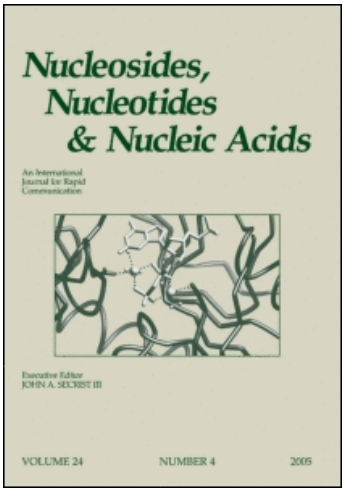

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LARGE-SCALE MANUFACTURING OF ALL FOUR 2′-DEOXYNUCLEOSIDES VIA NOVEL STRATEGIES INCLUDING A CHEMO-ENZYMATIC PROCESS

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ABSTRACT

A chemical synthesis of 2-deoxyribose-1-phosphate **2** and its enzymatic conversion into purine 2′-deoxynucleosides (dNus) are shown. Besides the chemo-enzymatic process for purine dNus, a modified process for practical dC preparation is also established. Consequently, a series of practical manufacturing processes of all four dNus have been realized via novel strategies.

Due to the recent success with clinical development of antisense drugs, demand for 2′-deoxynucleosides (dNus) is increasing rapidly. The dNus are key raw materials for the preparation of antisense drugs. Since current supply completely depends on salmon milt, development of an effective large-scale production method that avoids the dependence of such natural resources has been an important objective for us. Although, thymidine is presently synthesized in a large scale all over the world including our plant, synthesis of 2′-deoxycytidine (dC) **7** requires alternative chemistry for its scale-up. Furthermore, the synthesis of purine dNus still remains a practical challenge using strategies reported in the literature (1).

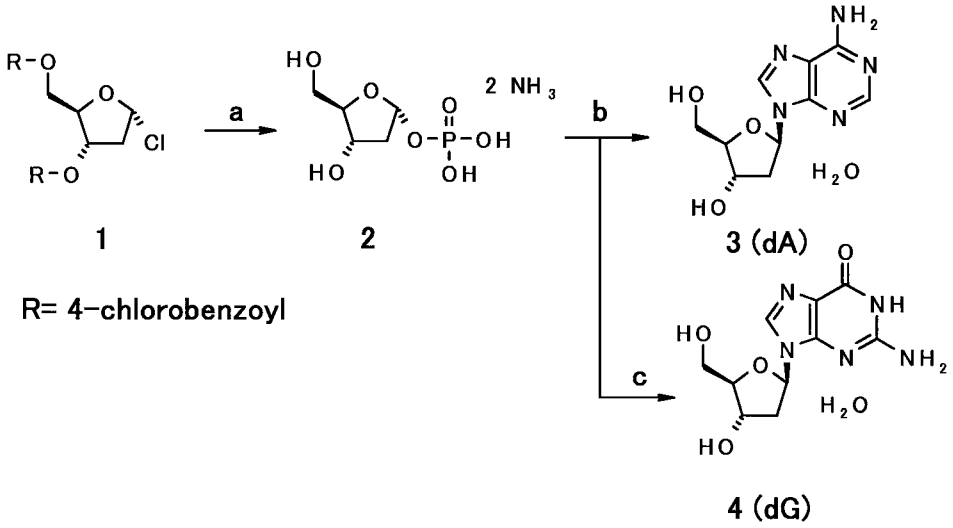

Figure 1. **a**, 1) phosphate; 2) hydrolysis, 63%; **b**, adenine, PNPase, 82%; **c**, guanine, PNPase, 72%.

Chemo-Enzymatic Process for dA and dG (Fig. 1)

Preparation of purine dNus, dA **3** and dG **4** is a practical challenge since the reaction of purine base and activated 2-deoxyribose produces both anomeric and regio-isomers (1). A combination of chemical synthesis of enzymic substrate **2** and its enzymatic conversion (2) has realized a practical way for the manufacturing of dA and dG. Thus, a phosphate addition to 3, 5-*O*-bis(4-chlorobenzoyl)-2-deoxyribosyl-1-chloride **1** followed by hydrolysis afforded **2** in 63% isolated yield. Following enzymatic conversion of the synthetic 2-deoxyribose-1-phosphate **2** using purine nucleoside phosphorylase (PNPase) gave dA **3** or dG **4** as a single product in 82% and 72% isolated yields, respectively. Optimization of the reaction conditions and the reaction mechanism are further investigated. Their details will be reported elsewhere.

A Practical Method for dC Preparation (Fig. 2)

Many experimental applications have been reported for preparation of various dC derivatives (3). However, they weren't suitable to manufacture of dC **7** for practical reasons like the requirement of excess reagents, slow reaction, or requirement of high-dilution conditions. An alteration of conventional reactive amines into N-methylpiperidine has accelerated the reaction rate enough to establish a manufacturing method for dC **7**. Thus, dC **7** was synthesized through an ammonolysis step (**5** → **6**) in 53% isolated total yield starting from **1**.

In summary, a series of practical manufacturing processes of dNus are demonstrated. For purine dNus, a chemo-enzymatic strategy using a practically applicable

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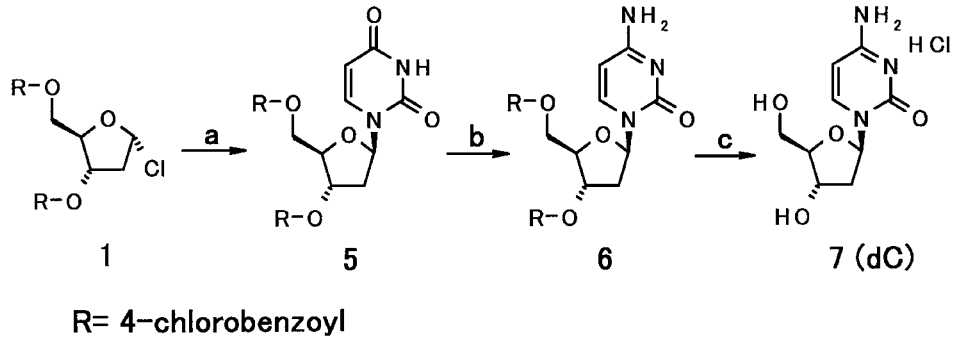

Figure 2. **a**, persililated uracil; **b**, 1) TsCl, TEA, N-methylpiperidine; 2) NH_4OH, 55%; **c**, hydrolysis then HCl, 96%.

process resulted in an anomer-specific conversion into dA **3** or dG **4**. By a modified synthetic method, dC **7** was prepared in a practical way.

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