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Regio- and stereocontrolled synthesis and conformational analysis of benzimidazole nucleosides

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Abstract—Regio- and stereocontrolled synthesis and conformational analysis of a series of benzimidazole nucleosides were achieved. A simple method by ^{1}H NMR 1D NOE experiment was developed for estimation of *syn* or *anti* conformation of benzimidazole nucleosides. Substituents at C2 of benzimidazole demonstrated to play a key role both in the unexpected regioselectivity of the glycosidic reaction and in the conformation distributions of the final products.

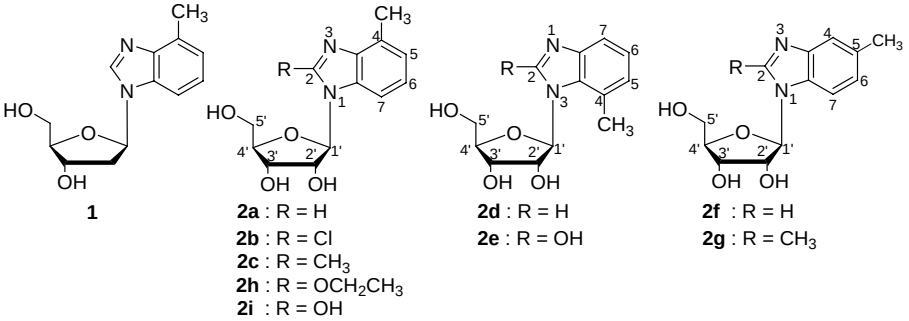
1. Introduction

Benzimidazole nucleosides, as a component of naturally occurring vitamin B12,[1] have shown considerable biological activities recently. For example, 1-[2-deoxy-β-D-erythro-pentofuanosyl]-4-methyl-1*H*-benzimidazole (**1**, Scheme 1) reported by Kool et al. was a close mimicry of 2′-deoxy-adenosine and was shown to be selectively inserted into DNA pairing with 2′-deoxy-thymidine.[2] A great number of benzimidazole nucleosides have been reported by Townsend et al. to show significant antiviral activities.[3] Thus, the unique structural features and pharmaceutical activities of benzimidazole nucleosides have rendered them attractive targets for development of efficient synthesis and conformational analysis. As 8-substituted purine nucleosides have been proved to be an effective class of antitumor reagents,[4] we were interested in their isosteres—2-substituted-4-methyl-benzimidazole nucleosides. Because the 2-substituted benzimidazole nucleosides (IUPAC numbering) may be considered analogous to the 8-substituted purine nucleosides (purine numbering), conformational analysis of these newly synthesized benzimidazole nucleosides may provide insights into the stereoelectronic factors that regulate the conformation of biologically important purine nucleosides.

2. Results and discussion

2.1. Synthesis

In our previous communication,[5] compound **2a–e** were synthesized regioselectively as mimicries of adenosine and the anticancer drug—8-Cl–adenosine. Under appropriate reaction conditions, either N1-isomer (**2a**) or N3-isomer (**2d**) of the benzimidazole nucleoside could be obtained selectively by reaction between 4-methyl-1*H*-benzimidazole and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose



Scheme 1.

Keywords: Nucleosides; Regioselectivity; Glycosylation; Stereoselectivity; Conformation.
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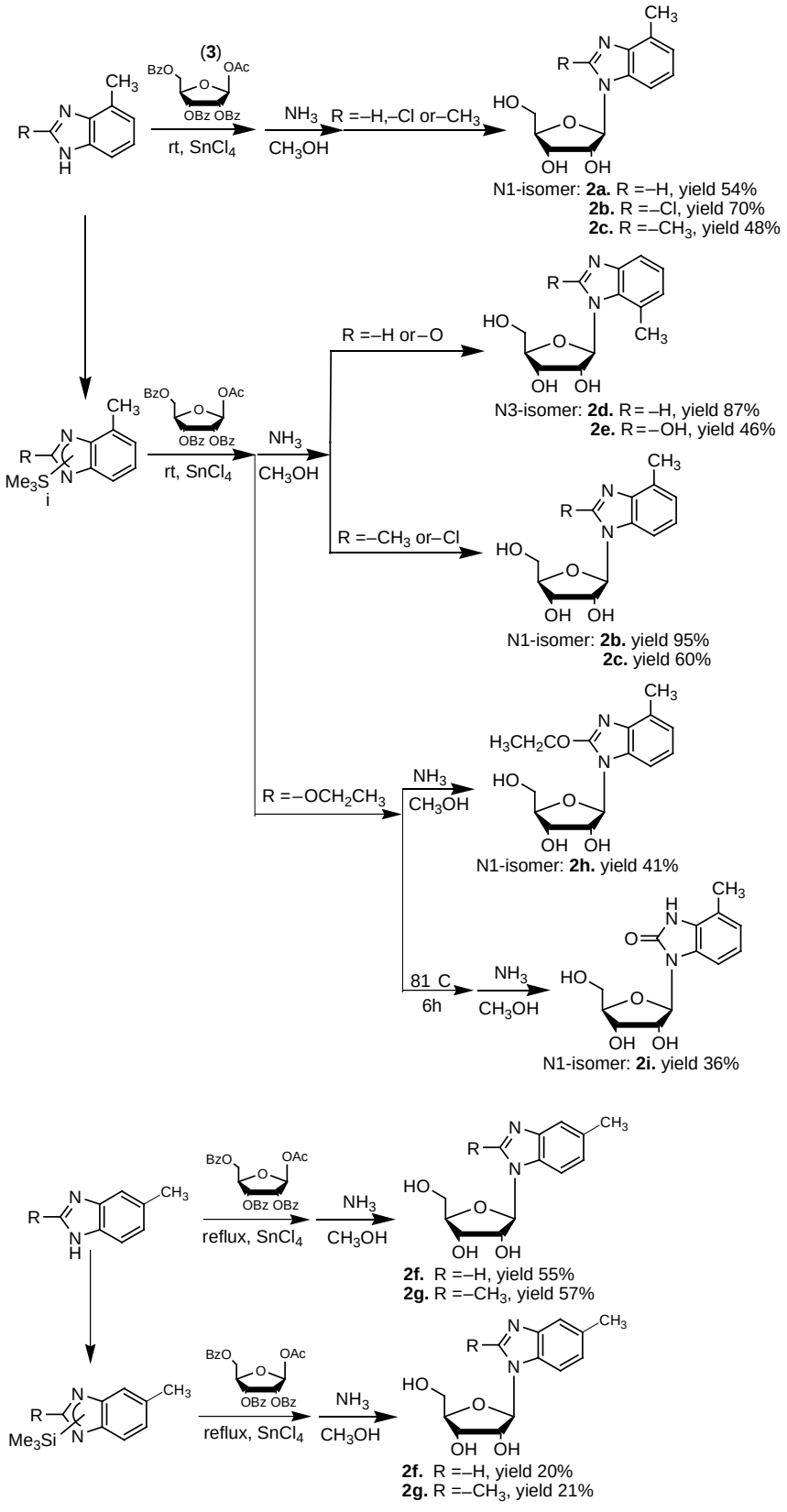
(**3**, Scheme 2). However, for the glycosidation between silylated 4-methyl-1*H*-benzimidazol-2-one and **3**, only N3-isomer (**2e**) was produced under acid-catalyzed conditions and no N1-isomer (**2i**) could be isolated by reaction between **3** and silylated or unsilylated 4-methyl-1*H*-benzimidazol-2-one under various conditions. We reasoned that the failure might be caused by the side reaction of the relatively active carbonyl group in 4-methyl-1*H*-benzimidazol-2-one.



Scheme 2. Regioselective synthesis of benzimidazole nucleosides.

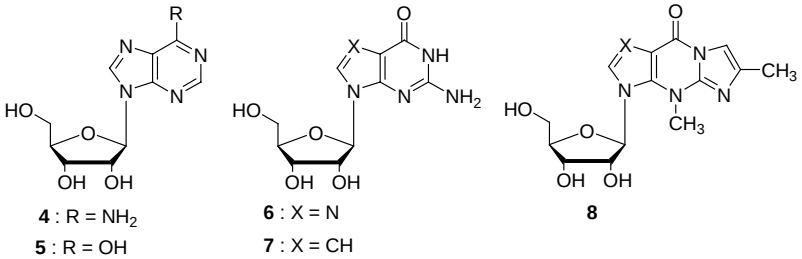
Accordingly, the 2-*O*-protected base (2-ethoxy-4-methyl-1*H*-benzimidazole) was silylated and tested for the glycosidation with **3**. To our pleasure, the reaction proceeded smoothly via N1-glycosidation, and the CH_3CH_2–O bond at 2-position of the product could be easily cleaved by heating the acid-containing reaction solution. N1-isomer **2h** was obtained after deprotection in 41% overall yield from **3** and silylated 2-ethoxy-4-methyl-1*H*-benzimidazole in the presence of $SnCl_4$ in acetonitrile at room temperature for 3 h, and N1-isomer **2i** was also obtained from **3** and silylated 2-ethoxy-4-methyl-1*H*-benzimidazole in presence of $SnCl_4$ in acetonitrile at room temperature for 3 h followed by reflux for further 6 h and deprotection in 36% overall yield (Scheme 2). Thus, the CH_3CH_2–O bond in 2-ethoxy-4-methyl-1*H*-benzimidazole moiety of the nucleoside showed a temperature-dependent cleavage by $SnCl_4$. Compounds **2f** and **2g** were synthesized as analogs of the 5-methyl-benzimidazole-α-riboside, which was isolated from the degradation of vitamin B12.[1b] In the preparation of some 4-methyl-benzimidazole nucleosides (**2b–e** and **2h–i**), silylation of the bases proved to be an effective step to improve the reaction yields and selectivities, however, in the preparation of 5-methyl-benzimidazole nucleosides (**2f–g**), unsilylated bases proved to be more effective than silylated base in the reaction (Scheme 2).

2.2. Conformational analysis

As activities of nucleosides and nucleotides might be correlated with their preferred structure in solution, the evaluation of their conformational parameters in solution is of key importance in elucidating the relevant mechanism of a biological process involving them. Concerning the overall shape of a nucleoside, the most important conformational parameters are the torsion angle around the glycosidic bond (χ) as well as the sugar puckering, which are interdependent to each other.[6] Considerable attention has been devoted towards understanding the glycosidic conformation of nucleosides, and the 1D ^{1}H Nuclear Overhauser enhancement (NOE) difference spectroscopy has been employed by Seela et al. as an efficient and straightforward approach to estimate qualitative or semiquantitative information about the preferred conformation of nucleosides in solution,[7] and they established a semiquantitative calibration graph method for estimation of *syn–anti* conformer populations of a variety of regular or modified nucleosides by comparison of their 1D ^{1}H NOE values (at H1′, H2′, and H3′ when H8 was irradiated) with the yardstick NOE values of the conformationally fixed model nucleosides N^3,5′-anhydroisoguanosine (*syn*) and 2′-deoxywyosine (*anti*). The results were applied as calibration benchmark in our conformational analysis of benzimidazole nucleosides. However, in most of the newly synthesized compounds (**2a–i**), H2 (IUPAC numbering, corresponding to H8 of purine nucleosides in purine numbering) was substituted by other groups, thus rendering them not to be amenable to the conformational analysis using the same method of Seela et al. by irradiating H2.[7] For these compounds, we took advantage of H7 in benzimidazole nucleosides, which does not exist in purine nucleosides, to develop a practical method for analysis of conformation of benzimidazole nucleosides. Molecular model studies of these compounds (Hyperchem 7.5) showed that in the *anti* conformation, H7 was much closer to H1′ than H2′ and H3′, whereas when rotated to *syn* conformation, H7 was much closer to H2′ than H1′ and H7 was closer to H3′ than in *anti* form. Therefore, when H7 was irradiated, the value x-H7 = η(H1′)/[η(H2′) + η(H3′)] (η is the enhancement at a certain hydrogen) can provide us a qualitative information on the *syn–anti* conformational distributions: the larger the x-H7 value, the more conformer population of *anti*. When H2 of the compounds **2a**, **2d** or **2f** was irradiated, the value x-H2 = η(H1′)/[η(H2′) + η(H3′)] can also provide us with qualitative information of the corresponding *syn–anti* conformation equilibria: the smaller the x-H2 value, the more conformer population of *anti* form.

Because H2 of benzimidazole nucleoside (IUPAC numbering) is equivalent to H8 of purine nucleosides (purine numbering), the x-H2 values of the reference compounds **8**, **7**, **6**, **5** and **4** (Scheme 3) were calculated using the literature NOE data and the results were given in Table 1 along with conformer populations estimated by Seela's method.[7] A calibration curve for estimation of *syn* and *anti* conformer populations of the β-nucleosides using their x-H2 values was easily established by simply linking the data points of **8**, **7**, **6**, **5** and **4** (Fig. 1), and the linearity was quite good within the two regions of **8–6** and **6–4**. Using this curve, the *anti* conformer populations of **2d**, **2a** and **2f** were estimated to be 98, 59 and 55%, respectively, based on their corresponding x-H2 values. By comparing the NOE values of **2e** and **2d** when 4-CH_3 is irradiated (Table 2), **2e** was concluded to have a larger *anti* conformer population than **2d**, between 98 and 100% *anti* (Molecular model studies showed that in the *anti* conformation, 4-CH_3 is much closer to H1′ than H2′, whereas when rotated to *syn* conformation, 4-CH_3 was much closer to H2′ than H1′). As seen from Table 2, x-H7 values of **2b**, **2c**, **2g**, **2h** and **2i** were extremely small comparing to the x-H7 value of **2f**, which adopted a 55% *anti* conformation. Therefore, **2b**, **2c**, **2g**, **2h** and **2i** were concluded to adopt predominantly *syn* conformations.

In order to obtain a semiquantitative estimation of *syn–anti* conformation for **2b**, **2c**, **2g**, **2h** and **2i** using the results of



Scheme 3. Compound taken from literature[7] as calibrations.

Table 1. Data from literature[7]

Compound	Irradiated	NOE (%)	*x*-H2	*anti* (%)
4	H8	H1′ (6.7), H2′ (3.2), H3′ (0.8)	1.68	40
5	H8	H1′ (4.1), H2′ (4.2), H3′ (1.5)	0.72	65
6	H8	H1′ (3.6), H2′ (5.7), H3′ (1.1)	0.53	70
7	H8	H1′ (2.1), H2′ (7.3), H3′ (1.3)	0.24	86
8	H8	H1′ (0.5), H2′ (7.4), H3′ (2.1)	0.05	100

anti (%) Values were from their analysis results.

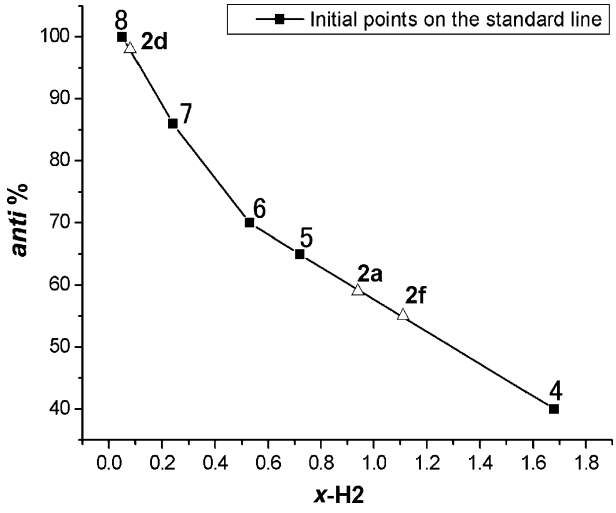


Figure 1. Conformation evaluation of **2d**, **2a** and **2f** on the standard line.

Table 2. ^{1}H 1D NOE data measured in DMSO and the calculated *x* values

Compound	Irradiated	NOE (%)	*x*-H2	*x*-H7
2e	CH_3	H1′ (11.85), H2′ (0.84), H3′ (0.33)		
2d	CH_3	H1′ (10.5), H2′ (1.14)		
2d	H2	H1′ (0.61), H2′ (5.85), H3′ (1.58)	0.08	
2a	H2	H1′ (2.91), H2′ (2.42), H3′ (0.68)	0.94	
2a	H7	H1′ (3.48), H2′ (2.26), H3′ (0.30)		1.36
2f	H2	H1′ (2.10), H2′ (1.57), H3′ (0.33)	1.11	
2f	H7	H1′ (3.54), H2′ (2.48), H3′ (0.30)		1.27
2b	H7	H1′ (1.51), H2′ (6.63), H3′ (0.51)		0.21
2c	H7	H1′ (1.78), H2′ (5.60), H3′ (0.79)		0.28
2g	H7	H1′ (1.05), H2′ (3.73), H3′ (0.73)		0.24
2h	H7	H1′ (1.29), H2′ (3.67), H3′ (0.24)		0.32
2i	H7	H1′ (1.76), H2′ (3.34), H3′ (0.57)		0.45

Seela et al.[7] as calibration, we sought for some type of relationship between the value of *x*-H2 and *x*-H7. As seen from data of **2a** and **2f** in Table 2, when *x*-H2 values increased, *x*-H7 values decreased almost by the same extent. So we hypothesized that *x*-H2 value and *x*-H7 value were added up to a constant: $x\text{-H2}+x\text{-H7}=c$. From the data of **2a** and **2f**, the constant *c* was calculated by average to be 2.34. Although the expression may not be accurate, it was considered to be adequate for a semiquantitative estimation as the final results of the conformational analysis were in good agreement with the experimental data (1D and 2D NOE data, X-ray single crystal diffraction analysis). The *x*-H2 value of **2b**, **2c**, **2g**, **2h** and **2i** were calculated by the expression ($x\text{-H2}+x\text{-H7}=2.34$) and the conformer populations were estimated by inserting the calculated *x*-H2 value listed in Table 3 into the extended calibration curve (Fig. 2).

Table 3. Measured *J* values, calculated *x*-H2 values and conformation analysis results

Compound	*x*-H2	*anti* (%)	$J_{1'2'}$	$J_{3'4'}$	*S* (%)
2b	2.13	28	7.5	2.4	76
2c	2.06	30	7.5	2.7	74
2g	2.10	29	7.8	2.4	76
2h	2.02	31	6.9	3.0	70
2i	1.89	34	6.9	2.4	74
2a	0.94	59	6.3	3.3	66
2f	1.11	55	6.0	2.7	69
2d	0.08	98	5.1	3.9	67
2e	—	98–100	5.7	4.2	56

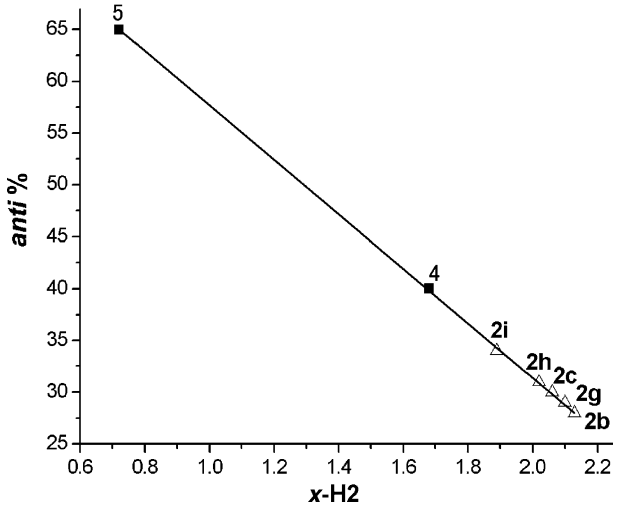


Figure 2. Conformation estimation of **2b**, **2c**, **2g**, **2h** and **2i** on the standard line.

As shown in Table 3, N3-isomers (**2d**, **2e**) had extremely high *anti* conformer populations, while the glycosidic orientations of N1-isomer depended on the 2-substituents. When the 2-positions of N1-isomers were not substituted, the nucleosides (**2a**, **2f**) adopted preferably *anti* conformation. However, when the 2-positions of N1-isomers were substituted (by groups bigger than –H), the nucleosides (**2b**, **2c**, **2g**, **2h**, **2i**) adopted primarily *syn* conformation. Thus, the blockage of 4-methyl and 2-substituents of the nucleosides played a key role in their conformation distributions.

The sugar puckering of **2a–i** in DMSO solution were determined by the literature method.[8] The coupling constants were measured with assist of NMR double-resonance experiment (Table 3) and *S*% was calculated using the following expression: $S\%=100\,J_{1'2'}/(J_{1'2'}+J_{3'4'})$. As seen from the results listed in Table 3, all of the nine nucleosides adopted primarily *S* type sugar puckering. Substituents at 2-position seemed to affect the sugar puckering of the nucleosides greatly. The nucleosides with substituents (bigger than –H) at 2-position (**2b**, **2c**, **2g**, **2h**, **2i**) generally had more *S* conformer population than the nucleosides without substituents at 2-position (**2a**, **2d**, **2f**). However, there was an exception of **2e**, which had the lowest *S* conformer population.

Although conformation of nucleosides in solution is generally considered to be of more importance, X-ray

crystal structure of nucleosides always provide the most accurate and reliable information of their solid-state structure and the two types of data can effectively supplement each other to furnish an integrated structure picture of the investigated compound. In the experiment compounds **2e**[9] and **2h** were obtained as single crystals and their solid-state structures were elucidated by X-ray crystallographic analyses.

The crystal structure of **2e** was showed in Figure 3 with the atom-labeling scheme. In the sugar ring, atom C10 was displaced by 0.538 Å on the same side of the C9/O2/C12/C11 plane as atom C13, suggesting that the sugar ring was in a C2′-*endo* envelope (*S*) conformation. The glycosidic torsion angle χ=O2–C9–N2–C1 was 69.8°, suggested that the glycosidic bond rotation was *anti*. The formation of hydrogen bond C10–H10···O1 (equivalent to C2′–H2′···O2 in normal numbering system) was consistent with the observation that H2′ in **2e** showed an extraordinarily high chemical shift (4.98) of ^{1}H NMR spectra in DMSO solution.[10] The existence of this hydrogen bond confirmed the *anti* glycosidic orientation of compound **2e** in DMSO solution, consistent with the conformational analysis result mentioned above. The conformation of the C5′–O5′ bond around the C4′–C5′ bond was *gauche–gauche*, the dihedral angles O5–C13–C12–O2 and O5–C13–C12–C11 being −70.0 and 49.0°, respectively. It was also evident from the crystal structure data that the benzimidazole moiety of **2e** existed in the ketonic form rather than the enol form (C1–O1 bond length is 1.232 Å).

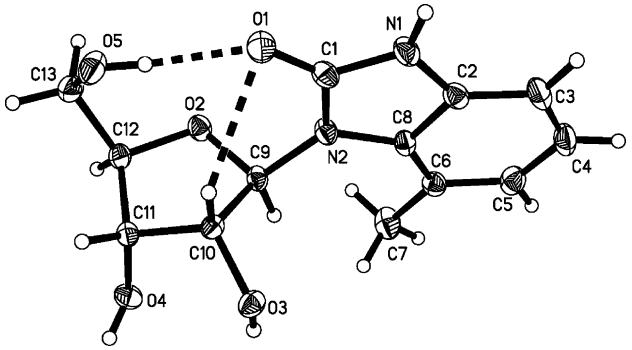


Figure 3. The structure of **2e**, showing 30% probability displacement ellipsoids and the atom-labeling scheme. Hydrogen bonds were shown as dashed lines.

Compound **2h** crystallized with 1 equiv of water included. A perspective view of **2h** with the atom-labelling scheme was shown in Figure 4. In the furanose ring, the atom C2 and C3 were displaced by 0.586 and 0.867 Å, respectively, on the same side of the C1/O1/C4 plane as the C5 atom. Therefore, the furanose ring was in neither envelope conformation nor twist conformation but in a nontypical *N* conformation. The glycosidic torsion angle χ= O1–C1–N1–C6 was 138.2°, suggesting a *syn* glycosidic orientation. Thus, compound **2h** exibited similar glycosidic orientation in crystal state and in DMSO solution. The torsion angles O4–C5–C4–O1 and O4–C5–C4–C3 were

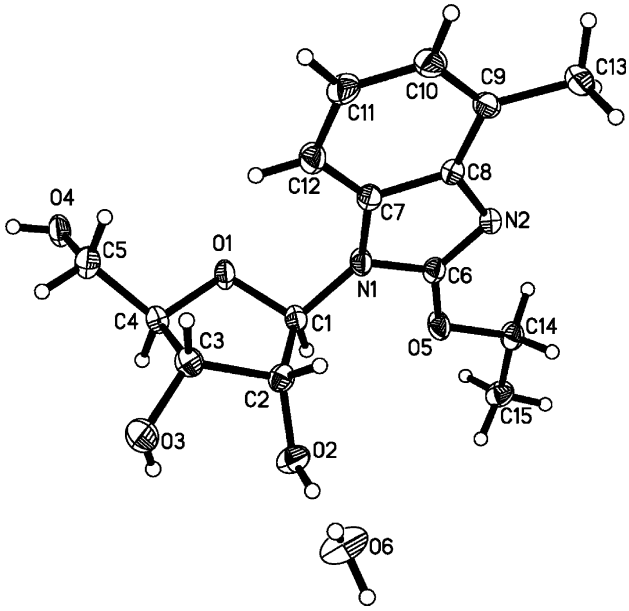
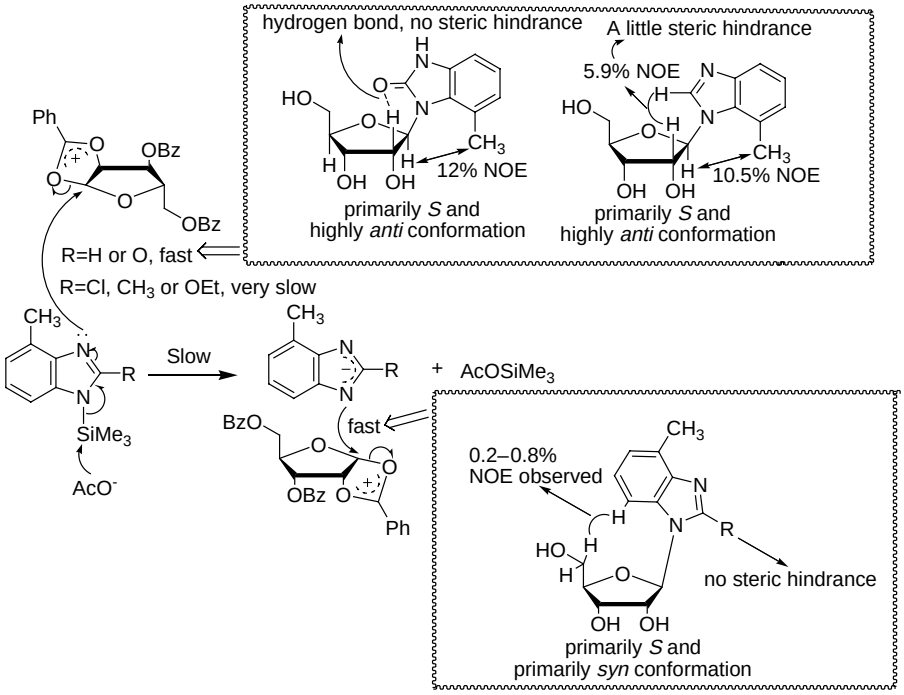


Figure 4. The structure of **2h** (with one molecule water), showing 30% probability displacement ellipsoids and the atom-labeling scheme. Hydrogen bonds were shown as dashed lines.

67.8 and −177.1°, respectively, defining the conformation around C4–C5 as *gauche*-trans. No intramolecular hydrogen bond was found in **2h**. Atom O6 of water molecular formed three intermolecular hydrogen bonds, O2–H2···O6, O6–H6B···O2 and O6–H6A···O4. Atom O4 formed two intermolecular hydrogen bonds, O6–H6A···O4 and O4–H4···N2. Atom O2 also formed two intermolecular hydrogen bonds, O2–H2···O6 and O3–H3···O2. These intermolecular O–H···O and O–H···N hydrogen bonds linked the molecules into a three-dimensional network.

The conformational analysis was found helpful for understanding the reaction mechanism. In the previous communication,[5] a plausible mechanism for the unexpected regioselectivity in the synthesis of **2a–e** was proposed, which was further supported by the results of the conformational analysis of **2a–i** (Scheme 4). Since the N3-isomers (**2d**, **2e**) of the products were tightly restricted to a highly *anti* and primarily *S* conformation, a little increase in the size of the 2-substituents may cause great steric repulsion between 2-substituents and H2′, thus making it very difficult for formation of 2-substituted N3-isomers. In contrast, N1-isomers of the products adopted primarily *syn* and *S* conformation, so the 2-substituents could not cause too much steric hindrance. Therefore, N1-isomers were obtained for every 4-methyl-benzimidazole bases, but N3-isomers were obtained only when there were no bulky substituents at the 2-position of 4-methyl-benzimidazole base. For 5-methyl-benzimidazole-nucleosides, no N3-isomer was obtained. One possible explanation for this phenomenon was given as the followings: as an electron-donor substituent, methyl group could activate *ortho*- and *para*-position of the benzene ring and thus activate the substituents at *ortho*- and *para*-position. Therefore, N1 was more reactive than N3 in 5-methyl-benzimidazoles, and N1-isomer was easier to form than N3-isomer for 5-methyl-benzimidazole nucleoside.



Scheme 4. Possible reaction mechanism supported by conformation analysis results.

3. Summary

A series of benzimidazole nucleosides were synthesized with different regioselectivity and β-stereoselectivity. All the selected benzimidazoles exhibited N1-regioselective glycosidation with **3** using the Vorbrüggen procedure[11] except for the silylated 4-methyl-1*H*-benzimidazole and 4-methyl-1*H*-benzimidazol-2-one, which exhibited N3-regioselective glycosidation with **3**. The CH_3CH_2–O bond in 2-ethoxy-4-methyl-1*H*-benzimidazole moiety of the nucleoside showed a temperature-dependent cleavage by $SnCl_4$. Conformations of these newly synthesized nucleosides were analyzed by ^1H NMR spectroscopy in DMSO solution, and the solid-state conformations of **2e** and **2h** were studied by X-ray single crystallography. The N3 isomers of benzimidazole nucleosides (**2d**, **2e**) were in highly *anti* conformation while the N1 isomers exhibited predominantly *syn* conformation when 2-position was substituted (**2b**, **2c**, **2g**, **2h**, **2i**) but exhibited primarily *anti* conformation when 2-position was unsubstituted (**2a**, **2f**). The sugar moieties in all of the benzimidazole nucleoside products were of primarily *S* conformation in DMSO solution. The conformation analysis provided further evidences for the proposed reaction mechanism.

4. Experimental

4.1. General

Melting points were determined with Yanagimoto MP-35 melting point apparatus and uncorrected. The ^1H spetra (1D) were recorded with a Varian Mercury Vx400 and Vx300 spectrometer and the ^1H 1D NOE, ^1H 2D NOE, ^1H double-resonance and ^{13}C spetra were recorded with a Varian Mercury Vx300 spetrometer, both using tetramethylsilane as the internal standard. Coupling constants are given in Hertz. All NMR measurements were performed with 0.1 M DMSO-d_6 solution at 298 K. The Mass spectra were recorded on Thermo Finnigan LCQAdvantage spectrometer in ESI mode, I Spray Voltage 4.8 kV. A Yamaco CHN corder MT-3 apparatus was used for elemental analysis. Optical rotations were determined with WZZ-1 polarimeter made by Shanghai Physico-optical Instrument Factory. X-ray crystallographic analysis was performed on a Bruker SMART 1000 diffractometer.

2-Ethoxy-4-methyl-1*H*-benzimidazole was prepared by similar procedures as described by literature.[12] 5-Methyl-1*H*-benzimidazole and 2,5-dimethyl-1*H*-benzimidazole were purchased from Acros and used without further purification. Silylation of the benzimidazoles was followed the procedure described by Takuzo Nishimura and Issei Iwai.[13] Acetonitrile and 1,2-dichloroethane were distilled over CaH_2 and P_2O_5, respectively, while $SnCl_4$ was redistilled freshly.

4.1.1. 5-Methyl-1-(β-D-erythro-pentofuranosyl)-1*H*-benzimidazole (2f). 5-Methyl-1*H*-benzimidazole (3.8 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (3.6 mmol) were dissolved in acetonitrile (30 ml) and a solution of tin tetrachloride (0.84 ml) in acetonitrile (18 ml) was added dropwise with stirring under a nitrogen atmosphere at reflux temperature. The solution was refluxed for 6 h and cooled to room temperature. Sodium bicarbonate (7.5 g) in water (50 ml) was added and stirring was continued for another 1 h. The resulting solution was extracted three times with chloroform. The organic layers were combined, dried over anhydrous sodium sulfate,

filtered, and evaporated to give a solid. The solid was dissolved in methanol (40 ml) and the solution was saturated with ammonia gas and stirred overnight in a sealed container. The resulting solution was evaporated to dryness to give the crude product, which was purified by silica-gel column chromatography using chloroform–methanol (9/1 v/v) as eluent to give 0.52 g target compound as a white powder, yield 55%. $[\alpha]_D^{20}$ −39.3 (*c* 0.2, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.39 (s, 1H, H2), 7.61 (d, J=8.0 Hz, 1H, H7), 7.56–7.53 and 7.46 (ms, 1H, H4), 7.07 (t, J=8.4 Hz, 1H, H6), 5.82 (d, J=5.3 Hz, 1H, H1′), 5.47 (d, J=5.3 Hz, 1H, 2′-OH), 5.22 (d, J=4.8 Hz, 1H, 3′-OH), 5.15–5.10 (m, 1H, 5′-OH), 4.39–4.33 (m, 1H, H2′), 4.13–4.08 (m, 1H, H3′), 3.97–3.94 (m, 1H, H5′), 3.70–3.57 (m, 2H, H5′), 2.41 (s, 3H, 5-CH_3); ^{13}C NMR (300 MHz, DMSO-d_6) δ 144.9, 143.0, 142.5, 131.7, 124.7, 120.0, 111.7, 89.3, 86.0, 74.2, 70.8, 61.9, 21.8; MS (ESI) *m*/*z* 265 $[M+H]^+$. Anal. Calcd for $C_{13}H_{16}N_2O_4$: C 59.08, H 6.10, N 10.60. Found: C 58.99, H 5.97, N 10.55.

4.1.2. 2,5-Dimethyl-1-(β-D-erythro-pentofuranosyl)-1*H*-benzimidazole (2g). 2,5-Dimethyl-1*H*-benzimidazole (3.8 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (3.6 mmol) were dissolved in 1,2-dichloroethane (30 ml) and a solution of tin tetrachloride (0.84 ml) in 1,2-dichloroethane (18 ml) was added dropwise with stirring under a nitrogen atmosphere at reflux temperature. The solution was refluxed for 5 h and cooled to room temperature. Sodium bicarbonate (7.5 g) in water (50 ml) was added and stirring was continued for another 1 h. The resulting solution was extracted three times with chloroform. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to give a solid. The solid was dissolved in methanol (40 ml) and the solution was saturated with ammonia gas and stirred overnight in a sealed container. The resulting solution was evaporated to dryness to give the crude product, which was purified by silica-gel column chromatography using chloroform–methanol (9/1 v/v) as the eluent to give 0.57 g **2g** as a white powder, yield 57%. $[\alpha]_D^{20}$ −54.5 (*c* 0.3, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.69 and 7.67 (sd, J=4.9 Hz, 1H, H7), 7.38 and 7.31 (ds, J=7.9 Hz, 1H, H4), 6.95 (t, J=9.3 Hz, 1H, H6), 5.71 (d, J=7.4 Hz, 1H, H1′), 5.34 (d, J=7.0 Hz, 1H, 2′-OH), 5.24 (d, J=3.8 Hz, 1H, 3′-OH), 5.19–5.12 (m, 1H, 5′-OH), 4.38–4.30 (m, 1H, H2′), 4.12–4.06 (m, 1H, H3′), 3.94–3.91 (m, 1H, H4′), 3.72–3.67 (m, 2H, H5′), 2.54 (s, 3H, 2-CH_3), 2.37 (s, 3H, 5-CH_3); ^{13}C NMR (300 MHz, DMSO-d_6) δ 152.4, 143.7, 134.3, 131.1, 123.6, 118.9, 112.8, 89.1, 86.2, 72.4, 70.3, 62.1, 21.8, 15.1; MS (ESI) *m*/*z* 279 $[M+H]^+$. Anal. Calcd for $C_{14}H_{18}N_2O_4$: C 60.42, H 6.52, N 10.07. Found: C 60.16, H 6.25, N 9.82.

4.1.3. 2-Ethoxy-4-methyl-1-(β-D-erythro-pentofuranosyl)-1*H*-benzimidazole (2h). Silylated 2-ethoxy-4-methyl-1*H*-benzimidazole (3.8 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (3.6 mmol) were dissolved in acetonitrile (30 ml) and a solution of tin tetrachloride (0.84 ml) in acetonitrile (18 ml) was added dropwise with stirring under a nitrogen atmosphere at room temperature. The solution was stirred for 3 h at room temperature. Sodium bicarbonate (7.5 g) in water (50 ml) was added and stirring was continued for another 1 h. The resulting solution was extracted three times with chloroform. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to give a solid. The solid was dissolved in methanol (40 ml) and the solution was saturated with ammonia gas and stirred overnight in a sealed container. The resulting solution was evaporated to dryness to give the crude product, which was purified by silica-gel column chromatography using chloroform–methanol (9/1 v/v) as eluent to give 0.45 g target compound as a white powder, yield 41%. Single crystals suitable for X-ray diffraction measurements were obtained by slow evaporation of its aqueous solution at room temperature. $[\alpha]_D^{20}$ −20.8 (*c* 0.1, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.42 (d, J=7.5 Hz, 1H, H7), 6.98–6.91 (m, 2H, H6 and H5), 5.71 (d, J=6.9 Hz, 1H, H1′), 5.31 (d, J=6.6 Hz, 1H, 2′-OH), 5.14 (d, J=4.8 Hz, 1H, 3′-OH), 5.02–4.99 (m, 1H, 5′-OH), 4.58–4.47 (m, 2H, H2′ and 2-O–CH_2), 4.09–4.05 (m, 1H, H3′), 3.87–3.83 (m, 1H, H4′), 3.62–3.58 (m, 2H, H5′), 2.43 (s, 3H, 4-CH_3), 1.41 (s, 3H, CH_3 of 2-OEt); ^{13}C NMR (300 MHz, DMSO-d_6) δ 156.9, 139.6, 132.3, 127.1, 122.8, 121.3, 109.4, 87.4, 85.6, 71.1, 70.6, 66.7, 62.3, 17.1, 15.1; MS (ESI) *m*/*z* 309 $[M+H]^+$. Anal. Calcd for $C_{15}H_{20}N_2O_5$: C 58.43, H 6.54, N 9.09. Found: C 58.17, H 6.81, N 8.84.

4.1.4. 4-Methyl-1-(β-D-erythro-pentofuranosyl)-3*H*-benzimidazol-one (2i). Silylated 2-ethoxy-4-methyl-1*H*-benzimidazole (3.8 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (3.6 mmol) were dissolved in acetonitrile (30 ml) and a solution of tin tetrachloride (0.84 ml) in acetonitrile (18 ml) was added dropwise with stirring under a nitrogen atmosphere at room temperature. The solution was stirred for 3 h at room temperature then refluxed for 6 h and cooled to room temperature. Sodium bicarbonate (7.5 g) in water (50 ml) was added and stirring was continued for another 1 h. The resulting solution was extracted three times with chloroform. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to give a solid. The solid was dissolved in methanol (40 ml) and the solution was saturated with ammonia gas and stirred overnight in a sealed container. The resulting solution was evaporated to dryness to give the crude product, which was purified by silica-gel column chromatography using chloroform–methanol (9/1 v/v) as the eluent to give 0.36 g **2i** as a white powder, yield 36%. $[\alpha]_D^{20}$ −30.4 (*c* 0.1, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.05 (s, 1H, H3), 7.20 (d, J=7.5 Hz, 1H, H7), 6.90–6.81 (m, 2H, H6 and H5), 5.66 (d, J=6.8 Hz, 1H, H1′), 5.20 (d, J=6.0 Hz, 1H, 2′-OH), 5.05 (d, J=4.8 Hz, 1H, 3′-OH), 4.99–4.95 (m, 1H, 5′-OH), 4.58–4.51 (m, 1H, H2′), 4.09–4.04 (m, 1H, H3′), 3.84–3.81 (m, 1H, H4′), 3.65–3.52 (m, 2H, H5′), 2.28 (s, 3H, 4-CH_3); ^{13}C NMR (300 MHz, DMSO-d_6) δ 154.8, 128.8, 127.9, 123.2, 121.3, 119.2, 108.3, 86.7, 85.4, 70.7, 70.1, 62.4, 16.8; MS (ESI) *m*/*z* 279 $[M-H]^-$. Anal. Calcd for $C_{13}H_{16}N_2O_5$: C 55.71, H 5.75, N 9.99. Found: C 55.46, H 5.38, N 9.98.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.12.047. Supplementary material includes NMR ^{1}H 2D NOE spetra of compound **2a–i**. CCDC 280082 contain the supplementary crystallographic data and collection parameters for **2h**. These data can be obtained free of charge via www.ccdc.cam.ac,uk/conts/retrieving.html.

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