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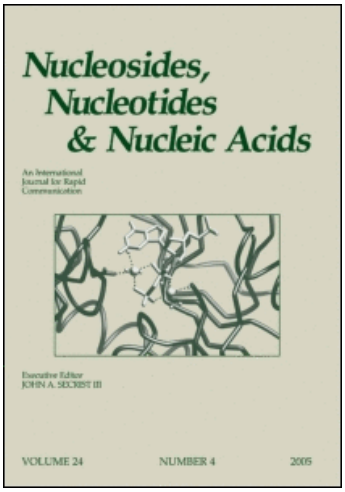

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Synthesis of 2-Deoxy-β-D-ribose 1-Phosphate, NMR Comparison and Its Enzymatic Activity for Structural Elucidation of Synthetic α-Isomer

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Synthesis of 2-Deoxy-β-D-ribose 1-Phosphate, NMR Comparison and Its Enzymatic Activity for Structural Elucidation of Synthetic α-Isomer

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ABSTRACT

2-Deoxy-β-D-ribose 1-phosphate (**1**) was synthesized in a stereoselective manner and isolated with no detectable contamination by its α-isomer (**4**). Explicit configuration of **4** was first determined by NMR comparison with **1** judging from NOE results and their coupling constants. Natural purine nucleoside phosphorylase (PNPase) did not recognize **1** and gave no products such as α- or β-deoxynucleosides.

Key Words: Chemo-enzymatic; 2-Deoxyribose 1-phosphate.

INTRODUCTION

A first stereoselective synthesis of 2-deoxy-α-D-ribose 1-phosphate (**4**)[1] has been established in our laboratory. Since **4** is a substrate for an enzymatic conversion into various 2′-deoxynucleosides (dNus), the result enabled us the development of

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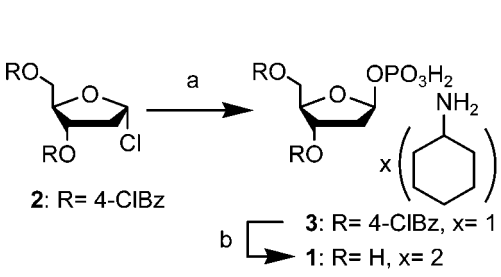

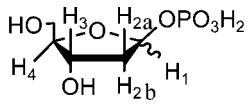

compd	irradiated	enhanced	NOE (%)
1	H_1	H_{2b}	**7.4**
		H_4	**1.7**
	H_4	H_{2b}	**1.3**
		H_1	**2.0**
4	H_1	H_{2a}	**6.2**

Figure 1. Stereoselective synthesis of 2-deoxy-β-D-ribose 1-phosphate (**1**), and NOE results of **1** its α-isomer (**4**).[1] (a) *o*-H_3PO_4, Oct_3N, MEK then c-$C_6H_{11}NH_2$, 84%; (b) c-$C_6H_{11}NH_2$, MeOH, 87%.

scalable processes for dNus.[2] Even though α-selectivity of the synthetic reaction for **4** was significantly high, effects of the residual β-isomer (**1**) against the enzyme had been obscure for us. Therefore, an enzymatic reaction using **1** has been required for a direct evaluation to eliminate subliminal concern with the possible contamination by the α-isomer of dNus. Additionally, since the absolute configuration of **4** has remained ambiguous,[3] it should be confirmed by spectroscopic analyses by comparing **4** with **1** (Fig. 1).

RESULTS AND DISCUSSION

Nucleophilic substitution of chlorosugar (**2**) is rapid and undergoes inversion. MacDonald's method[3] was modified by using tri(n-octyl)amine (Oct_3N) to increase the solubility of the corresponding H_3PO_4 salt that effectively facilitated the substitution (β:α = 90:10). Formation of cyclohexylamine (c-$C_6H_{11}NH_2$) salt, followed by recrystallization from MeOH-acetone gave **3** in 84% yield with no detectable α-isomer on HPLC assay. Finally, deprotection by c-$C_6H_{11}NH_2$ in MeOH gave **1** in 87% yield. It rotated $\alpha_D^{25} = -22.2°$ (c 3, H_2O) (lit.[3] $\alpha_D^{20} = -15.8°$ (c 1.2, H_2O)). NMR experiments of **1** and **4**,[1] such as Nuclear Overhauser Effect (NOE) and ^1H–^1H spin decoupling supported the absolute configuration proposed by MacDonald that was based on the analogous property with α- and β-D-ribose. In enzymatic reaction using adenine, **1** was not recognizable by natural PNPase and gave neither α- nor β-dNus.

In summary, we showed the synthesis of **1** with no contamination by **4**. The result allowed us to confirm the absolute configuration of **1** and **4**, and to certify that **1** was not recognizable by natural PNPase.

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