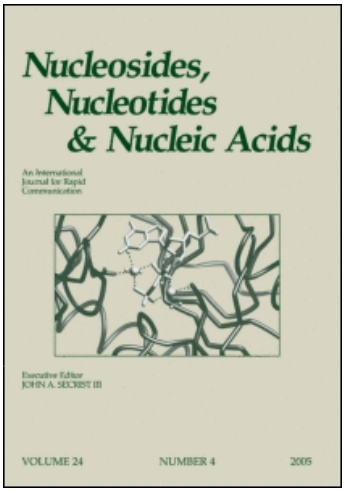

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Moon Woo Chun[a]; Myung Jung Kim[a]; Un Hee Jo[a]; Joong Hyup Kim[b]; Hee-Doo Kim[c]; Lak Shin Jeong[d]
[a] College of Pharmacy, Seoul National University, Seoul, Korea [b] Korea Institute of Science and Technology, Seoul, Korea [c] College of Pharmacy, Sookmyung Women's University, Seoul, Korea [d] College of Pharmacy, Ewha Womans University, Seoul, Korea

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SYNTHESIS OF NOVEL D- AND L-3′-DEOXY-3′-*C*-HYDROXYMETHYL NUCLEOSIDE WITH EXOCYCLIC METHYLENE AS POTENTIAL RIBONUCLEOTIDE REDUCTASE INHIBITOR

Moon Woo Chun,[1,*] Myung Jung Kim,[1] Un Hee Jo,[1] Joong Hyup Kim,[2] Hee-Doo Kim,[3] and Lak Shin Jeong[4]

[1]College of Pharmacy, Seoul National University, Seoul 151-742, Korea
[2]Korea Institute of Science and Technology, Seoul 136-791, Korea
[3]College of Pharmacy, Sookmyung Women's University, Seoul 140-742, Korea
[4]College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea

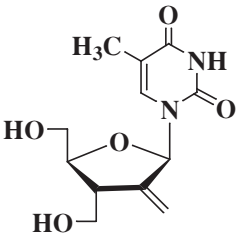
ABSTRACT

D- and L-3′-Deoxy-3′-*C*-hydroxymethyl thymidine substituted with exocyclic methylene at 2′-position were synthesized, starting from D- and L-xylose as potential ribonucleotide reductase inhibitor, respectively, but they were found to be inactive against several tumor cell lines.

INTRODUCTION

Ribonucleotide reductase (1) catalyzes the conversion of ribonucleotides to the 2′-deoxyribonucleotides and has been regarded as an attractive target for the development of antitumor agents. Among compounds reported, 2′-deoxy-2′-vinyl-substituted nucleoside (2) has been known to act as ribonucleotide reductase

*Corresponding author.



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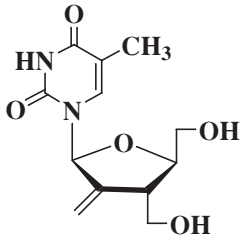

ent-1

inhibitor and its spirocyclopropyl (3) or difluoro (4) analogue also appears to act as the same inhibitor. Based on the biological activity of 2′-vinyl substituted nucleoside, we were interested in designing and synthesizing the corresponding 3′-homologated derivative. We also synthesized the corresponding L-nucleoside because L-nucleoside sometimes shows better biological activity profile than the corresponding D-nucleoside (5).

Here, we report the synthesis of D- and L-3′-deoxy-3′-*C*-hydroxymethyl nucleoside substituted with exocyclic methylene at 2′-position starting from D- and L-xylose as potential ribonucleotide reductase inhibitor, respectively.

RESULTS AND DISCUSSION

Synthesis of D-thymidine analogue began with D-xylose. D-Xylose was converted to **2** by treating with acetone and conc-sulfuric acid followed by partial hydroysis of diacetonide with 0.2% HCl. Primary hydroxyl group of **2** was protected as TBDPS ether **3**. Oxidation of **3** with PDC and acetic anhydride gave keone **4** which was subjected to the Wittig reaction to yield methylene **5**. Hydroboration-oxidation of **5** gave hydroxymethyl derivative **6** which was treated with tetra-*n*-butylammonium fluoride to give diol **7**. Treatment of diol **7** with benzoyl chloride gave the dibenzoate **8** which was hydrolyzed with 85% formic acid and then successively acetylated to give diacetate **9**. Condensation of diacetate98 with silylated thymine afforded the protected nucleoside **10**. Deprotection of **10** with sodium methoxide gave triol **11** whose primary two hydroxyl groups were silylated with TBDPSCl to give **12**. Oxidation of **12** with PDC yielded ketone **13** which was treated with methyl triphenylphosphonium bromide and *n*-butyl lithium to afford methylene derivative **14**. Desilylation of **14** with tetra-*n*-butylammonium fluoride produced the final D-thymidine analogue **1**. The corresponding L-analogue **ent-1** was synthesized starting from L-xylose according to the same procedure used in the preparation of **1**.

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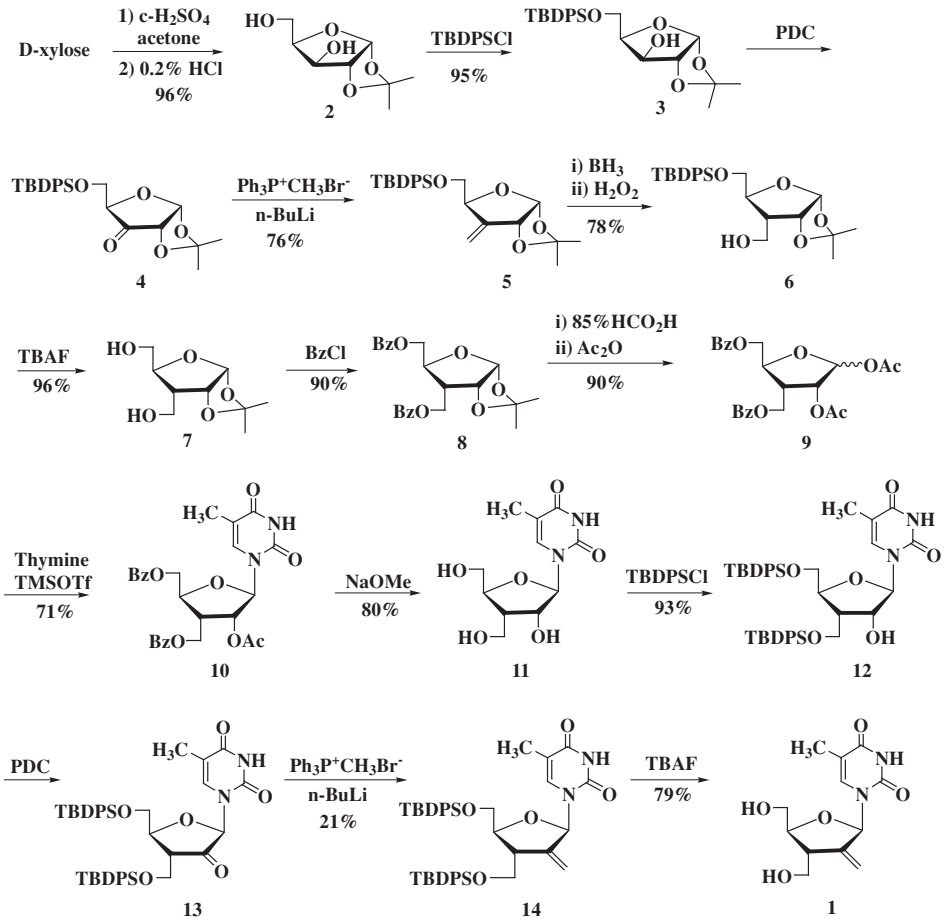

Scheme 1.

The final nucleosides **1** and **ent-1** were tested against several tumor cell lines, but they were found to be inactive in tested cell lines.

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