

**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<sup>#, 1</sup>**

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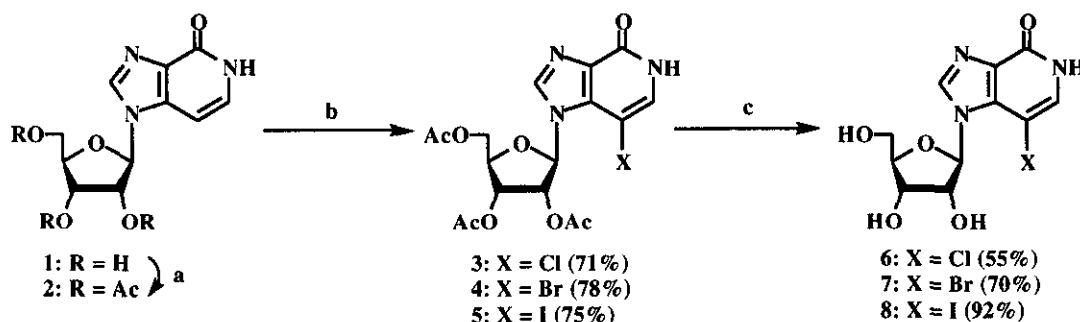
**Abstract** - Synthesis of 3-chloro-, bromo-, and iodo-3-deazainosines (**6-8**) can be done by treatment of the 3-deazainosine derivative (**2**) with *N*-halosuccinimides. Treatment of the 5-formylimidazole derivative (**11**) with vinylmagnesium bromide gave 5-(1-hydroxy-2-propenyl)imidazole derivative (**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.<sup>2</sup> In a previous paper,<sup>3</sup> 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.

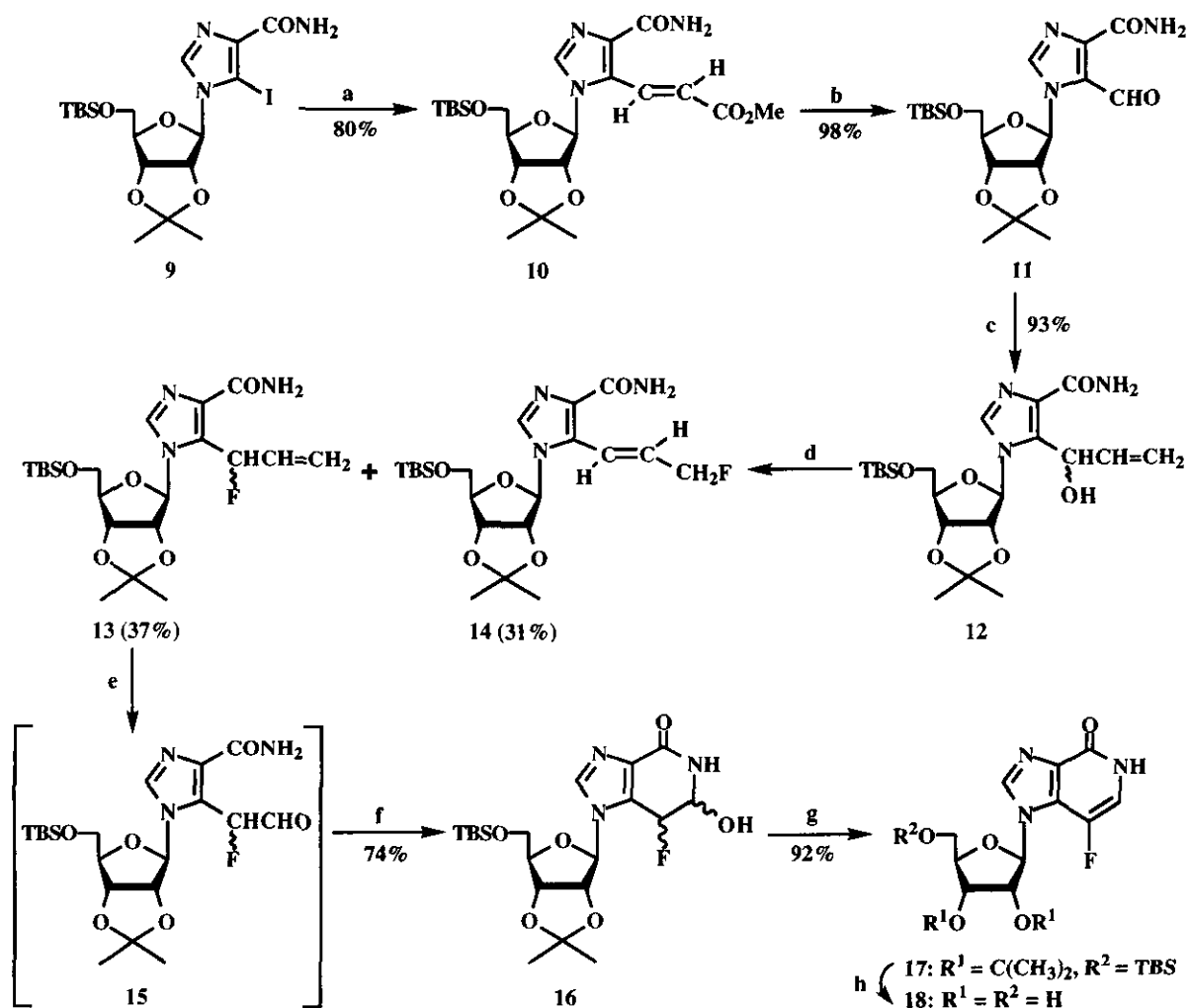
their sugar puckering. However, 3-deazainosine itself and its alkylated derivatives at the 3-position appreciably alter physico-chemical properties such as  $pK_a$  values for the base moiety. In this communication, we describe a synthesis and conformational analysis of 3-halo-3-deazainosines, which 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<sup>a</sup>

<sup>a</sup>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**<sup>4</sup> 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<sup>5</sup> and  $F_2$  gas, or a halogen-exchange reaction<sup>6</sup> 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  $\text{NaHCO}_3$  at  $80^\circ\text{C}$  furnishing **16**. Since **16** was stable under the alkaline and even acidic conditions,<sup>4</sup> dehydrated product (**17**) was obtained after a further activation of the hydroxyl group.

Scheme II<sup>a</sup>

<sup>a</sup>Reagents and conditions: a) methyl acrylate,  $\text{Et}_3\text{N}$ ,  $(\text{PhCN})_2\text{PdCl}_2$  in  $\text{MeCN}$ ,  $100^\circ\text{C}$ , 14 h; b)  $\text{O}_3$  in  $\text{MeOH}$ ,  $-78^\circ\text{C}$ , then  $\text{Me}_2\text{S}$ ; c) vinylmagnesium bromide in  $\text{THF}$ ,  $-40^\circ\text{C}$ , 3.5 h; d) DAST in  $\text{CH}_2\text{Cl}_2$ ,  $-15^\circ\text{C}$ , 1 h; e)  $\text{KMnO}_4$ , 18-crown-6 in aqueous  $\text{THF}$ , 1 h, then  $\text{NaIO}_4$  in  $\text{CH}_2\text{Cl}_2$ - $\text{H}_2\text{O}$ , 17 h; f) 5% aqueous  $\text{NaHCO}_3$ - $\text{CHCl}_3$ ,  $80^\circ\text{C}$ , 1 h; g)  $\text{Ac}_2\text{O}$ , DMAP in pyridine, room temperature, then  $100^\circ\text{C}$ ; h) 75% aqueous TFA, room temperature, 1 h.

Compound (**16**) was treated with  $\text{Ac}_2\text{O}$  in the presence of catalytic amount of DMAP in pyridine at room temperature, and then the reaction mixture was heated at  $100^\circ\text{C}$  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*<sup>3</sup>,5'-anhydroisoguanosine (19)<sup>7</sup> and 2'-deoxywyosine (20),<sup>8</sup> 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 <sup>1</sup>H nmr spectroscopy.<sup>7</sup> 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.<sup>9</sup> The results of the nOe experiments and coupling constants are listed in Table 1.

Figure 1. Structures of conformationally fixed nucleosides.

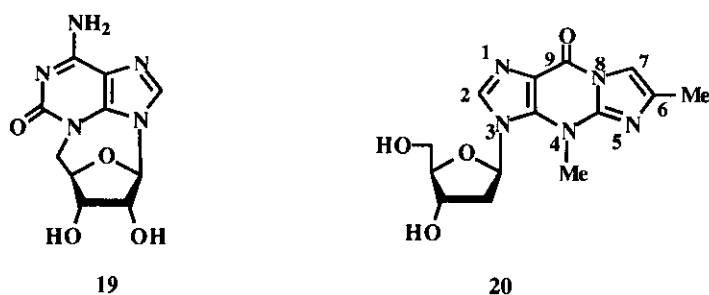


Table 1. Results of <sup>1</sup>H nmr and nOe experiments on 3-deazainosine derivatives.

	19	20	inosine	1	18	6	7	8
nOe of H-1' (%) <sup>a,b</sup>	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) <sup>b</sup>			5.4	6.6	5.7	5.0	5.0	5.5
$J_{3,4}$ (Hz) <sup>b</sup>			3.9	3.3	3.4	3.8	3.8	3.3
C2'-endo (%)			60	70	60	60	60	60

<sup>a</sup>On irradiation of H-2 or H-8 (purine numbering). <sup>b</sup>Measured in DMSO-*d*<sub>6</sub> (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,<sup>10</sup> 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<sub>a</sub> value of N<sup>1</sup>H of **1**, **6-8**, and **18**, compared with inosine. The pK<sub>a</sub> 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<sup>1</sup>H to about two pK<sub>a</sub> units [pK<sub>a</sub> 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<sub>a</sub> at the N<sup>1</sup>H 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.

## REFERENCES AND NOTES

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

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