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## Nucleosides, Nucleotides and Nucleic Acids

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

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

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**ABSTRACT**

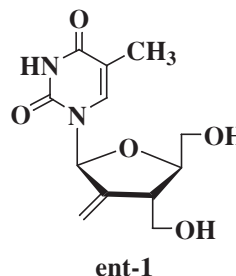
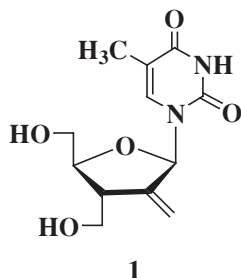
D- and L-3'-Deoxy-3'-C-hydroxymethyl thymidine substituted with exocyclic methylene at 2'-position were synthesized, starting from D- and L-xylose as potential ribonucleotide reductase inhibitor, respectively, but they were found to be inactive against several tumor cell lines.

**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

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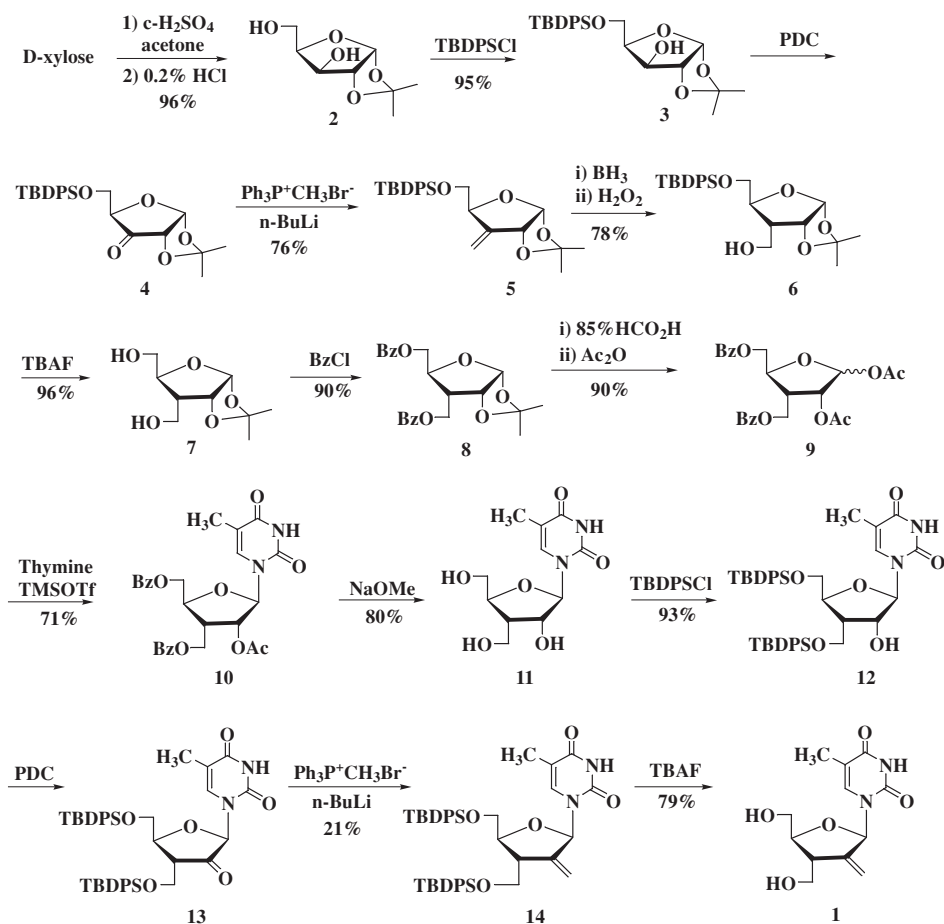
inhibitor and its spirocyclopropyl (**3**) or difluoro (**4**) analogue also appears to act as the same inhibitor. Based on the biological activity of 2'-vinyl substituted nucleoside, we were interested in designing and synthesizing the corresponding 3'-homologated derivative. We also synthesized the 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 hydrolysis of diacetone with 0.2% HCl. Primary hydroxyl group of **2** was protected as TBDPS ether **3**. Oxidation of **3** with PDC and acetic anhydride gave ketone **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 diacetate **9** 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**.





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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