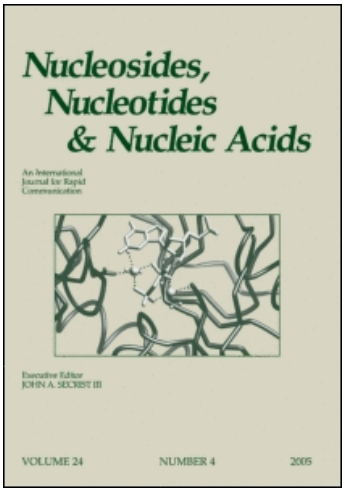

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Synthesis of 2'-*C*-Methyl-β-d-Ribofuranosylimidazo[4,5-d]Pyridazine Derivatives (2-AZA-3-Deazapurine Nucleoside Analogues)

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SYNTHESIS OF 2′-*C*-METHYL-β-D-RIBOFURANOSYLIMIDAZO [4,5-d]-PYRIDAZINE DERIVATIVES (2-AZA-3-DEAZAPURINE NUCLEOSIDE ANALOGUES)

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▫ *In order to evaluate their antiviral properties, two imidazo[4,5-d]pyridazine 2′-C-methyl-β-D-ribofuranonucleoside derivatives have been synthesized.*

Keywords 2′-*C*-Methyl Branched Nucleosides, 2-Aza-3-Deazapurines Derivatives

INTRODUCTION

In the search for improved therapeutic agents against chronic hepatitis C virus (HCV) infection, a purine ribonucleoside analog, 2′-*C*-methyladenosine **1** (Scheme 1), was discovered several years ago as a potent and selective inhibitor in cell culture of a number of related RNA viruses, including bovine viral diarrhea (BVDV), yellow fever (YFV) and West Nile (WNV) viruses.[1,2] Subsequently, the synthesis and biological evaluation of other *C*-branched-sugar nucleoside analogues bearing natural or modified nucleic acid bases have been investigated extensively.[3–7]

We report here the chemical syntheses of two hitherto unknown imidazo[4,5-d]pyridazine 2′-*C*-methyl-β-D-ribofuranonucleoside derivatives, **2** and **3** (Scheme 1). Until now, the few literature reports regarding imidazo[4,5-d]pyridazine nucleoside analogues have dealt only with the ribose series.[8–11]

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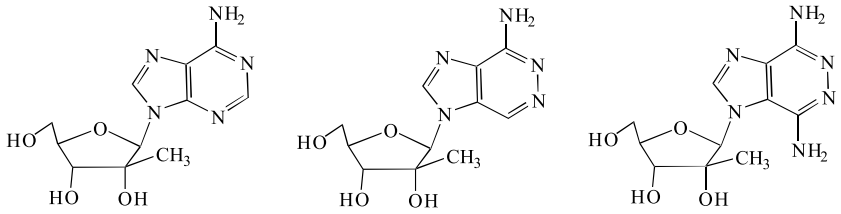
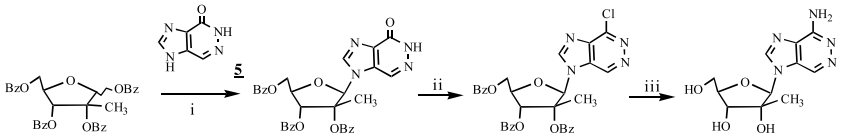


1 **2** **3**

SCHEME 1 2′-C-methyladenosine (**1**) and title compounds (**2**, **3**).



4 **5** **6** (16%) **7** (95%) **2** (13%)

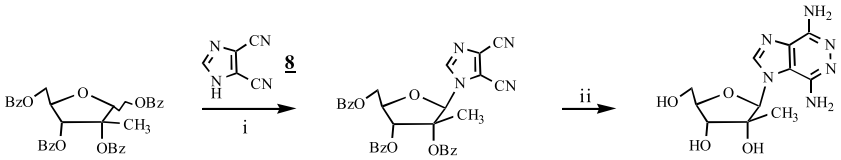
(i) DBU, TMSOTf, CH_3CN, 80°C, 20h. (ii) $POCl_3$, NN-Diethylaniline, reflux, 4h. (iii) NH_3/MeOH, 150°C, 3h.

SCHEME 2 Synthesis of 4-amino-1-(2-C-methyl-β-D-ribofuranosyl)imidazo[4,5-d]pyridazine.

CHEMISTRY

4-Amino-1-(2-*C*-methyl-β-D-ribofuranosyl)imidazo[4,5-d]pyridazine **2** was synthesized by direct glycosylation of imidazo[4,5-d]pyridazin-4-one **5**[12] with 1,2,3,5-tetra-O-benzoyl-2-*C*-methyl-β-D-ribofuranose **4**[13] using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) as coupling agents. The chlorination of **6** followed by ammonolysis led to the desired 2′-*C*-methyl-2-aza-3-deazaadenosine **2** (Scheme 2).

For the synthesis of 2′-*C*-methyl-3-amino-2-aza-3-deazaadenosine **3**, the 4,5-dicyanoimidazole **8**[14] was proved to be a useful starting material. Reaction of **8** with 1,2,3,5-tetra-*O*-benzoyl-2-C-methyl-β-D-ribofuranose **4**[13] in the presence of



4 **8** **9** (62%) **3** (15%)

(I) DBU, TMSOTf, CH_3CN, 60°C, 1h. (II) NH_2-NH_2,H_2O, acetic acid, 75°C, 1.5h.

SCHEME 3 Synthesis of 4,7-diamino-1-(2-C-methyl-β-D-ribofuranosyl)imidazo[4,5-d] pyridazine.

DBU and TMSOTf gave the protected compound **9**. The ring closure of **9** was carried out with hydrazine hydrate in acetic acid to give the desired 2′-*C*-methyl-3-amino-2-aza-3-deazaadenosine **3** (15% yield) (Scheme 3).

CONCLUSION

An original synthetic method using DBU/TMSOTf as coupling agent and imidazo[4,5-d] pyridazin-4-one has been described for the synthesis of 2′-*C*-methyl-2-aza-3-deazaadenosine **2**. A simple synthesis of 2′-*C*-methyl-3-amino-2-aza-3-deazaadenosine **3** has been accomplished starting from 4,5-dicyanoimidazole. The biological evaluation of these two imidazo[4,5-d]pyridazine 2-*C*-methyl-β-D-ribofuranonucleosides is currently in progress.

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