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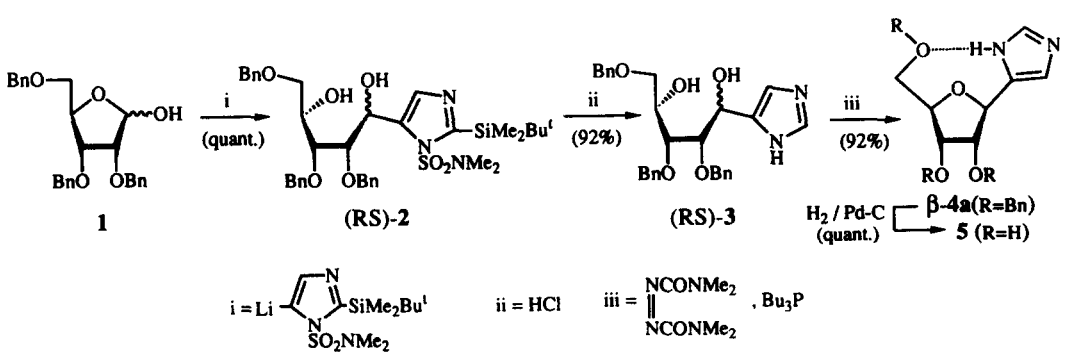
Stereoselective Synthesis of the C-4 Linked Imidazole Nucleosides Using Modified Mitsunobu Reaction

Shinya Harusawa, Yoshihiko Murai, Hideki Moriyama, Hirofumi Ohishi, Ryuji Yoneda, and Takushi Kurihara*

Osaka University of Pharmaceutical Sciences, 2-10-65 Kawai, Matsubara, Osaka 580, Japan

Abstract: A highly stereoselective synthesis of the novel 4-(β-D-ribofuranosyl)imidazole **5** was accomplished in 4 steps and 85% overall yield from protected D-ribose **1**. Cyclization of the diol (RS)-**3** having an intact imidazole by modified Mitsunobu reaction exclusively afforded benzylated β-ribofuranosylimidazole β-**4a**, accompanied by α-**4a**, in a ratio of 26:1. Reductive debenzylation completed the synthesis. 2'-Deoxy derivative **8** was also synthesized stereoselectively in the same manner.

C-Ribonucleosides have attracted much attention in view of their remarkable antitumor and antiviral activities.[1,2] However, the synthetic method of imidazole *C*-nucleosides, in general, is limited and requires many steps.[3] Although several imidazole *C*-nucleosides linked through C-2 have been synthesized,[4] only one synthetic study on C-4 linked 2'-deoxy-β-D-ribofuranosylimidazoles has been reported.[2] Since excellent Mitsunobu reagents were developed recently by Tsunoda *et al*,[5] we applied them to the synthesis of a novel 4-(β-D-ribofuranolsyl)imidazole **5** and its 2'-deoxy derivative **8**.[2] The results are described herein.

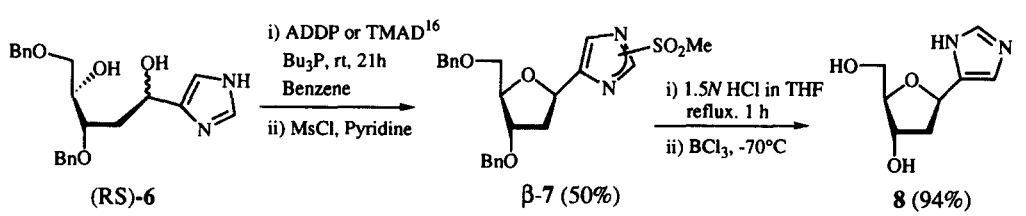


Scheme 1

A protected D-ribose **1**[6] was allowed to react with an imidazole-lithium salt[7] to give the corresponding adduct **2**, as illustrated in Scheme 1. Hydrolysis of **2** in refluxing HCl afforded a 1:1 epimeric mixture of diol (RS)-**3**. Cyclization of (RS)-**2** under the common Mitsunobu conditions [diethyl azodicarboxylate (DEAD) / Ph_3P][8] brought about a small amount of cyclization products, whose structures were not determined. Alternatively, (RS)-**3** afforded crystalline derivative β-**4b** (15%)[9] with an ethoxycarbonyl group at N-1 under the same conditions, after a partial chromatographic separation followed by recrystallization from hexane. X-ray crystallography established its structure as the desired β-anomer.[9] When (RS)-**3** was subjected to the new Mitsunobu reagent [1,1'-(azodicarbonyl)dipiperidine (ADDP) / Bu_3P][5a], β-**4a** was obtained in a modest yield. The structure was confirmed by a conversion of β-**4a** into β-**4b** with ethyl chloroformate. Importantly, cyclization of (R)- and (S)-**3** separated by column chromatography afforded only β-anomer under the same conditions, respectively. The reaction was very clear, but the isolated yields were less satisfactory owing to the difficulty of the product isolation from hydrazine by-product. The problem has been solved by the use of N,N,N',N'-tetramethylazodicaboxamide (TMAD)[5b] to give the excellent yield of β-**4a** (91.7%), together with a small amount of α-**4a** (3.6%).[10] The ratio of α/β is 1/26.

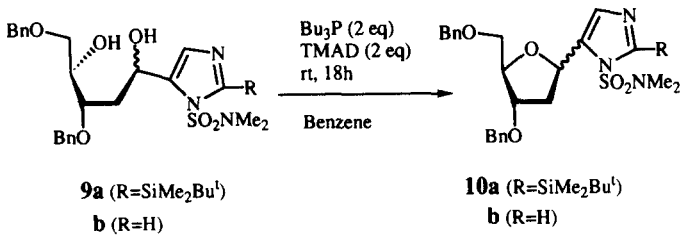
Yokoyama *et al* [11a] very recently reported the synthesis of *C*-ribonucleosides having aromatic heterocycles, in which the cyclization under Mitsunobu condition proceeded through an intramolecular SN2 reaction, and the orientation of glycosidic linkage was controlled by the configuration of the substrate. Interestingly, these facts were in contrast to our results. Hydrogenolytic debenzylation (quant.) of β-**4a** over Pd/C was carried out, and we attained the synthesis of 4-(β-D-ribofuranosyl)imidazole **5**[12] from **1** in 4 steps and 85% overall yield.

Next, we synthesized 4-(2'-deoxy-β-D-ribofuranosyl)imidazole **8** using this method. Thus, cyclization of a 1:1 mixture of (RS)-**6**, which was similarly prepared from D-2-deoxyribose, brought about an inseparable mixture of β- and α-anomers in a satisfactory ratio (5:1) (Scheme 2). Their mesyl derivatives could be separated by column chromatography on SiO_2, giving β- and α-**7** in 50% and 11% yields, respectively. Deprotection of β-**7** by treatments with 1.5*N* HCl followed by BCl_3[11b] completed the synthesis of **8** in 94% yield.[13]



Scheme 2

Cyclization of **9a,b** having a substituted imidazole proceeded *via* a process of the common Mitsunobu reaction (Scheme 3, Table). Accordingly, the intact-imidazole moiety is indispensable for the exclusive formation of β-anomer. The results suggest that the intramolecular hydrogen bonding between the nitrogen atom in the imidazole and oxygen-functional groups play a significant role for determination of the ratio of β- *vs* α-glycosidation.



Scheme 3

Table Cyclization of **9a,b**

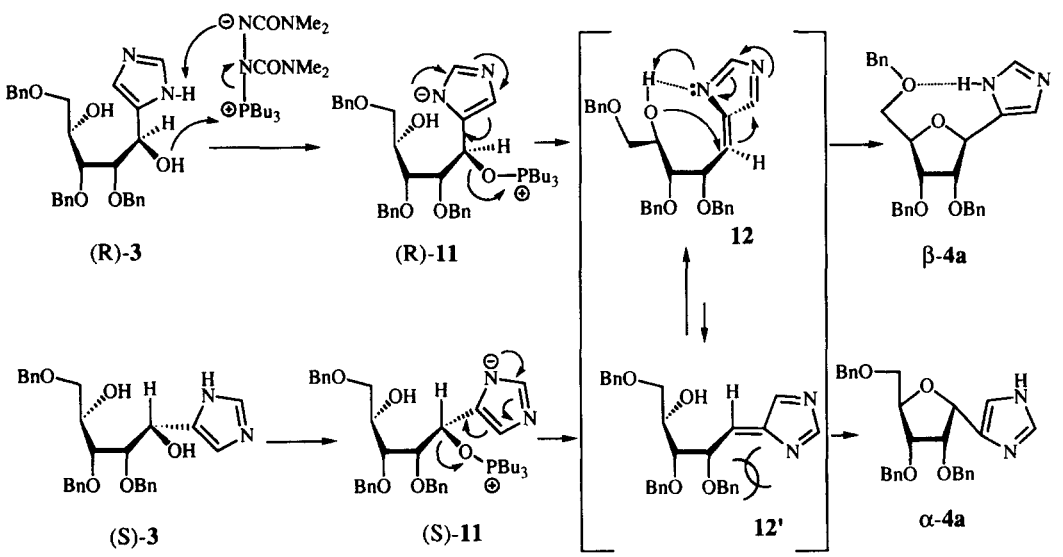
Run	9	10 (%)
1	(S)-**9a**	β-**10a** (12)[1)]
2	(R)-**9a**	α-**10a** (7)[2)]
3	(S)-**9b**	β-**10b** (94)
4	(R)-**9b**	α-**10b** (88)

1) Recovery of (S)-**9a** (65%)

2) Recovery of (R)-**9a** (67%)

The β-selectivity in our reaction can be rationalized as shown in Scheme 4.[15] Reaction of TMAD-Bu_3P adduct with (R)-**3** forms a zwitterion **11**. Preferential elimination of $Bu_3P{=}O$ from **11** leads to an isoimidazole **12**. Spontaneous cyclization of **12** assisted by the hydrogen bond gives β-**4a**.[14] Although (S)-**3** similarly leads to an activated species **12'**, it exclusively gives β-anomer *via* the rotamer **12** being thermodynamically more stable.

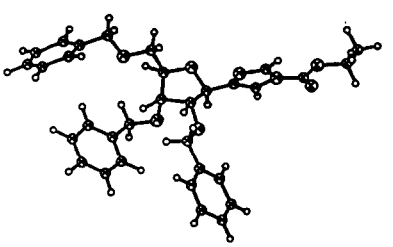
The synthetic approach of the imidazole *C*-nucleosides described here should promise to supply a variety of derivatives to assess their biological activities.



Scheme 4

References and Notes

1. Suhadolnik, R.J. Nucleosides as Biological Probes, Wiley-Interscience, New York, 1979.
2. Bergstrom, D.E.; Zhang, P. *Tetrahedron Lett.*, **1991**, *32*, 6485.
3. Postema, M.H.D. *Tetrahedron*, **1992**, *48*, 8545.
4. Poonian, M.S.; Nowoswiat, E.F. *J. Org. Chem.*, **1980**, *45*, 203. Igolen, J.; Dinh, T.H. *J. Chem. Soc., Chem. Commun.*, **1971**, 1267. Kolb, A.; Gouyette, C.; Tam, H.D.; Igolen, J. *Tetrahedron Lett.*, **1973**, 2971. Ferris, J.P.; Hung, H.C. *J. Chem. Soc., Chem. Common.* **1978**, 1094. Ferris, J.P.; Badesha, S.S.; Ren, W.Y.; Huang, H.C.; Sorcek, R.J. *ibid.*, **1981**, 110.
5. 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.
6. Barker, R.; Fletcher Jr, H.G. *J. Org. Chem.*, **1961**, *26*, 4605.
7. Kudzma, L.V.; Turbull Jr, S.P. *Synthesis*, **1991**, 1021.
8. Hughes, D.L., "The Mitsunobu Reaction," *Organic Reactions*, ed by Paquette, L.A., John Wiley & Sons, Inc., New York, **1992**, *42*, p 335-669.
9. m.p. 71-73°C {$[\alpha]_D$ -1.27° (c = 1.09, $CHCl_3$), $C_{32}H_{34}N_2O_6$, Monoclinic, $P2_1$ }
   More details on the crystal structure analysis were submitted to the Cambridge Crystallographic Data Centre.
10. Diol [(RS)-**3**, 2.32 mmol) and Bu_3P (3.47 mmol) were dissolved in dry benzene (70 ml) with stirring at 0°C, and TMAD (3.47 mmol) was added to the solution. After a few min, the reaction mixture was warmed up to room temperature and the stirring was continued for 16h. The insoluble material was removed by filtration, and the filtrate was condensed *in vacuo*. The resulting crude oil was diluted with EtOAc, and the organic layer was washed with H_2O (× 2), brine, dried over anhydrous Na_2SO_4, and then evaporated. The residue was purified by flash chromatography on SiO_2 using EtOAc-hexane (8:2) for elution to give β-**4a** (91.7%) and α-**4a** (3.6%).



ORTEP view of β-**4b**

β-**4a**: colorless oil, IR (neat) 3640-2290, 1180-870 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.68 (1H, dd, *J* = 10.4, 1.9 Hz), 3.95 (2H, overlapped), 4.14 (1H, dd, *J* = 7.2, 4.8 Hz), 4.31 (1H, dt, *J* = 7.2, 2.1 Hz), 4.34-4.74 (6H, m), 5.21 (1H, d, *J* = 2.4 Hz), 6.78 (1H, s), 6.83 (1H, s), 7.15-7.50 (15H, br). ^{13}C-NMR ($CDCl_3$): 69.9, 72.1, 73.6, 76.9, 77.2, 80.2, 81.3, 120.1, 127.9, 128.1, 128.2, 128.5, 128.7, 135.0, 137.4, 137.6, 137.8. $[\alpha]_D$ +52.3° (c = 3.08, $CHCl_3$). EI-MS *m/z*: 470 (M^+), HR-MS *m/z*: Calcd for $C_{29}H_{30}N_2O_4$, 470.2204, Found: 470.2209.
11. a) Yokoyama, M.; Toyoshima, A.; Akiba, T.; Togo, H. *Chem. Lett.*, **1994**, 265. b) Yokoyama, M.; Tanabe, T.; Toyoshima, A.; Togo, H. *Synthesis*, **1993**, 517.
12. **5**: white wax, IR(Nujol) 3700-3050, 1150-1000 cm^{-1}. ^{1}H-NMR (200 MHz, CD_3OD): 3.72 (1H, dd, *J* = 12.3, 3.9 Hz), 3.80 (1H, dd, *J* = 12.3, 3.5 Hz), 3.98-4.19 (3H, m), 4.83 (1H, d, *J* = 6.9 Hz), 7.58 (1H, s), 8.87 (1H, s). ^{13}C-NMR(CD_3OD): 63.2, 72.7, 77.2, 77.5, 87.5, 118.1, 135.3, 136.2. $[\alpha]_D$ -30.3° (c = 1.67, MeOH). EI-MS *m/z*: 200 (M^+), HR-MS *m/z*: Calcd. for $C_8H_{12}N_2O_4$, 200.0796, Found: 200.0800.
13. ^{1}H- and ^{13}C-NMR of **8** were consistent with those of reference 2.
14. Very recent report on an X-ray crystallographic analysis of a pyrrole analogue of β-**4a** revealed a strong hydrogen bonding between N1-H and O-5'. Patil, S.A.; Otter, B.A.; Klein, R.S. *Tetrahedron Lett.*, **1994**, *35*, 5339. ^{1}H-NMR data on the sugar moiety of β-**4a** are consistent with those of a pyrrole analogue. These facts support the existence of the hydrogen bonding in β-**4a**.
15. Epimerization between β-**4a** and α-**4a** was not observed.
16. The difference between two reagents could not be observed.

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