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## Nucleosides, Nucleotides and Nucleic Acids

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## Sulfur Isosteres of Orotidine

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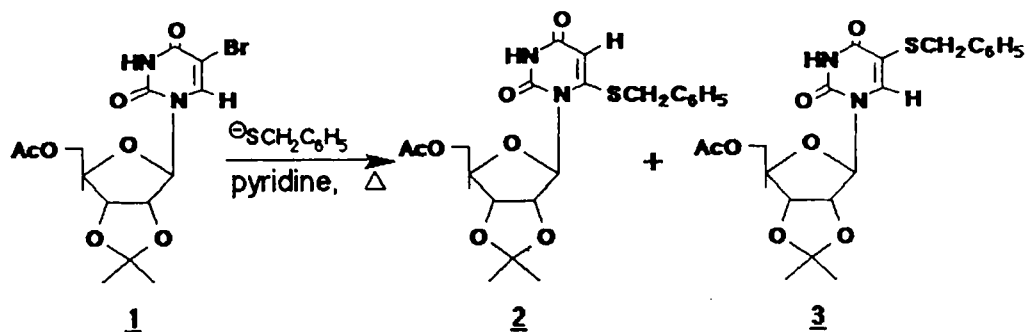
## SULFUR ISOSTERES OF OROTIDINE

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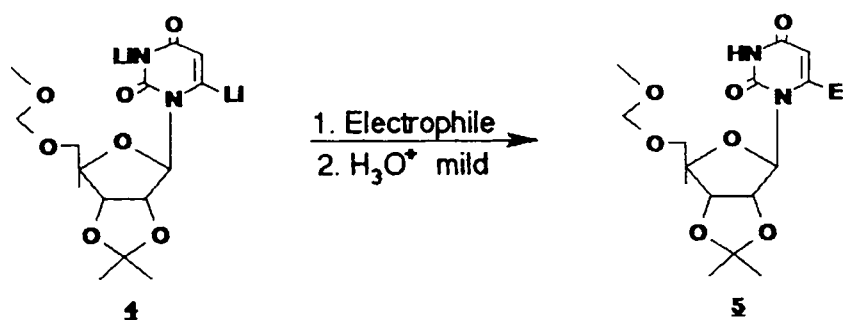
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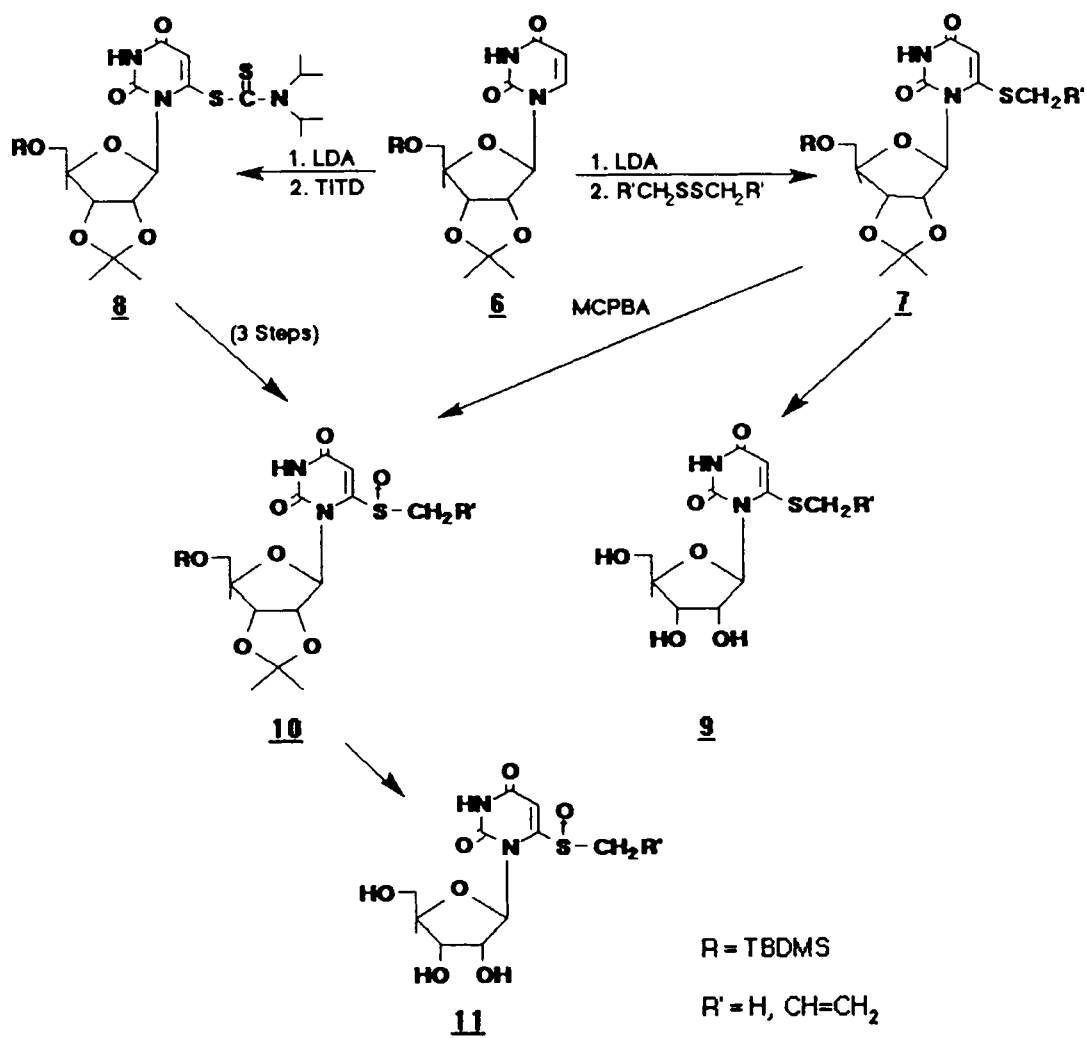
The preparation of 6 - substituted pyrimidine nucleosides has received limited attention and undoubtedly reflects the difficulty in synthesizing nucleosides of this type. Condensation of 6-substituted pyrimidines with suitable sugar derivatives leads to the formation of mixtures of N3 and N1 nucleosides where the N3 isomer usually predominates <sup>1</sup>. This is exemplified by the direct ribosylation of the silyl derivative of 6-methylthiouracil, which furnished only the N3 ribonucleoside <sup>2</sup>. Ueda and coworkers<sup>3</sup> addressed this problem with moderate success. When 5'-O-acetyl-2',3'-O-isopropylidene-5-bromouridine (**1**) was reacted with cyanide ion, a Michael-type addition occurred at C6 with concomitant dehydrobromination to give the corresponding 6-cyanouridine in quantitative yield. Treatment of **1** (Scheme 1) with benzyl mercaptan, however,



Scheme 1



Scheme 2



Scheme 3

furnished a 1:1 mixture of the C6 and C5 isomers 2 and 3 respectively <sup>4</sup>. Attempts to alter the course of this reaction so that 2 predominated met with little success. It is worth mentioning that in our hands when this reaction was scaled-up, 3 predominated (2:3 = 1:4). Also the use of other sulfur nucleophiles, such as <sup>o</sup>SEt, afforded only the C5-substituted derivative <sup>3</sup>. Thus, a new synthetic approach was sought which would furnish only the desired C6-substituted isomer and in reasonable yield.

Tanaka and coworkers <sup>5</sup> have recently demonstrated that metallation of a protected uridine with LDA took place at the C6 position in a regio-specific manner (Scheme 2). The resulting dilithio derivative (4) was then subjected to a variety of carbon electrophiles and one disulfide to provide C6-functionalized uridines. Application of this synthetic methodology in our study has now provided a convenient route to certain sulfur isosteres of orotidine.

The starting material for our project is 2',3'-O-isopropylidene-5'-O-tert-butyldimethylsilyluridine (6, Scheme 3), a nucleoside conveniently prepared from uridine <sup>6</sup>. Preliminary studies have shown that metallation of 6 with LDA in THF at -78 °C followed by treatment with a disulfide furnished a good yield of the C6-thiated product 7, e.g. dimethyl disulfide afforded 7 (where R = H) in 65-70% yield.

Complete deprotection of 7 provided the nucleosides 9. It is noteworthy that 6-methylthiouridine (9, where R = H) prepared by our method is identical to the nucleoside synthesized by Ueda <sup>4</sup>. Oxidation of 7 with MCPBA followed by deprotection afforded the sulfoxide 11. An alternate route to 11 is also being explored via the intermediate 8. This nucleoside has been prepared by reacting 6 with tetra isopropylthiuram disulfide.

#### ACKNOWLEDGEMENTS

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