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Nucleosides and Nucleotides. 115. Synthesis of 3-Alkyl-3-Deazainosines via Palladium-Catalyzed Intramolecular Cyclization: A New Conformational Lock with the Alkyl Group at the 3-Position of the 3-Deazainosine in *Anti*-Conformation[1]

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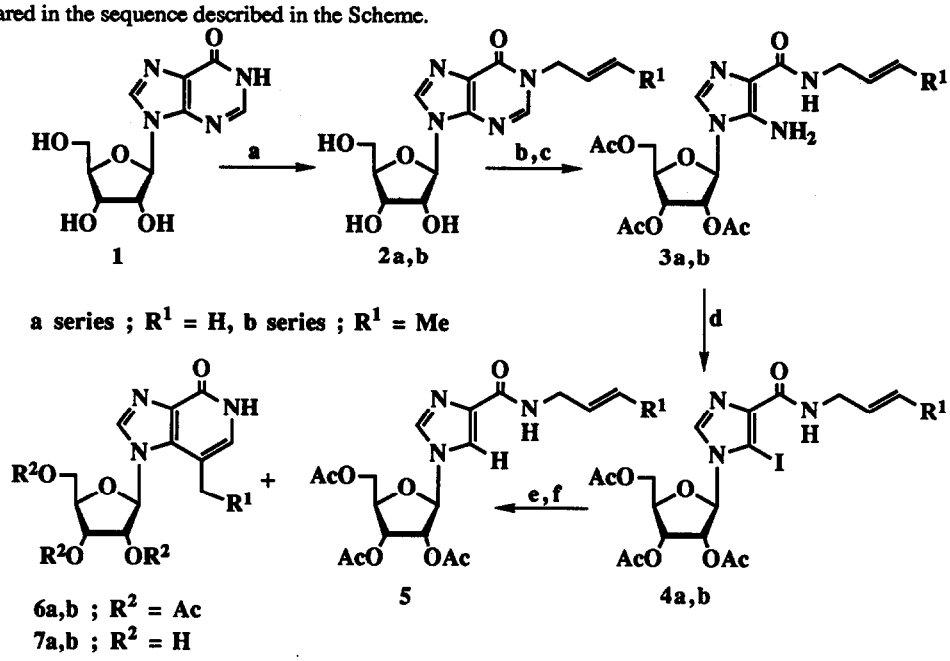
Key Words : Palladium-catalyzed cyclization; allyl amine; nucleoside; conformation; NOE

Abstract: Synthesis of 3-methyl-3-deazainosine (**7a**) and 3-ethyl-3-deazainosine (**7b**) can be done by intramolecular cyclization of 5-iodoimidazole-4-(*N*-allyl and -crotyl)carboxamide ribosides **4a,b** with palladium catalysts. The glycosyl conformer population of **7a,b** was analyzed by NOE experiments to be fixed in *anti*-conformation.

The *anti-syn* conformation of nucleosides around the glycosyl linkage is one of the most important conformational aspects of nucleoside-enzyme interactions acting as substrates or inhibitors. For the stereochemical studies of the interactions, nucleosides with restricted conformations at various glycosyl torsion angles are useful. Such fixation is possible in cyclonucleosides, in which the conformation about the glycosyl bond is constrained by an extra covalent linkage between the sugar and the base.[2,3] These cyclonucleosides cover a wide range of glycosyl torsion angles and the correlation between the direction of sign and magnitude of their CD spectra and the glycosyl torsion angles are well-studied.[2] However, they are rather rigid and the sugar ring is frequently forced to adopt a conformation that is not normally seen in unconstrained nucleosides.[4] Therefore, it would be of interest to devise a new type of conformational lock[5] of nucleosides where the base is still held in a particular region, but where the sugar ring is sufficiently flexible to adopt whatever puckering the enzyme normally imposes on its substrates. As an example of such compounds that fulfill, or partly fulfill, these requirements, we designed 3-deazapurine nucleosides having a bulky substituent at the 3-position, such as 3-methyl-3-deazainosine (**7a**) and 3-ethyl-3-deazainosine (**7b**). These nucleosides would only be restricted rotation around the glycosyl bond by the bulky substituents at the 3-position but the sugar ring conformation would not be largely affected by the substituent. We report in this communication the synthesis of these nucleosides via palladium-catalyzed intramolecular cyclization of 5-iodoimidazole-4-(*N*-allyl and crotyl)carboxamide ribosides, which were readily obtained from a naturally-occurring nucleoside, inosine, and initial conformational studies of **7a,b** in NOE experiments.

To synthesize the target nucleosides via intramolecular Heck reactions[6] using palladium catalysts, 5-iodoimidazole-4-(*N*-allyl and -crotyl)carboxamide ribosides are required as starting materials. When inosine (**1**) was treated with allyl bromide and K_2CO_3 in the presence of 18-crown-6 in DMF, N^1-allylinosine (**2a**) was exclusively obtained in quantitative yield without formation of the corresponding O^6-allyl derivative. Ring opening of the pyrimidine moiety of **2a** was then done using 5 N NaOH in EtOH at reflux temperature, followed by acetylation of the sugar hydroxyls to give 5-aminoimidazole-4-(*N*-allyl)carboxamide derivative **3a** in 55% yield from **2a**, which was further converted into the corresponding 5-iodo derivative **4a** on treatment of **3a** with

isopentyl nitrite in diiodomethane in 41% yield.[7] In a similar way, 4-(*N*-2-crotyl)carboxamide derivative **4b** was prepared in the sequence described in the Scheme.



Reagents and conditions: a) allyl bromide or crotyl bromide, K_2CO_3, 18-crown-6, DMF, r. t. ; b) 5 N NaOH, EtOH, reflux; c) Ac_2O, pyridine, r. t.; d) isopentyl nitrite, CH_2I_2, 100° C; e) $(dba)_3Pd_2CHCl_3$ (10 mol%), Et_3N, DMF, 100° C; f) Et_3N, MeOH, r. t.

The cyclization of **4a** to **6a** with a variety of Pd catalysts ($(dba)_3Pd_2CHCl_3$, $Pd(Ph_3P)_4$, $Pd(OAc)_2$, $Pd(PhCN)_2Cl_2$, etc.) and in solvents (DMF, CH_3CN, or dioxane) was examined. As results, the reaction of **4a** with 10 mol% of $(dba)_3Pd_2CHCl_3$ in the presence of Et_3N (1.5 equiv.) in DMF at 100° C for 24 h gave the best result to furnish the desired cyclized 3-methyl-3-deazainosine derivative **6a** in 63% yield with a trace of **5**. However, when **4b** was treated under similar conditions, it gave only 27% **6b** along with 37% reduced **5**. Treatment of **6a,b** with Et_3N in MeOH gave the target nucleosides **7a,b** in good yields, respectively.[8]

As a next step, the conformations of 3-alkyl-3-deazainosines, in comparison with inosine and 3-deazainosine were analyzed by ^1H NMR spectroscopy. The sugar ring conformation was calculated using the correlation between coupling constants ($J_{1',2'}$ and $J_{3',4'}$) and the C2'-endo/C3'-endo conformer ratio.[9] The *anti-syn* conformation around the glycosyl linkage was estimated according to the calculation (NOE vs. *anti/syn* ratio) proposed by Seela.[10] These results are listed in Table 1.

In purine nucleosides, it is known that *anti* and *syn* conformers are present almost in the same ratio in solution and C2'-endo puckering is slightly predominant over C3'-endo puckering.[11] It was found that the glycosyl conformations of inosine and 3-deazainosine were not constrained around the glycosyl bond in this study but the base moieties of **7a,b** were almost fixed in the *anti*-region due to bulkiness of the substituent at the 3-position. Furthermore, the predominant sugar puckering of **7a,b** was C2'-endo and is quite similar to those of inosine and 3-deazainosine.

Table 1. Estimation of the conformer population of inosine, 3-deazainosine, and 3-alkyl-3-deazainosines (7a,b).

	Inosine	3-Deazainosine	7a	7b
NOE of 1'-H (%)[a,b]	4.7	5.2	0.4	1.1
2'-H (%)	4.2	4.0	6.8	7.3
3'-H (%)	0.8	1.4	1.8	2.1
Anti %	53	58	92	99
$J_{1',2'}$ (Hz)[b]	5.4	6.4	5.4	5.4
$J_{3',4'}$ (Hz)[b]	3.9	2.9	3.4	3.9
C2'-endo (%)	60	70	60	60

[a]On irradiation of H-8 (purine numbering). Values were the mean of three separate experiments. [b]Measured in DMSO-d_6 (0.05 M, 400 MHz).

Although 3-methylinosine, a methyl group being attached to the N^3 position of the base moiety, was synthesized and would be able to function for similar purposes, the glycosyl linkage was reported to be unusually susceptible to acidic hydrolysis.[12] Therefore, stability of the glycosyl linkage of **7a,b** against acid was also examined. When they were incubated in 0.1 N HCl for 48 h at 37° C, none of the corresponding 3-deazapurines was detected by HPLC analyses.

Thus, introduction of the alkyl groups 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, this type of conformational lock fulfills the requirement described above and they would be useful model compounds to understand the conformational aspects of nucleoside-enzyme interactions. Further synthesis of 3-deazaadenosine and 3-deazaguanosine having a bulky substituent at the 3-position and the use of these analogues for enzyme reactions will be reported in due course.

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8. **7a:** Mp 207-210° C. EI-MS *m/z* 281 (M^+), 149 (B^++1); UV λ_{max} (H_2O) 261 nm (ε 8,500); UV λ_{max} (0.5 N HCl) 277 nm (ε 8,000); UV λ_{max} (0.5 N NaOH) 267 nm (ε 8,800); ^{1}H-NMR (DMSO-d_6) δ 11.04 (1H, br s, NH), 8.37 (1H, s, H-8), 6.91 (1H, d, H-2, $J_{2,NH}$ = 3.9 Hz), 6.00 (1H, d, H-1', $J_{1',2'}$ = 5.4 Hz), 5.33 (1H, br s, 2'-OH), 5.23 (1H, br s, 3'-OH), 5.09 (1H, br s, 5'-OH), 4.30 (1H, dd, H-2', $J_{2',1'}$ = 5.4, $J_{2',3'}$ = 4.9 Hz), 4.09 (1H, dd, H-3', $J_{3',4'}$ = 4.4, $J_{3',2'}$ = 4.9 Hz), 3.94 (1H, dd, H-4', $J_{4',3'}$ = 4.4, $J_{4',5'}$ = 3.4 Hz), 3.67 (1H, dd, H-5'a, $J_{5'a,4'}$ = 3.4, $J_{a,b}$ = 12.2 Hz), 3.57 (1H, dd, H-5'b, $J_{5'b,4'}$ = 3.4, $J_{a,b}$ = 12.2 Hz), 2.34 (3H, s, Me). *Anal.* Calcd for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.38; N, 14.94. Found: C, 51.04; H, 5.14; N, 14.76.
7b: Mp 202-205° C. EI-MS *m/z* 295 (M^+); UV λ_{max} (H_2O) 261 nm (ε 9,300); UV λ_{max} (0.5 N HCl) 276 nm (ε 9,100); UV λ_{max} (0.5 N NaOH) 267 nm (ε 9,900); ^{1}H-NMR (DMSO-d_6) δ 11.12 (1H, br s, NH), 8.39 (1H, s, H-8), 6.88 (1H, d, H-2, $J_{2,NH}$ = 4.9 Hz), 5.92 (1H, d, H-1', $J_{1',2'}$ = 5.4 Hz), 5.55 (1H, br s, 2'-OH), 5.24 (1H, br s, 3'-OH), 5.15 (1H, br s, 5'-OH), 4.32 (1H, dd, H-2', $J_{2',1'}$ = 5.4, $J_{2',3'}$ = 4.9 Hz), 4.10 (1H, dd, H-3', $J_{3',4'}$ = 3.9, $J_{3',2'}$ = 4.9 Hz), 3.95 (1H, dd, H-4', $J_{4',3'}$ = 3.9, $J_{4',5'}$ = 3.4 Hz), 3.66 (1H, dd, H-5'a, $J_{5'a,4'}$ = 3.4, $J_{a,b}$ = 12.2 Hz), 3.57 (1H, dd, H-5'b, $J_{5'b,4'}$ = 3.4, $J_{a,b}$ = 12.2 Hz), 2.75 (2H, m, CH_2CH_3), 1.19 (3H, t, CH_2CH_3, J = 7.3 Hz). *Anal.* Calcd for $C_{13}H_{17}N_3O_5$1/4 H_2O: C, 52.08; H, 5.89; N, 14.02. Found: C, 52.23; H, 5.84; N, 14.08.
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