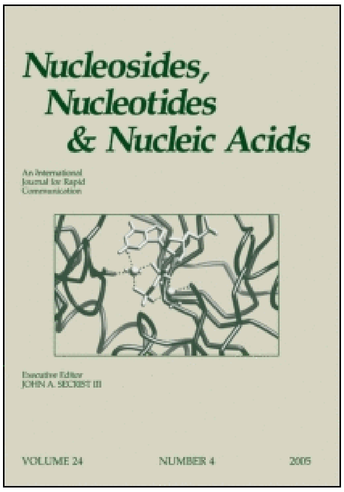

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Stereoselective Synthesis of Conformationally Rigid Apio Carbanucleosides as Potential Antiviral Agents

Hyung Ryong Moon[a]; Kyung Ran Kim[a]; Bum Tae Kim[b]; Ki Jun Hwang[b]; Moon Woo Chun[c]; Lak Shin Jeong[d]
[a] College of Pharmacy, Pusan National University, Pusan, Korea [b] Department of Chemistry, Chonbuk National University, Chonju, Korea [c] College of Pharmacy, Ewha Womans University, Seoul, Korea [d] College of Pharmacy, Seoul National University, Seoul, Korea

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STEREOSELECTIVE SYNTHESIS OF CONFORMATIONALLY RIGID APIO CARBANUCLEOSIDES AS POTENTIAL ANTIVIRAL AGENTS

Hyung Ryong Moon and Kyung Ran Kim ▫ *College of Pharmacy, Pusan National University, Pusan, Korea*

Bum Tae Kim and Ki Jun Hwang ▫ *Department of Chemistry, Chonbuk National University, Chonju, Korea*

Moon Woo Chun ▫ *College of Pharmacy, Ewha Womans University, Seoul, Korea*

Lak Shin Jeong ▫ *College of Pharmacy, Seoul National University, Seoul, Korea*

▫ *Apio north-methanocarbocyclic nucleosides* **1–3** *with bicyclo[3.1.0]hexane template were first synthesized. Introduction of hydroxymethyl substituent was efficiently and stereoselectively accomplished by aldol and retro-aldol reaction and fixed conformation was achieved from a modified Simmons-Smith cyclopropanation on a cyclopentane ring.*

INTRODUCTION

Due to the lack of anomeric effect and *gauche* effect, carbocyclic nucleosides have a different conformation at the sugar moiety from that of conventional nucleosides and have seldom showed biological activities. Conventional nucleosides exist in the equilibrium between *south* and *north* conformations in solution. Since it has been suggested that conformation in sugar moiety of nucleosides was closely related with their biological activities, a number of nucleosides with a fixed conformation have been synthesized and evaluated for antiviral activity to identify relationships between conformation and biological activity. Among them, the representative is the nucleoside built on bicyclo[3.1.0]hexane template,[1] which exists in one conformation, *north* or *south*, and the nucleoside analogues showed significant antiviral activity. As a part of efforts to search for antiviral agents with better biological profile, several groups including our laboratory have studied on

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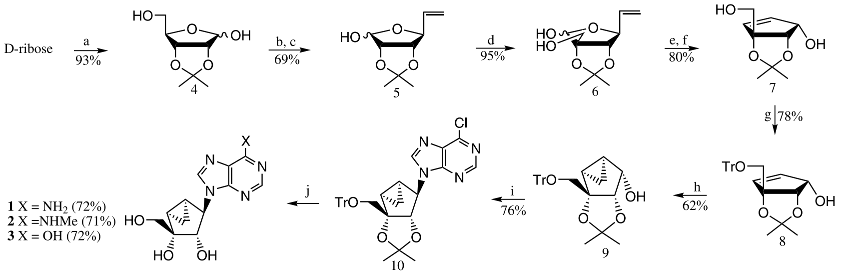
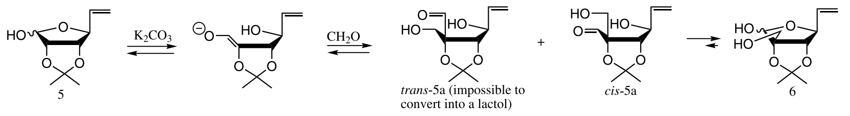
Address correspondence to Hyung Ryong Moon, College of Pharmacy, Pusan National University, Pusan 609-735, Korea.



SCHEME 1 Reagents and conditions: (a) acetone, conc. H_2SO_4, rt, 2.5 h; (b) vinylmagnesium bromide, THF, -78°C to 0°C, 3 h; (c) $NaIO_4$, CH_2Cl_2, H_2O, 0°C to rt, 40 min; (d) K_2CO_3, 37% CH_2O, MeOH, 80°C, 36 h; (e) CH_3PPh_3Br, KO*t*-Bu, THF, rt, overnight; (f) Grubbs catalyst 2nd generation, CH_2Cl_2, rt, 2 h; (g) TrCl, DMAP, pyridine, rt, 20 h; (h) Et_2Zn, CH_2I_2, CH_2Cl_2, rt, 9 h; (i) 6-chloropurine, PPh_3, DEAD, THF, 42°C, 4 h; (j) NH_3/MeOH, 80°C, 8 h, then 50% aq. CF_3CO_2H, THF, rt, 4 d for **1**; 40% methylamine, MeOH, 80°C, 5 h, then 50% aq. CF_3CO_2H, THF, rt, 4 d for **2**; 1N HCl, 1,4-dioxane, reflux, overnight for **3**.



SCHEME 2 The plausible mechanism of hydroxymethylation reaction.

the syntheses and biological activities of apio and isonucleosides. In addition to isonucleosides, apio nucleosides have been reported to show better stability in acidic conditions and potent biological activity.[2] On the basis of the hypothesis that the fix of conformation in sugar moiety of carbocyclic nucleosides may elicit a biological activity lost and the fact that apio nucleosides have potent biological activity with an increased stability under acidic conditions, we designed and synthesized apio *north*-methanocarbocyclic nucleosides **1**, **2**, and **3**. Lactol **5** was obtained starting from D-ribose via stereoselective Grignard reaction. In order to synthesize apio-type sugar hydroxymethyl substituent was introduced at the C2-position of **5** in stereoselective manner,[3] as shown in Scheme 1. The expected mechanism may be explained, as depicted in Scheme 2. Carbocyclic sugar **7** was synthesized by RCM reaction using second generation Grubbs catalyst and stereoselective fusion of cyclopropane on a cyclopentane ring to fix conformation was achieved by a modified Simmons-Smith cyclopropanation reaction using diethyl zinc and diiodomethane. The final apio carbanucleosides were synthesized via Mitsunobu reaction as a key step. The antiviral assay of the final nucleosides **1**–**3** is in progress and will be reported in due course.

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