NUCLEOSIDES AND NUCLEOTIDES. 138. SYNTHESIS OF 3-HALO-3-DEAZAINOSINES: CONFORMATIONAL LOCK WITH THE HALOGEN AT THE 3-POSITION OF THE 3-DEAZAINOSINE IN *ANTI*-CONFORMATION[#, 1]

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Abstract - Synthesis of 3-chloro-, bromo-, and iodo-3-deazainosines (**6**-**8**) can be done by treatment of the 3-deazainosine derivative (**2**) with *N*-halosuccinimides. Treatment of the 5-formylimidazole derivative (**11**) with vinylmagnesium bromide gave 5-(1-hydroxy-2-propenyl)imidazole derivative (**12**), followed by fluorination and appropriate manipulations to cyclize, affording 3-fluoro-3-deazainosine (**18**). Although free rotation around the glycosyl linkage in 3-deazainosine (**1**) and **18** was observed, those of **6**, **7**, and **8** were rather fixed in the *anti*-conformation as analyzed by nOe experiments.

The *anti-syn* conformation of nucleosides around the glycosyl linkage is one of the most important conformational aspects of nucleoside-enzyme interactions when acting as substrates or inhibitors. For the stereochemical studies of the interaction of nucleosides with enzymes using them, nucleosides with fixed glycosyl torsion angles would be useful.[2] In a previous paper,[3] we reported the synthesis and the conformational analysis of 3-alkyl-3-deazainosines, in which the bulky substituent at the 3-position (purine numbering) prevented free rotation around the glycosyl linkages and subsequently fixed in the *anti*-region, without changing greatly in

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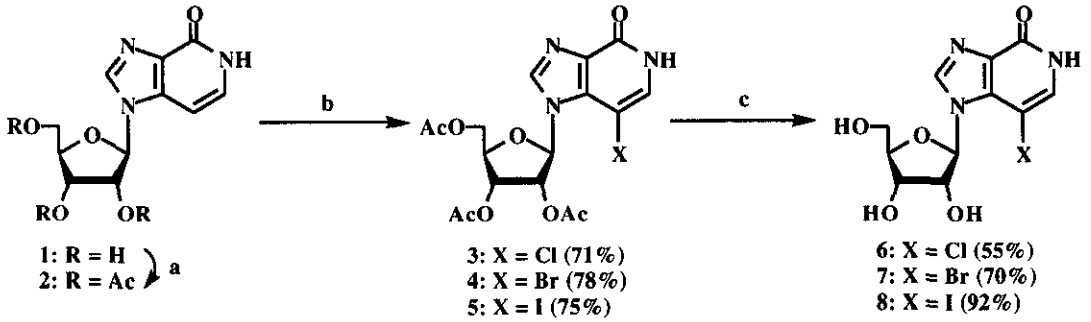
[#] Dedicated to the memory of the late Professor Yoshio Ban.

their sugar puckering. However, 3-deazainosine itself and its alkylated derivatives at the 3-position appreciably alter physico-chemical properties such as pK_a values for the base moiety. In this communication, we describe a synthesis and conformational analysis of 3-halo-3-deazainosines, which are expected to be restricted in the *anti*-region and have pK_a values for the base moiety close to those of inosine.

Scheme I[a]

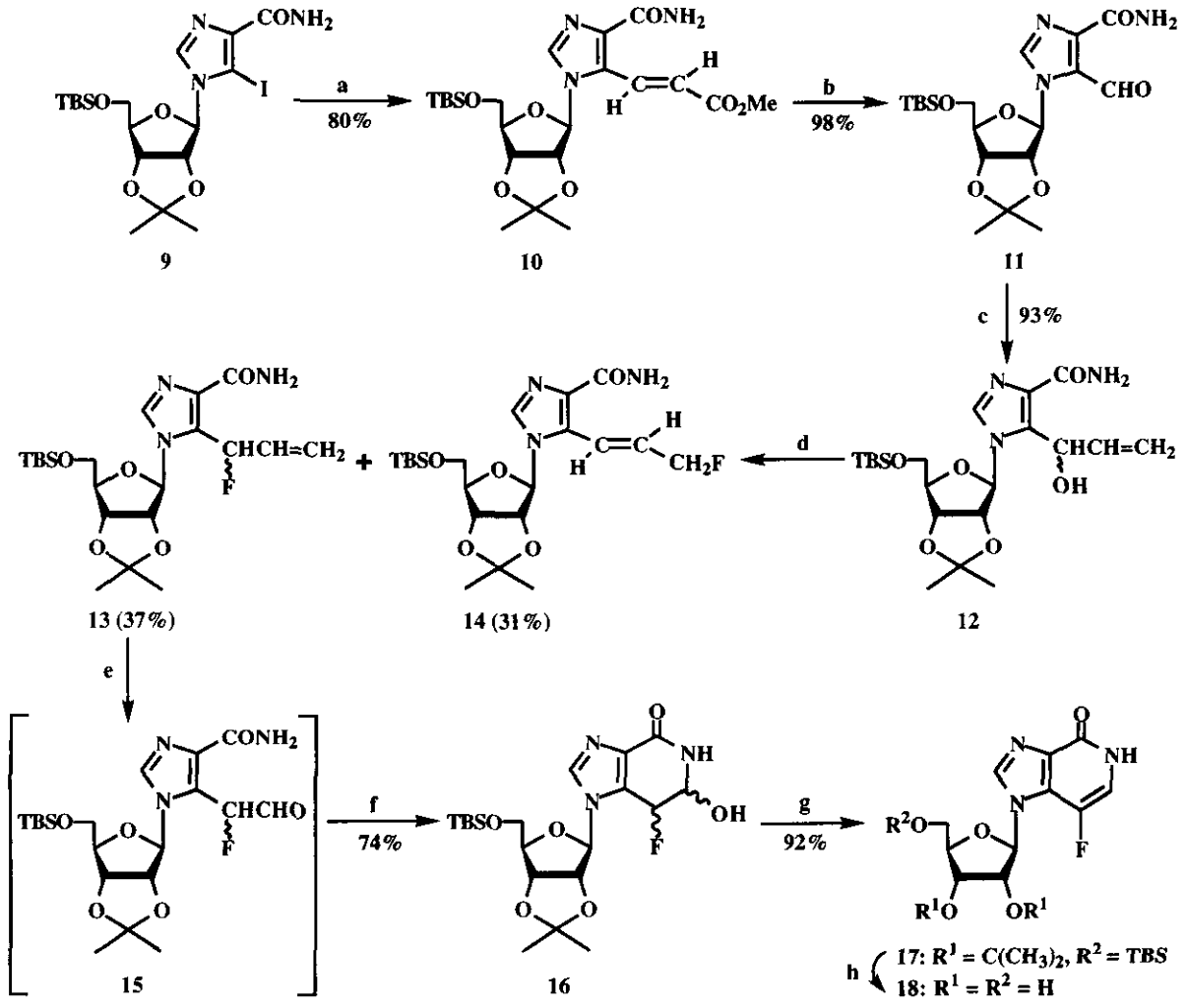


[a]Reagents and conditions: a) Ac_2O in pyridine; b) *N*-halosuccinimide in CH_2Cl_2 or DMF, room temperature; c) NH_3 / MeOH, room temperature

Introduction of chloro, bromo, and iodo substituents into the 3-position of **1**[4] could be done easily by treatment of 3-deazainosine derivative (**2**) with *N*-halosuccinimides. Treatment of **2** with *N*-chlorosuccinimide or *N*-bromosuccinimide in CH_2Cl_2 at room temperature gave 3-chloro and 3-bromo derivatives (**3**) and (**4**), in 71 and 78% yields, respectively. Iodination was done by treatment of **2** with *N*-iodosuccinimide in DMF to give **5** in 75% yield. Deprotection of 3-halo derivatives (**3-5**) by NH_3/MeOH gave target compounds (**6-8**) in moderate yields (Scheme I). Attempts to direct fluorination of **2** with using *N*-fluoropyridinium salts[5] and F_2 gas, or a halogen-exchange reaction[6] using **5** gave unfruitful results in recovery or decomposition of the starting material. Therefore, we next examined another route to synthesize **18** as shown in Scheme II. Compound (**9**) was heated with methyl acrylate and $(PhCN)_2PdCl_2$ in the presence of Et_3N to give **10** in 80% yield. Conversion of **10** to formyl derivative (**11**) was done by ozonolysis in methanol, followed by treatment with methyl sulfide. Treatment of 5-formyl derivative (**11**) with vinylmagnesium bromide in THF at -40 °C gave 5-(1-hydroxy-2-propenyl)imidazole derivative (**12**) in 93% yield. When **12** was treated with diethylaminosulfur trifluoride (DAST) in CH_2Cl_2 at -15 °C, the desired fluorinated product (**13**) was obtained in 37% yield as a diastereomixture, along with an undesirable product (**14**) in 31% yield. Compound (**13**) was first treated with potassium

permanganate, followed by sodium periodate to give **15**, which was then heated in aqueous $NaHCO_3$ at 80 °C furnishing **16**. Since **16** was stable under the alkaline and even acidic conditions,[4] dehydrated product (**17**) was obtained after a further activation of the hydroxyl group.

Scheme II[a]



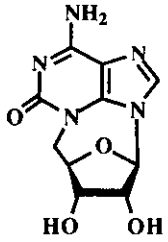
[a]Reagents and conditions: a) methyl acrylate, Et_3N, $(PhCN)_2PdCl_2$ in MeCN, 100 °C, 14 h, b) O_3 in MeOH, -78 °C, then Me_2S; c) vinylmagnesium bromide in THF, -40 °C, 3.5 h; d) DAST in CH_2Cl_2, -15 °C, 1 h; e) $KMnO_4$, 18-crown-6 in aqueous THF, 1 h, then $NaIO_4$ in CH_2Cl_2-H_2O, 17 h; f) 5% aqueous $NaHCO_3$-$CHCl_3$, 80 °C, 1 h; g) Ac_2O, DMAP in pyridine, room temperature, then 100 °C; h) 75% aqueous TFA, room temperature, 1 h.

Compound (**16**) was treated with Ac_2O in the presence of catalytic amount of DMAP in pyridine at room temperature, and then the reaction mixture was heated at 100 °C to complete dehydration to give desired **17** in good yield. Compound (**17**) was then deprotected by aqueous trifluoroacetic acid to give 3-fluoro-3-deazainosine

(**18**), quantitatively.

As a next step, the conformational properties of 3-halo-3-deazainosines (**6-8** and **18**), inosine, and 3-deazainosine (**1**) in comparison with N^3,5'-anhydroisoguanosine (**19**)[7] and 2'-deoxywyosine (**20**),[8] which are used as *syn*-fixed and *anti*-fixed model nucleosides (Figure 1), respectively by Rosemeyer *et al.* for their nuclear Overhauser effect (nOe) measurements, were analyzed by ^{1}H nmr spectroscopy.[7] Sugar puckerings of these nucleosides were calculated using the correlation between coupling constants ($J_{1',2'}$ and $J_{3',4'}$) and showed as percentage of C2'-endo conformer.[9] The results of the nOe experiments and coupling constants are listed in Table 1.

Figure 1. Structures of conformationally fixed nucleosides.



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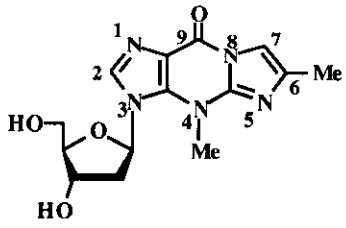

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Table 1. Results of ^{1}H nmr and nOe experiments on 3-deazainosine derivatives.

	19	**20**	**inosine**	**1**	**18**	**6**	**7**	**8**
nOe of H-1' (%)[a,b]	7.8	1.1	5.1	5.2	2.4	1.0	0.6	0.6
H-2'	0	9.4	4.7	3.3	4.8	7.8	10.1	10.8
H-3'	0	3.0	0.9	0.8	0.8	1.5	1.4	1.8
H-2'+H-3' (%)	0	12.4	5.6	4.1	5.6	9.3	11.5	12.6
$J_{1',2'}$ (Hz)[b]			5.4	6.6	5.7	5.0	5.0	5.5
$J_{3',4'}$ (Hz)[b]			3.9	3.3	3.4	3.8	3.8	3.3
C2'-endo (%)			60	70	60	60	60	60

[a]On irradiation of H-2 or H-8 (purine numbering). [b]Measured in DMSO-d_6 (0.05 M, 400 MHz).

When irradiated at H-8 of the *syn*-fixed **19** and at H-2 of the *anti*-fixed **20**, nOes were observed at H-1' (1.1%) and [H-2'+H-3'] (12.4%) for **20**, while for **19**, only at H-1' (7.8%). Since inosine and **1** showed nOe values at both H-1' and [H-2'+H-3'] in almost equal amounts, it is clear that these nucleosides freely rotate around their glycosyl linkages. In both **7** and **8**, a similar tendency of nOe values at H-1' and [H-2'+H-3'] to **20** was observed and these nucleosides are rather fixed at *anti*-conformational ranges. Further, in 3-chloro derivative

(**6**), the nOe value at [H-2'+H-3'] reduced slightly with reducing the van der Waals radius of the substituent at the 3-position but the nOe at H-1' was hardly observed. Therefore, it was suggested that **6** was also fixed at *anti*-conformational ranges. However, in the case of 3-fluoro derivative (**18**), a ratio of the values [H-1'/H-2'+H-3'] is increased and rotation around the glycosyl linkage in **18** are more flexible than those in the other 3-halo derivatives. As we previously reported that 3-alkyl-3-deazainosines were fixed in *anti*-regions, by nOe and X-ray crystallographic analysis,[10] steric hindrance of the substituents at the 3-position of 3-deazainosine would largely influence the free rotation around the glycosyl linkage. Furthermore, the predominant sugar puckering of all 3-halo-3-deazainosines (**6-8** and **18**) was the C2'-endo conformation and is quite similar to those of inosine and **1**.

We also measured a pK_a value of N^1H of **1**, **6-8**, and **18**, compared with inosine. The pK_a value of inosine was 9.1, while that of **1** was calculated as 13.1. The effects of the nitrogen atom at the 3-position influenced these differences. Introduction of the halogen atoms at the 3-position of **1** increased the acidity of the N^1H to about two pK_a units [pK_a values; **6** (11.1), **7** (11.3), **8** (11.7), and **18** (11.2)]. From these properties together with conformational analysis data, 3-chloro-, bromo-, and iodo-3-deazainosines (**6-8**) would be good model compounds for studying nucleoside-enzyme interactions with fixed glycosyl torsion angles in the *anti*-region, flexible sugar conformation, and the pK_a at the N^1H close to inosine. On the other hand, 3-fluoro-3-deazainosine (**18**) would also be a good probe for such studies with a free rotational model around the glycosyl bond.

In conclusion, introduction of the halogens (chloro, bromo, and iodo) into the 3-position of 3-deazainosine forces the fixation of the glycosyl torsion angle in the *anti*-region but does not influence their sugar puckering abnormally. Therefore, they would be useful model compounds to understand the conformational aspects of nucleoside-enzyme interactions. Further synthesis of 3-halo-3-deazaadenosines and 3-deazaguanosines having halogen substituents at the 3-position and the use of these analogues for enzyme reactions will be reported in due course.

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10. In the crystal state, the glycosidic torsion angle of 3-methyl-3-deazainosine was -79 ° which indicated the glycosidic conformation is in the *anti* (χ -180 ° ~ -60 °), especially *high anti* (χ: -90 ° ~ -60 °) region. Y. Yamagata, M. Kato, S. Fujii, M. Aoyagi, N. Minakawa, and A. Matsuda, *Nucleosides Nucleotides*, 1994, **13**, 1327.

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