl)imidazoles.** C-2′-Deoxy-D-ribonucleosides are of interest as potential antiviral and antitumor agents.[16] However, relatively few examples have been reported, and the number of direct synthetic procedures remains limited.[17] Bergstrom *et al.*[6] recently reported the synthesis of 4(5)-(2-deoxy-$\beta$-D-ribofuranosyl)imidazole-2-carboxamide designed as a universal nucleoside. The synthetic intermediate, 4(5)-(2-deoxy-$\beta$-ribofuranosyl)-1*H*-imidazole (**2**), was synthesized from 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-$\beta$-D-ribofuranosyl cyanide in six steps, in only 9.2% overall yield. The synthetic approach is construction of the C-linked imidazole from the cyano group on C-1 of sugar, but it would be difficult to make **2** on a large scale owing to the use of an unstable intermediate. Yokoyama *et al.*[10b] very recently reported the conversion yields of Mitsunobu cyclization to be low (30−40%) for the synthesis of C-2′-deoxy-D-ribonucleosides bearing typical aromatic heterocycles as the base moiety. The authors thus intend to synthesize the 2′-deoxy compound **2** and its ethoxycarbonyl derivative **4** as an extension of our synthetic methodology.

Reaction of 3,5-di-*O*-benzyl-2-deoxy-D-ribose (**12**),[18] readily available in three steps from D-2-deoxyribose, with 5-lithioimidazole **6** afforded an adduct **13*RS*** in 99% yield, as shown in Scheme 3. Double deprotection of the adduct by treatment with 1.5 N HCl afforded a 1:1 epimeric mixture of diols **14*RS*** in 92% yield. Mitsunobu cyclization (TMAD−$Bu_3P$) of the mixture produced an inseparable mixture of $\beta$- and $\alpha$-anomers in a ratio of ca. 5:1. The ratio was assigned from methylene protons at C-2′ in $^1$H NMR ($\delta$ 2.20, 2.35 for **15**$\beta$ *vs* 2.19, 2.60 for **15**$\alpha$).[6,19] The signals for the two C-2′ protons of **15**$\beta$ spanned a total region of 0.27 ppm, which is typical of the $\beta$-anomer. The large total region (0.55 ppm) of **15**$\alpha$ provides evidence for the $\alpha$-anomer.

Their mesyl derivatives **16** could be separated by flash column chromatography, giving $\beta$- and $\alpha$-anomers (**16**$\beta$, **16**$\alpha$) in 59% and 11% yields from **14*RS***, respectively. Deprotection of **16**$\beta$ with 1.5 N HCl followed by treatment with $BCl_3$[10c] completed the synthesis of **2** in 94% yield, and the spectroscopic data were consistent with those reported by Bergstrom *et al.* Ethoxycarbonyl derivative **4** was similarly synthesized (Scheme 3), and deprotection with hydrazine hydrate also afforded **2** *via* an alternative route. We thus achieved an efficient and stereocontrolled synthesis of *C*-2′-deoxy-D-ribonucleoside **2** bearing the imidazole in 59% overall yield from **12**.

The advantageous feature of this approach is the supply of **2** or **4** on a multigram scale; for example, we obtained 6.65 g (72%) of the $\beta$-anomer (**17**$\beta$) from 8.08 g of **14*RS***.

**Mechanistic Considerations on $\beta$-Stereoselective Glycosylation on the Mitsunobu Cyclization.** Mitsunobu cyclization of the diols (**8*RS***, **14*RS***) bearing an unsubstituted imidazole exhibited excellent $\beta$-selective glycosylation. Importantly, the reaction supplied exclusively the desired $\beta$-anomers from both *R*- and *S*-isomers. Mitsunobu cyclization of diols **13** and **18** bearing monosubstituted or disubstituted imidazole proceeded *via* a $S_N2$ process of the standard Mitsunobu reaction, as shown in Table 2. The intact-imidazole moiety is thus shown to be indispensable for the exclusive formation of $\beta$-anomers. Intramolecular hydrogen bonding between the nitrogen in the imidazole and OH groups in the sugar

(14) The $J_{1',2'}$ and NOE values of **11*R*** and **11*S*** did not show significant differences at 24 °C.

(15) (a) Rashed, N.; Ibrahim, E. I.; El Ashry, E. S. H. *Carbohydr. Res.* **1994**, 254, 295. (b) Khadem, H. E.; Horton, D.; Wander, J. D. *J. Org. Chem.* **1972**, *37*, 1630.

(16) (a) Chu, C. K.; Reichmann, U.; Watanabe, K. A.; Fox, J. J. *J. Heterocycl. Chem.* **1977**, *14*, 1119. (b) Matsuda, A.; Chu, C. K.; Reichman, U.; Pankiewicz, K.; Watanabe, K. A.; Fox, J. J. *J. Org. Chem.* **1981**, *46*, 3603. (c) Matsuda, A.; Pankiewicz, K.; Marcus, B. K.; Watanabe, K. A.; Fox, J. J. *Carbohydr. Res.* **1982**, *100*, 297.

(17) Reference 10b and references cited therein.

(18) (a) Huang, B.; Hui, Y. *Nucleosides Nucleotides* **1993**, *12*, 139. (b) Wierenga, W.; Skulnick, H. I. *Carbohydr. Res.* **1981**, *90*, 41.

(19) Srivastava, P. C.; Robins, R. K.; Takusagawa, F.; Berman, H. M. *J. Heterocycl. Chem.* **1981**, *18*, 1659.

**Scheme 3**

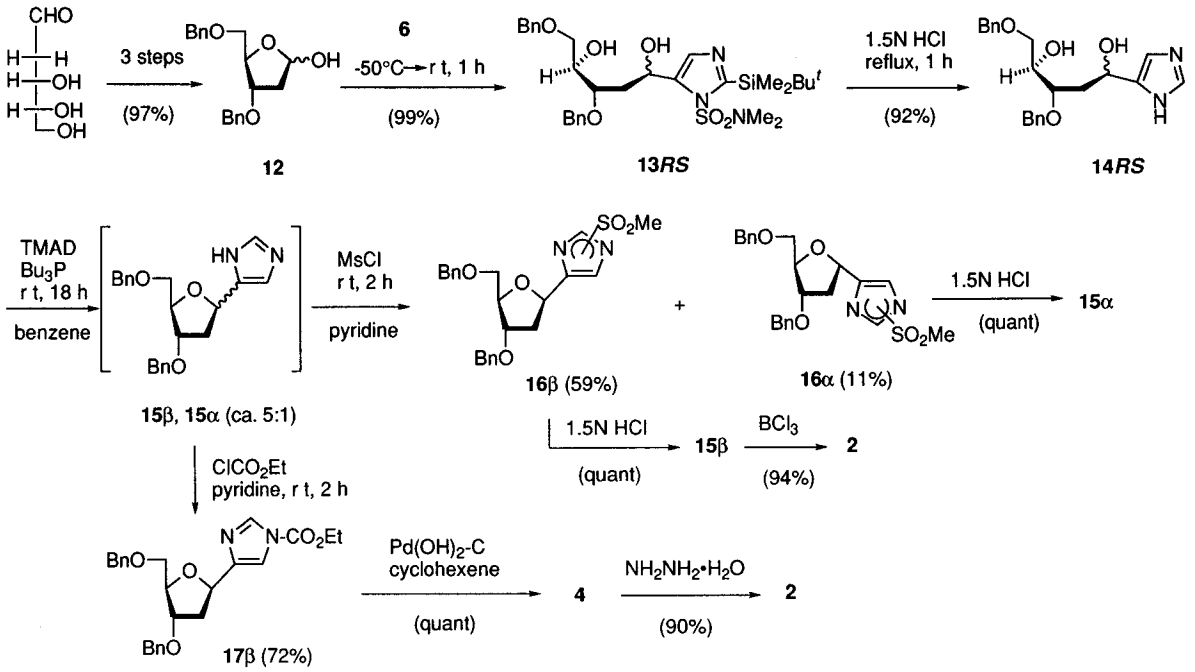
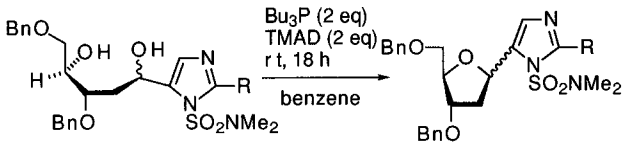



**Table 2. Mitsunobu Cyclization of Substituted Imidazoles 13 and 18**




**13** : R = $SiMe_2Bu^t$
**18** : R = H

**19** : R = $SiMe_2Bu^t$
**20** : R = H

| run | **13** or **18** | products (%) |
|---|---|---|
| 1 | **13***S* | **19***β* (12)[a] |
| 2 | **13***R* | **19**α (7)[b] |
| 3 | **18***S* | **20***β* (94) |
| 4 | **18***R* | **20**α (88) |

[a] Recovery of **13*S*** (65%). [b] Recovery of **18*R*** (67%).

moiety should be essential to the determination of the ratio of *β*- *vs* α-glycosylation. Epimerization between α- and *β*-anomers did not take place under the present reaction conditions. From these results, *β*-selectivity in our reaction may be explained as in Scheme 4.

Reaction of the TMAD−$Bu_3P$ adduct with **8*R*** forms the zwitterion **21*R***. Preferential elimination of $Bu_3P$=O from **21*R*** leads to isoimidazole **22**. Spontaneous cyclization assisted by a hydrogen bond gives the *β*-anomer (**9***β*), which is stabilized by intramolecular hydrogen bonding. Although the *S*-isomer (**8*S***) similarly leads to the active species **22′,** it exclusively gave the *β*-anomer *via* rotomer **22** which is thermodynamically more stable. The remarkable stereoselectivity (*β*/α = 26/1) of the ribofuranosylimidazoles **9** is facilitated by electronic repulsion in **22′**. The somewhat low selectivity (*β*/α = 5.4/1) of the 2′-deoxy compounds **16** may be due to lack of the OBn group at C-2′.

Compounds **1** and **2**[6] were tested for antiviral[20] and anticancer[21] activity, but no activity or toxicity was found.

(20) HIV in MT-4 cells and type A Influenza virus in MDBK cells.
(21) CCD-19 Lu, CCRF-CEM, p388, p388/ADM, B16, Lewis, Lu-65, Lu-99, A549, RERF-LC-AI, and HT-29 cell lines.

In conclusion, we describe an efficient and highly stereocontrolled synthesis of novel 4(5)-(*β*-D-ribofuranosyl)imidazoles (**1**, **3**) and their 2′-deoxy derivatives (**2**, **4**). The synthetic approach should supply a variety of derivatives by which their biological activity of C-4-linked imidazole nucleosides can be assessed.

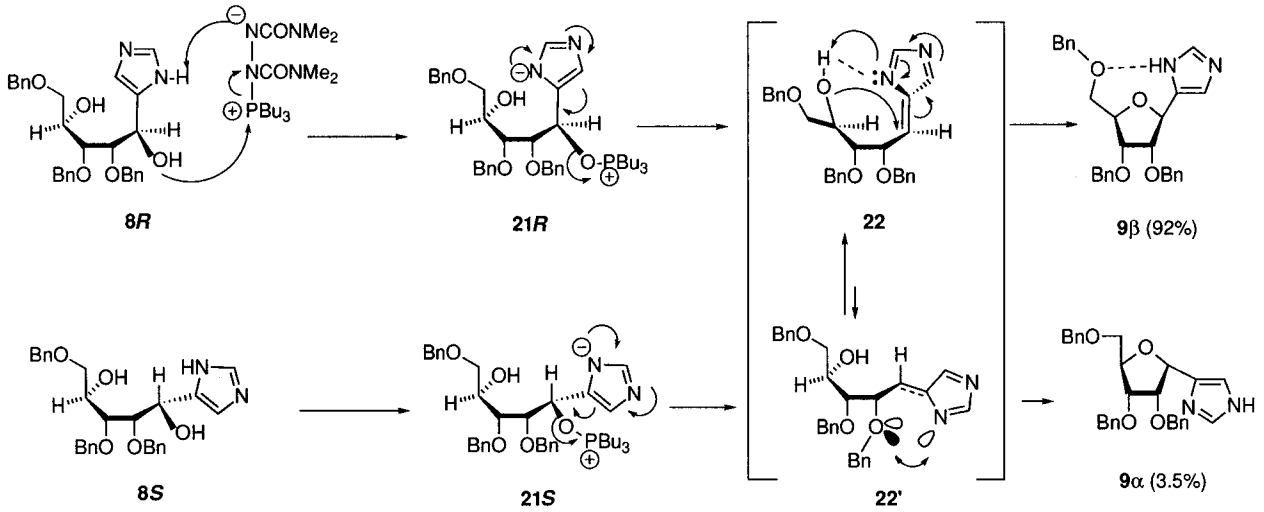
## Experimental Section

**General Procedure**. Melting points were determined with a hot-stage apparatus and are uncorrected. Optical rotation measurements were recorded at 20 °C. $^1H$ and $^{13}C$ NMR spectra were taken with tetramethylsilane as the internal standard in $CDCl_3$ unless otherwise noted. All reactions with air- and moisture-sensitive compounds were carried out under an argon atmosphere. Unless otherwise noted, all extracts were dried over $Na_2SO_4$, and the solvent was removed by rotary evaporation under reduced pressure. THF was distilled from sodium−benzophenone.

**2-(*tert*-Butyldimethylsilyl)-5-(2,3,5-tri-*O*-benzyl-D-ribosyl)-N,N-dimethylimidazole-1-sulfonamide (7*RS*).** A solution of 2-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethylimidazole-1-sulfonamide[9a] (918 mg, 3.18 mmol) in THF (7.0 mL) was cooled to −60 °C and treated dropwise with 1.6 M BuLi−hexane (2.0 mL, 3.18 mmol), and the resulting mixture was stirred for 15 min at −55 °C. The mixture was cooled to −70 °C, and a solution of **5**[8] (445 mg, 1.06 mmol) in THF (5.0 mL) was added slowly. The dry ice bath was removed, and the reaction mixture was stirred at rt. After 2 h, the reaction was quenched with $H_2O$, and the THF was removed under reduced pressure. The residue was dissolved in EtOAc, and the solution was washed with $H_2O$, dried, and evaporated to give a crude oil. Flash chromatography on silica gel using 20% and 60% EtOAc−hexane as eluent gave **7*RS*** (751 mg, quantitative) as a pale yellow oil. $^1H$ NMR indicated a ca. 1:1 mixture of *R*- and *S*-isomers: IR (neat, $cm^{-1}$) 3400, 1375, 1150; $^1H$ NMR *δ* 0.40 (br s, 6H), 1.00 (s, 9H), 2.66 (s, 2.4 H), 2.73 (s, 3.6H), 3.51−3.82 (m, 2H), 3.82−4.28 (m, 3H), 4.35−4.77 (m, 6H), 5.35 (br s, 0.6H), 5.39 (br s, 0.4H), 7.11−7.43 (m, 16H); HRMS (SIMS) ($M^+$) 710.3292 calcd for $C_{37}H_{52}N_3O_7SSi$, found 710.3300.

**4(5)-(2,3,5-Tri-*O*-benzyl-D-ribosyl)imidazole (8*R* and 8*S*).** A solution of **7*RS*** (9.86 g, 13.9 mmol) in THF (45 mL) was refluxed with 1.5 N HCl (75 mL) for 2.5 h and then cooled. After neutralization by addition of 30% $NH_4OH$, the solvent was evaporated to give a residue, which was extracted with EtOAc. The extract was washed with $H_2O$ and brine, dried,

**Scheme 4**




and evaporated to give an oil, which was subjected to chromatography. Elution with MeOH−EtOAc (1:9) afforded a ca. 1:1 mixture of **8*R*** and **8*S*** (6.44 g, 95%). Although the separation of **8*R*** and **8*S*** was not required for the following experiment, they could be isolated by a use of MeOH−$CHCl_3$ (1:24) as eluent. **8*R*** (less polar): IR (neat, $cm^{-1}$) 3300, 1080; $^1H$ NMR $\delta$ 3.51−3.69 (m, 2H), 3.79 (br s, 2H), 4.23 (br d, $J$ = 4.1 Hz, 1H), 4.40−4.76 (m, 6H), 5.08 (d, $J$ = 5.1 Hz, 1H), 6.80 (s, 1H), 7.15−7.40 (m, 16H); HRMS ($M^+$) 488.2309 calcd for $C_{29}H_{32}N_2O_5$, found 488.2306. **8*S*** (more polar): IR (neat, $cm^{-1}$) 3250, 1090; $^1H$ NMR $\delta$ 3.56 (dd, $J$ = 6.0, 9.8 Hz, 1H), 3.65 (dd, $J$ = 3.0, 9.8 Hz, 1H), 3.77 (dd, $J$ = 2.3, 7.9 Hz, 1H), 4.11 (m, 1H), 4.16 (dd, $J$ = 2.3, 6.2 Hz, 1H), 4.35−4.66 (m, 6H), 5.06 (d, $J$ = 5.8 Hz, 1H), 6.77 (s, 1H), 7.13−7.40 (m, 16H); HRMS ($M^+$) 488.2309 calcd for $C_{29}H_{32}N_2O_5$, found 488.2300.

**Ethyl 4-(2,3,5-Tri-*O*-benzyl-*β*-D-ribofuranosyl)imidazole-1-carboxylate (10*β*). (A) Mitsunobu Cyclization using DEAD and $Ph_3P$.** To a stirred solution of the epimeric mixture of **8*RS*** (1.92 g, 3.93 mmol) and $Ph_3P$ (2.68 g, 10.2 mmol) in THF (40 mL) at rt was added dropwise over 10 min a solution of DEAD (1.33 mL, 8.66 mmol) in THF (3 mL). The reaction mixture was stirred at rt for 2 h. The solvent was evaporated to give a residual oil, which was chromatographed [EtOAc−benzene (1:9)] to give a crude oil that solidified on standing. This was recrystallized from hexane for single-crystal X-ray analysis[11] to give **10*β*** (320 mg, 15%) as colorless needles: mp 71−73 °C; $[\alpha]_D$ −1.27° ($c$ = 1.09, $CHCl_3$); IR (Nujol, $cm^{-1}$) 1750; $^1H$ NMR $\delta$ 1.41 (t, $J$ = 7.5 Hz, 3H), 3.61 (dd, $J$ = 4.6, 10.6 Hz, 1H), 3.71 (dd, $J$ = 4.6, 10.6 Hz, 1H), 4.04 (t, $J$ = 6.1 Hz, 1H), 4.21 (t, $J$ = 5.0 Hz, 1H), 4.33 (m, 1H), 4.38−4.64 (m, 8H), 5.08 (d, $J$ = 4.6 Hz, 1H), 7.26−7.32 (m, 15H), 7.41 (s, 1H), 8.10 (s, 1H); $^{13}C$ NMR $\delta$ 14.2, 64.4, 70.1, 72.0, 73.3, 77.5, 78.2, 80.4, 80.9, 115.2, 127.5−128.3, 137.2-138.3, 142.7, 148.5; HRMS ($M^+$) 542.2415 calcd for $C_{32}H_{34}N_2O_6$, found 542.2428. Anal. Calcd for $C_{32}H_{34}N_2O_6 \cdot 1/2H_2O$: C, 69.47; H, 6.40; N, 5.08. Found: C, 69.26; H, 6.31; N, 5.29.

(B) The mixture of **8*RS*** (2.45 g, 5.02 mmol), TMAD (1.04 g, 6.02 mmol), and $Bu_3P$ (1.60 mL, 6.02 mmol) was treated overnight in benzene (90 mL) to give a crude oil **9** (3.76 g). The solution of **9** obtained in benzene (40 mL) was refluxed with ethyl chloroformate (0.48 mL, 5.02 mmol) and pyridine (0.32 mL, 4.02 mmol) for 15 min. The standard workup and purification gave **10*β*** (2.34 g, 86%).

(C) A solution of **9*β*** (577 mg, 1.23 mmol), pyridine (129 $\mu$L, 1.60 mmol), ethyl chloroformate (117 $\mu$L, 1.23 mmol), and a catalytic amount of 4-DMAP in benzene (50 mL) was stirred at rt for 30 min. After addition of $H_2O$ (1 mL), the solvent was evaporated, and the residue was extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The residual oil was purified by flash chromatography using EtOAc−hexane (3:7) for elution to give **10*β*** (637 mg, 96%).

**4(5)-(2,3,5-Tri-*O*-benzyl-D-ribofuranosyl)imidazole (9*β* and 9α).** To a solution of **8*RS*** (1.13 g, 2.32 mmol) in dry benzene (50 mL) was added $Bu_3P$ (0.92 mL, 3.47 mmol) at rt. Then, TMAD (597 mg, 3.47 mmol) was added rapidly to the mixture at ice bath temperature. After a few min, the reaction mixture was warmed to rt and the stirring was continued for 16 h. The insoluble material was removed by filtration, and the filtrate was condensed to give a residue, which was diluted with EtOAc. The solution was washed with $H_2O$ (× 2) and brine, dried, and evaporated. The residue was purified by flash chromatography using EtOAc−hexane (8:2) for elution to give **9*β*** (1004 mg, 92%) and **9**α (38 mg, 3.5%). **9*β*** (less polar): colorless oil; $[\alpha]_D$ +52.3° ($c$ = 3.08, $CHCl_3$); IR (neat, $cm^{-1}$) 3280, 1210; $^1H$ NMR $\delta$ 3.68 (dd, $J$ = 1.9, 10.4 Hz, 1H), 3.95 (overlapped, 2H), 4.14 (dd, $J$ = 4.8, 7.2 Hz, 1H), 4.31 (dt, $J$ = 7.2, 2.1 Hz, 1H), 4.34−4.74 (m, 6H), 5.21 (d, $J$ = 2.4 Hz, 1H), 6.78 (s, 1H), 6.83 (s, 1H), 7.15−7.50 (m, 15H); $^{13}C$ NMR $\delta$ 69.1, 72.1, 73.6, 76.9, 77.2, 80.2, 80.3, 120.1, 127.9−128.7, 135.0, 137.4−137.8; HRMS ($M^+$) 470.2204 calcd for $C_{29}H_{30}N_2O_4$, found 470.2209. **9**α (more polar): colorless oil; IR (neat, $cm^{-1}$) 3300, 1220; $^1H$ NMR $\delta$ 3.54 (dd, $J$ = 3.7, 10.6 Hz, 1H), 3.59 (dd, $J$ = 3.8, 10.6 Hz, 1H), 4.21 (t, $J$ = 4.8 Hz, 1H), 4.31 (m, 2H), 4.36−4.71 (m, 6H), 5.27 (d, $J$ = 5.4 Hz, 1H), 7.09 (s, 1H), 7.10−7.39 (m, 15H), 7.54 (s, 1H); $^{13}C$ NMR $\delta$ 70.4, 73.0, 73.6, 74.0, 78.5, 79.4, 80.9, 125.8, 127.7−129.2, 135.4, 137.3−138.0; HRMS ($M^+$) 470.2204 calcd for $C_{29}H_{30}N_2O_4$, found 470.2202.

**4(5)-(*β*-D-Ribofuranosyl)imidazole (1).** A solution of **9*β*** (295 mg, 0.63 mmol) in EtOH (60 mL) was hydrogenated over 10% Pd on carbon (255 mg) at 4.0 kg/$cm^2$ for 14 h. After filtration through Celite, the filtrate was evaporated to give a residue, which was purified by column chromatography [MeOH−EtOAc (3:7)] to give a white amorphous product **1** (125 mg, quantitative): $[\alpha]_D$ −30.2° ($c$ = 1.67, MeOH); IR (Nujol, $cm^{-1}$) 3400; $^1H$ NMR ($CD_3OD$) $\delta$ 3.72 (dd, $J$ = 3.5, 12.3 Hz, 1H), 3.80 (dd, $J$ = 3.5, 12.3 Hz, 1H), 3.98−4.19 (m, 3H), 4.83 (d, $J$ = 6.9 Hz, 1H), 7.58 (s, 1H), 8.87 (s, 1H); $^{13}C$ NMR ($CD_3$-OD) $\delta$ 63.2, 72.7, 77.2, 77.5, 87.5, 118.1, 135.3, 136.2; HRMS ($M^+$) 200.0796 calcd for $C_8H_{12}N_2O_4$, found 200.0800.

**Ethyl 4-(*β*-D-Ribofuranosyl)imidazole-1-carboxylate (3).** A mixture of **10*β*** (1.73 g, 3.19 mmol), 20% $Pd(OH)_2$-C (1.13 g), and cyclohexene (29 mL, 288 mmol) in EtOH (100 mL) was refluxed for 9 h. After filtration through Celite, the filtrate was evaporated to give a residue which was purified by column chromatography [MeOH−EtOAc (3:17)] to give **3** (845 mg, 97%) as a pale yellow oil; IR (neat, $cm^{-1}$) 3340, 1760; $^1H$ NMR ($CD_3OD$) $\delta$ 1.43 (t, $J$ = 7.5 Hz, 3H), 3.65 (dd, $J$ = 4.3, 12.3 Hz, 1H), 3.81 (dd, $J$ = 3.1, 12.3 Hz, 1H), 3.95 (m, 1H), 4.12 (m, 2H), 4.49 (q, $J$ = 7.5 Hz, 2H), 4.72 (m, 1H), 7.61 (s, 1H), 8.28 (s, 1H); HRMS ($M^+$) 272.1007 calcd for $C_{11}H_{16}N_2O_6$, found 272.1021.

**1-Acetyl-4(5)-(1,2,3,4,5-penta-*O*-acetyl-D-ribosyl)imidazoles (11*R* and 11*S*).** (A) A solution of **8*R*** (490 mg, 1.00 mmol) in EtOH (50 mL) was hydrogenated over 10% Pd on carbon (355 mg) at 4.1 kg/$cm^2$ for 19 h. After filtration through Celite, the filtrate was concentrated to give an amorphous

material (245 mg). This was stirred with acetic anhydride (1.0 mL, 10.6 mmol) in pyridine (2.0 mL) at rt for 15 h. Ice was added to the mixture, and the stirring was continued for 1 min. The resulting mixture was dissolved in EtOAc−hexane−$H_2O$ (5:3:1) (20 mL), and the organic layer was washed with $H_2O$ and brine, dried, and evaporated. The residue was purified by column chromatography [EtOAc−hexane (3:2)] to give **11*R*** (171 mg, 36%) as a pale yellow oil: IR (neat, $cm^{-1}$) 1740; $^1H$ NMR $\delta$ 2.03−2.09 (m, 15H), 2.60 (s, 3H), 4.11 (dd, $J$ = 7.1, 12.2 Hz, 1H), 4.32 (dd, $J$ = 3.5, 12.2 Hz, 1H), 5.17 (quint, $J$ = 3.7 Hz, 1H), 5.35 (dd, $J$ = 4.4, 6.7 Hz, 1H), 5.61 (dd, $J$ = 4.3, 6.7 Hz, 1H), 6.04 (d, $J$ = 5.0 Hz, 1H), 7.46 (s, 1H), 8.07 (s, 1H); HRMS ($M^+$) 471.1613 calcd for $C_{20}H_{27}N_2O_{11}$, found 471.1615.

(B) By the same procedure as above, **8*S*** (240 mg, 0.49 mmol) was converted to **11*S*** (54 mg, 23%): IR (neat, $cm^{-1}$) 1740; $^1H$ NMR $\delta$ 2.04−2.10 (m, 15H), 2.60 (s, 3H), 4.09 (dd, $J$ = 6.6, 12.0 Hz, 1H), 4.42 (dd, $J$ = 2.8, 12.0 Hz, 1H), 5.27−5.41 (m, 2H), 5.70 (t, $J$ = 6.0 Hz, 1H), 5.97 (d, $J$ = 6.0 Hz, 1H), 7.49 (s, 1H), 8.06 (s, 2H); HRMS ($M^+$) 471.1613 calcd for $C_{20}H_{27}N_2O_{11}$, found 471.1614.

**2-(*tert*-Butyldimethylsilyl)-5-(2-deoxy-3,5-di-*O*-benzyl-D-ribosyl)-*N*,*N*-dimethylimidazole-1-sulfonamides (13*R* and 13*S*).** To a solution of 2-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethylimidazole-1-sulfonamide[9a] (3.855 g, 13.34 mmol) in THF (100 mL) was added dropwise at −50 °C 1.6 M BuLi in hexane (8.34 mL, 13.34 mmol), and the mixture was stirred for 20 min at the same temperature. A solution of **12** (1.676 g, 5.34 mmol) in THF (20 mL) was added slowly. The dry ice bath was removed, and the reaction mixture was stirred at rt for 1 h. The mixture was then treated as described for the preparation of **7*RS*** to give a ca. 1:1 mixture of a **13*R*** and **13*S*** (3.191 g, 99%), which were partially isolated by column chromatography [EtOAc−hexane (1:2)]. **13*S***[22] (less polar): pale yellow oil; IR (neat, $cm^{-1}$) 3320, 1390; $^1H$ NMR $\delta$ 0.40 (s, 6H), 1.00 (s, 9H), 2.11 (m, 2H), 2.70 (s, 6H), 3.34 (br s, 1H), 3.62 (m, 2H), 3.90 (m, 1H), 4.03 (m, 1H), 4.57 (s, 2H), 4.65 (dd, $J$ = 11.1, 22.7 Hz, 2H), 5.18 (br t, $J$ = 6.1 Hz, 1H), 7.20 (s, 1H), 7.25−7.45 (m, 10H). **13*R*** (more polar): pale yellow oil; IR (neat, $cm^{-1}$) 3400, 1370; $^1H$ NMR $\delta$ 0.40 (s, 6H), 1.00 (s, 9H), 2.24 (m, 2H), 2.73 (s, 6H), 3.60 (dd, $J$ = 5.5, 10.1 Hz, 1H), 3.68 (dd, $J$ = 3.5, 10.1 Hz, 1H), 3.78 (m, 1H), 4.04 (m, 1H), 4.55 (d, $J$ = 6.0 Hz, 4H), 5.20 (t, $J$ = 5.5 Hz, 1H), 7.23−7.44 (m, 11H); HRMS (SIMS/$M^+$ + 1) 604.2874 calcd for $C_{30}H_{46}N_3O_6SSi$, found 604.2888.

**4(5)-(2-Deoxy-3,5-di-*O*-benzyl-D-ribosyl)imidazole (14*RS*).** A mixture of **13*RS*** (136 mg, 0.23 mmol) in THF (1.5 mL) and 1.5 N HCl (6.0 mL) was refluxed for 1 h as described for the preparation of **8*RS*** to give **14*RS*** (81 mg, 92%) as an oil: $^1H$ NMR $\delta$ 2.10 (m, 2H), 3.60 (br s, 2H), 3.82 (m, 1H), 3.96 (m, 1H), 4.41−4.62 (m, 4H), 4.93 (m, 1H), 6.64 (s, 1H), 7.17−7.40 (m, 11H); HRMS (SIMS/$M^+$ + 1) 383.1969 calcd for $C_{22}H_{27}N_2O_4$, found 383.1964.

**[4(5)-(3,5-Di-*O*-benzyl-2-deoxy-D-ribofuranosyl)imidazolyl]methyl Sulfones (16$\beta$ and 16$\alpha$).** A mixture of **14*RS*** (184 mg, 0.48 mmol), $Bu_3P$ (194 mg, 0.96 mmol), and TMAD (165 mg, 0.96 mmol) in benzene (17 mL) was stirred at rt for 18 h. The mixture was diluted with hexane and allowed to stand for 0.5 h. The insoluble material was removed by filtration, and the filtrate was concentrated to give a crude oil, which was purified by column chromatography (EtOAc) to give a ca. 5:1 mixture of **15**$\beta$ and **15**$\alpha$. The obtained oil was treated with $MeSO_2Cl$ (82 mg, 0.72 mmol) in pyridine (3 mL) for 2 h at rt. After addition of cold $H_2O$, the mixture was extracted with a mixture of EtOAc−hexane (1:1), and the extract was washed with brine, dried, and evaporated. The residue was purified by column chromatography to give **16**$\beta$ [EtOAc−hexane (3:7)] (124 mg, 59%) and **16**$\alpha$ [EtOAc−hexane (6:4)] (24 mg, 11%). **16**$\beta$ (less polar): colorless needles (EtOAc−hexane); mp 97 °C; $[\alpha]_D$ +0.79° ($c$ = 0.38, $CHCl_3$); IR (KBr, $cm^{-1}$) 1382, 1175; $^1H$ NMR $\delta$ 2.19 (ddd, $J$ = 6.0, 10.3, 12.8 Hz, 1H), 2.39 (ddd, $J$ = 2.6, 6.0, 12.8 Hz, 1H), 3.22 (s, 3H), 3.54 (dd, $J$ = 5.1, 10.0 Hz, 1H), 3.62 (dd, $J$ = 5.1, 10.0 Hz, 1H), 4.18 (m, 1H), 4.27 (m, 1H), 5.16 (dd, $J$ = 6.0, 10.3 Hz, 1H), 7.20−7.40 (m, 10H), 7.92 (s, 1H); MS $m/z$ ($M^+$) 442. Anal. Calcd for $C_{23}H_{26}N_2O_5S$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.40; H, 5.88; N, 6.26. **16**$\alpha$ (more polar): oil; $[\alpha]_D$ +52.4° ($c$ = 1.1, $CHCl_3$); IR (neat, $cm^{-1}$) 1372, 1175; $^1H$ NMR $\delta$ 2.33 (ddd, $J$ = 4.0, 6.5, 14.0 Hz, 1H), 2.68 (dt, $J$ = 14.0, 7.0 Hz, 1H), 3.12 (s, 3H), 3.60 (d, $J$ = 5.0 Hz, 2H), 4.22 (m, 1H), 4.34 (m, 1H), 4.48 (d, $J$ = 2.5 Hz, 2H), 4.59 (s, 2H), 5.18 (t, $J$ = 6.5 Hz, 1H), 7.20−7.42 (m, 10H), 7.90 (s, 1H); HRMS ($M^+$) 442.1561 calcd for $C_{23}H_{26}N_2O_5S$, found 442.1558.

**Ethyl 4(5)-(3,5-Di-*O*-benzyl-2-deoxy-$\beta$-D-ribofuranosyl)-imidazole-1-carboxylate (17$\beta$).** To a solution of **14RS** (8.08 g, 21.2 mmol) in dry benzene (250 mL) was added $Bu_3P$ (6.85 mL, 27.46 mmol) at ice bath temperature. TMAD (4.73 g, 27.46 mmol) was added in two portions to the mixture at the same temperature. The resulting mixture was stirred at rt for 14 h. The insoluble material was filtered through Celite, and the filtrate was condensed. The resulting crude oil was diluted with EtOAc, and the organic layer was washed with $H_2O$ (× 3) and brine, dried, and evaporated. The obtained oil was dissolved in benzene (150 mL) containing pyridine (2.05 mL, 25.35 mmol), ethyl chloroformate (2.42 mL, 25.35 mmol) was added slowly at 0 °C to the solution, and the whole was subsequently stirred at rt for 20 min. After addition of $H_2O$ followed by evaporation of the benzene, the resulting residue was extracted with EtOAc. The extract was washed with $H_2O$ and brine, dried, and evaporated to give a crude oil, which was purified by flash chromatography using EtOAc−hexane for elution [EtOAc−hexane (3:7 to 4:6)] to give **17**$\beta$ (6.65 g, 72.1%) as a pale yellow oil: $[\alpha]_D$ −1.28° ($c$ = 10.45, $CHCl_3$); IR (neat, $cm^{-1}$) 1760; $^1H$ NMR $\delta$ 1.42 (t, $J$ = 7.2 Hz, 3H), 2.22 (ddd, $J$ = 6.2, 10.3, 13.8 Hz, 1H), 2.36 (ddd, $J$ = 2.1, 5.8, 13.8 Hz, 1H), 3.52 (dd, $J$ = 6.2, 10.3 Hz, 1H), 3.64 (dd, $J$ = 4.7, 10.3 Hz, 1H), 4.17 (dt, $J$ = 6.0, 2.3 Hz, 1H), 4.25 (m, 1H), 4.46 (q, $J$ = 7.2 Hz, 2H), 4.56 (d, $J$ = 3.5 Hz, 4H), 5.14 (dd, $J$ = 5.8, 10.3 Hz, 1H), 7.22−7.42 (m, 10H), 8.10 (d, $J$ = 1.0 Hz, 1H); HRMS ($M^+$) 436.1997 calcd for $C_{25}H_{28}N_2O_5$, found 436.1996.

**Ethyl 4(5)-(2-Deoxy-$\beta$-D-ribofuranosyl)imidazole-1-carboxylate (4).** A mixture of **17**$\beta$ (7.52 g, 17.23 mmol), 20% $Pd(OH)_2$-C (3.50 g), and cyclohexene (175 mL, 1.72 mol) in EtOH (200 mL) was refluxed for 6 h to give **4**[22] (4.40 g, quantitative) by the same procedure for the preparation of **3**: $[\alpha]_D$ +14.4° ($c$ = 1.7, MeOH); IR (neat, $cm^{-1}$) 3350, 1762; $^1H$ NMR ($CD_3OD$) $\delta$ 1.43 (t, $J$ = 7.1 Hz, 3H), 2.03−2.24 (m, 2H), 3.60 (dd, $J$ = 4.9, 11.9 Hz, 1H), 3.68 (dd, $J$ = 3.9, 11.9 Hz, 1H), 3.92 (td, $J$ = 4.9, 2.6 Hz, 1H), 4.36 (dt, $J$ = 5.1, 2.6 Hz, 1H), 4.49 (q, $J$ = 7.1 Hz, 2H), 5.11 (dd, $J$ = 2.2, 3.4 Hz, 1H), 7.57 (s, 1H), 8.26 (s, 1H); $^{13}C$ NMR ($CD_3OD$) $\delta$ 150.1, 145.0, 139.2, 116.0, 89.6, 75.6, 74.5, 66.3, 64.4, 42.7, 14.8.

**4(5)-(3,5-Di-*O*-benzyl-2′-deoxy-D-ribofuranosyl)-1*H*-imidazoles (15$\beta$ and 15$\alpha$).** (A) A solution of **16**$\beta$ (758 mg, 1.7 mmol) in THF (5 mL) was refluxed with 1.5 N HCl (20 mL) for 1 h as described in previous experimental procedures to give **15**$\beta$ (619 mg, quantitative) as an oil: $^1H$-NMR $\delta$ 2.20 (ddd, $J$ = 5.6, 9.0, 13.1 Hz, 1H), 2.35 (ddd, $J$ = 2.6, 6.6, 13.1 Hz, 1H), 3.64 (dd, $J$ = 3.6, 10.9 Hz, 1H), 3.73 (dd, $J$ = 4.1, 10.9 Hz, 1H), 4.23 (m, 2H), 4.47−4.63 (m, 4H), 5.24 (dd, $J$ = 6.6, 9.0 Hz, 1H), 6.88 (s, 1H), 7.23 (s, 1H), 7.28−7.45 (m, 10H); $^{13}C$ NMR $\delta$ 138.5, 138.1, 136.7, 135.7, 129.2, 129.0, 128.6, 128.2, 120.2, 83.6, 81.2, 74.1, 74.0, 71.6, 39.1; HRMS (SIMS/$M^+$ + 1) 365.1864 calcd for $C_{22}H_{25}N_2O_3$, found 365.1866.

(B) By the same procedure as above, **16**$\alpha$ (19 mg, 0.04 mmol) was converted to **15**$\alpha$ (14 mg, quantitative): oil; $^1H$ NMR $\delta$ 2.19 (ddd, $J$ = 2.7, 3.6, 14.5 Hz, 1H), 2.60 (ddd, $J$ = 6.4, 9.1, 14.5 Hz, 1H), 3.47 (dd, $J$ = 5.5, 10.5 Hz, 1H), 3.59 (dd, $J$ = 5.1, 10.5 Hz, 1H), 4.27 (dt, $J$ = 6.4, 2.0 Hz, 1H), 4.41 (td, $J$ = 5.1, 2.0 Hz, 1H), 4.56 (s, 2H), 4.60 (d, $J$ = 2.4 Hz, 2H), 5.29 (dd, $J$ = 3.6, 9.1 Hz, 1H), 6.98 (s, 1H), 7.28−7.42 (m, 4H), 7.44 (s, 1H); $^{13}C$ NMR 138.5, 137.8, 136.0, 134.6, 129.2, 129.0, 128.7, 128.5, 128.3, 128.2, 124.0, 83.4, 81.8, 73.9, 73.2, 72.0, 71.2, 37.6; HRMS (SIMS/$M^+$ + 1) 365.1864 calcd for $C_{22}H_{25}N_2O_3$, found 365.1865.

**4(5)-(2-Deoxy-$\beta$-ribofuranosyl)-1*H*-imidazole (2).** (A) To a solution of **15**$\beta$ (57 mg, 0.16 mmol) in $CH_2Cl_2$ (18 mL) was added dropwise a solution of 1 M $BCl_3$ in $CH_2Cl_2$ (0.7 mL. 0.7 mmol) at −70 °C. After being stirred for 75 min at −70 °C,

(22) The expected MS peaks were not obtained because of thermal instability.

the mixture was diluted with dry MeOH/$CH_2Cl_2$ (1:1, 7 mL) and then neutralized with powder $NaHCO_3$ at rt. The resulting mixture was filtered through Celite, and the filtrate was evaporated to give a syrup, which was purified by flash chromatography using 15% MeOH in EtOAc as the eluent to give a white solid of **2** (27 mg, 94%): colorless prisms from MeOH−$CHCl_3$; mp 164−166 °C; $[\alpha]_D$ +24.0° ($c$ = 1.0, MeOH); IR (neat, $cm^{-1}$) 3700−2200, 1082, 1028; the $^1H$ and $^{13}C$ NMR spectra were in agreement with those of the previous report;[6] $^1H$ NMR ($CD_3OD$) $\delta$ 2.09 (ddd, $J$ = 1.9, 5.7, 13.0 Hz, 1H), 2.24 (ddd, $J$ = 5.6, 10.6, 13.0 Hz, 1H), 3.60 (dd, $J$ = 4.6, 11.1 Hz, 1H), 3.68 (dd, $J$ = 4.6, 11.1 Hz, 1H), 3.90 (td, $J$ = 4.6, 2.4 Hz, 1H), 4.36 (dt, $J$ = 5.6, 1.9 Hz, 1H), 5.16 (dd, $J$ = 5.7, 10.6 Hz, 1H), 7.07 (s, 1H), 7.67 (s, 1H); $^{13}C$ NMR ($CD_3OD$) d 139.7, 137.1, 118.1, 89.4, 75.4, 74.5, 64.3, 42.9. Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 51.72; H, 6.36; N, 15.07.

(B) The mixture of **4** (191 mg, 0.75 mmol) and $NH_2NH_2 \cdot H_2O$ (0.04 mL, 0.75 mmol) in EtOH (5 mL) was refluxed for 1 h. The solvent was evaporated to give a residue, which was purified by the same procedure as above to give **2** (124 mg, 90%).

**5-(2-Deoxy-3,5-di-*O*-benzyl-D-ribosyl)-*N*,*N*-dimethylimidazole-1-sulfonamide (18*S* and 18*R*).** (A) To a solution of **13*S*** (132 mg, 0.22 mmol) in THF (5 mL) was added a 1 M solution of a $Bu_4NF$ (0.22 mL, 0.22 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min and then at rt for 45 min. Ice was added to the mixture, and the THF was evaporated to give a crude oil, which was extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The residue was purified by column chromatography [EtOAc−hexane (8:2)] to give **18*S***[22] (107 mg, quantitative) as an oil: $^1H$ NMR $\delta$ 2.15 (dd, $J$ = 5.0, 7.6 Hz, 2H), 2.80 (s, 6H), 3.63 (m, 2H), 3.89 (q, $J$ = 5.0 Hz, 1H), 4.04 (m, 1H), 4.59 (s, 2H), 4.63 (dd, $J$ = 11.1, 20.2 Hz, 2H), 5.17 (dd, $J$ = 5.0, 7.6 Hz, 1H), 7.07 (s, 1H), 7.28−7.43 (m, 10H), 7.88 (s, 1H).

(B) By the same procedure as above, **13*R*** (188 mg, 0.31 mmol) was converted into **18*R***[22] (145 mg, 95%): $^1H$ NMR $\delta$ 2.21 (t, $J$ = 6.0 Hz, 2H), 2.84 (s, 6H), 3.62 (m, 2H), 3.80 (q, $J$ = 6.0 Hz, 1H), 4.06 (m, 1H), 4.56 (s, 4H), 5.20 (dd, $J$ = 6.0, 7.6 Hz, 1H), 7.25−7.45 (m, 10H), 7.89 (s, 1H).

**2-(*tert*-Butyldimethylsilyl)-5-(2-deoxy-3,5-di-*O*-benzyl-D-ribofuranosyl)-*N*,*N*-dimethylimidazole-1-sulfonamide (19$\beta$ and 19$\alpha$).** (A) A mixture of **13*S*** (40 mg, 0.07 mmol), TMAD (24 mg, 0.14 mmol), and $Bu_3P$ (30 mg, 0.14 mmol) in benzene (3 mL) was stirred for 18 h at rt to give **19**$\beta$ (5 mg, 12%) as an oil, together with the recovery of **13S** (26 mg, 65%): $^1H$ NMR $\delta$ 0.40 (s, 6H), 1.00 (s, 9H), 2.02−2.18 (m, 1H), 2.45 (dd, $J$ = 4.1, 14.2 Hz, 1H), 2.88 (s, 6H), 3.48 (dd, $J$ = 5.1, 10.1 Hz, 1H), 3.57 (dd, $J$ = 5.1, 10.1 Hz, 1H), 4.15 (m, 1H), 4.55 (s, 4H), 5.32 (dd, $J$ = 4.6, 10.1 Hz, 1H), 7.20−7.40 (m, 11H).

(B) By the same procedure as above, **13*R*** (43 mg, 0.07 mmol) was converted into **19**$\alpha$ (3 mg, 7%) as an oil, together with the recovery of **13*R*** (29 mg, 67%): $^1H$ NMR $\delta$ 0.38 (s, 6H), 1.00 (s, 9H), 2.12−2.30 (m, 1H), 2.65 (dt, $J$ =14.2, 7.1 Hz, 1H), 2.80 (s, 6H), 3.48−3.60 (m, 2H), 4.10−4.28 (m, 2H), 4.44−4.62 (m, 4H), 5.37 (t, $J$ = 7.1 Hz, 1H), 7.23−7.40 (m, 11H).

**5-(2-Deoxy-3,5-di-*O*-benzyl-D-ribofuranosyl)-*N*,*N*-dimethylimidazole-1-sulfonamide (20$\beta$ and 20$\alpha$).** (A) A mixture of **18*S*** (99 mg, 0.20 mmol), TMAD (69 mg, 0.40 mmol), and $Bu_3P$ (87 mg, 0.40 mmol) in benzene (5 mL) was stirred for 18 h at rt to give **20**$\beta$ (88 mg, 94%) as an oil: $^1H$ NMR $\delta$ 2.12 (ddd, $J$ = 5.6, 10.3, 13.3 Hz, 1H), 2.47 (ddd, $J$ = 1.9, 5.3, 13.3 Hz, 1H), 2.92 (s, 6H), 3.49 (dd, $J$ = 4.7, 10.8 Hz, 1H), 3.58 (dd, $J$ = 5.2, 10.8 Hz, 1H), 4.11−4.25 (m, 2H), 4.47−4.63 (m, 4H), 5.38 (dd, $J$ = 5.6, 10.3 Hz, 1H), 7.10 (s, 1H), 7.20−7.41 (m, 10H), 7.93 (s, 1H).

(B) By the same procedure as above, **18*R*** (137 mg, 0.28 mmol) was converted into **20**$\alpha$ (116 mg, 88%) as an oil: $^1H$ NMR $\delta$ 2.24 (ddd, $J$ = 5.2, 6.5, 13.0 Hz, 1H), 2.65 (dt, $J$ = 13.0, 7.4 Hz, 1H), 2.88 (s, 6H), 3.57 (m, 2H), 4.12−4.28 (m, 2H), 4.46−4.52 (m, 4H), 5.44 (t, $J$ = 7.4 Hz, 1H), 7.25 (s, 1H), 7.25−7.40 (m, 10H), 7.91 (s, 1H).

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**Supporting Information Available:** Copies of spectra for the following compounds: $^1$NMR **1**−**4**, **7*RS***, **8*R*/S**, **9**$\alpha/\beta$, **10**$\beta$, **11*R*/*S***, **13*R*/*S***, **14*RS***, **15**$\alpha/\beta$, **16**$\alpha/\beta$, **17**$\beta$, **18*R*/*S***, **19**$\alpha/\beta$, and **20**$\alpha/\beta$; $^{13}C$ NMR **1, 2** , **4**, **9**$\beta$, **10**$\beta$, and **15**$\alpha/\beta$; $^1H$-$^{13}C$ shift-correlated 2-D NMR **9**$\alpha/\beta$ and **10**$\beta$; DEPT-NMR **9**$\alpha/\beta$, **10**$\beta$. ORTEP plots for **10** $\beta$ (40 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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