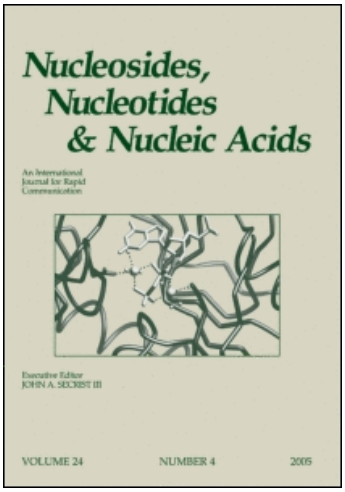

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Sulfur Isosteres of Orotidine

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SULFUR ISOSTERES OF OROTIDINE

BY

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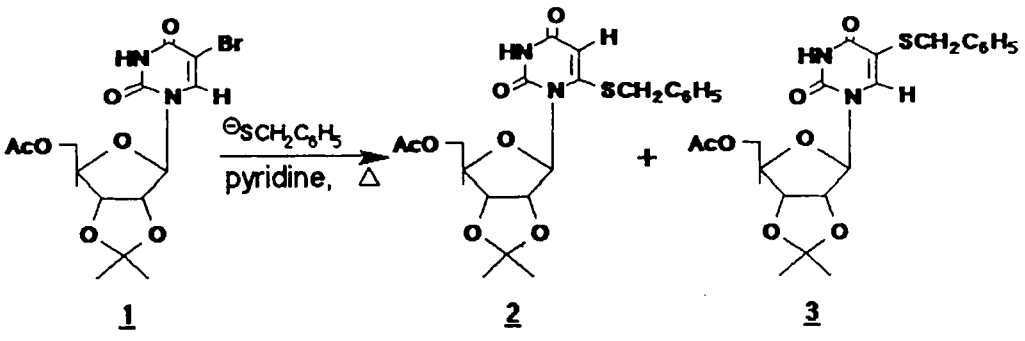
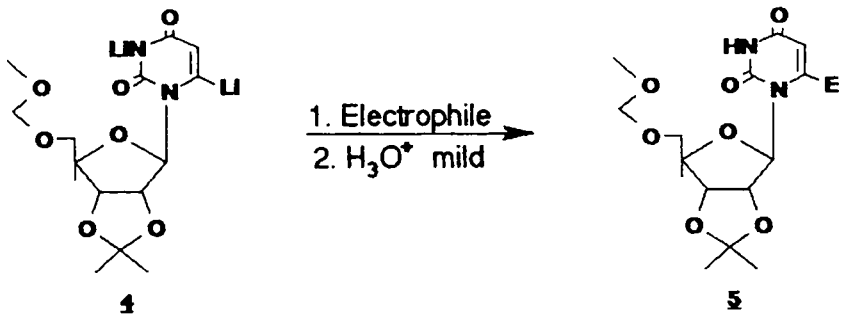
The preparation of 6 - substituted pyrimidine nucleosides has received limited attention and undoubtedly reflects the difficulty in synthesizing nucleosides of this type. Condensation of 6-substituted pyrimidines with suitable sugar derivatives leads to the formation of mixtures of N3 and N1 nucleosides where the N3 isomer usually predominates [1]. This is exemplified by the direct ribosylation of the silyl derivative of 6-methyl-thiouracil, which furnished only the N3 ribonucleoside [2]. Ueda and coworkers [3] addressed this problem with moderate success. When 5'-O-acetyl-2',3'-O-isopropylidine-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,



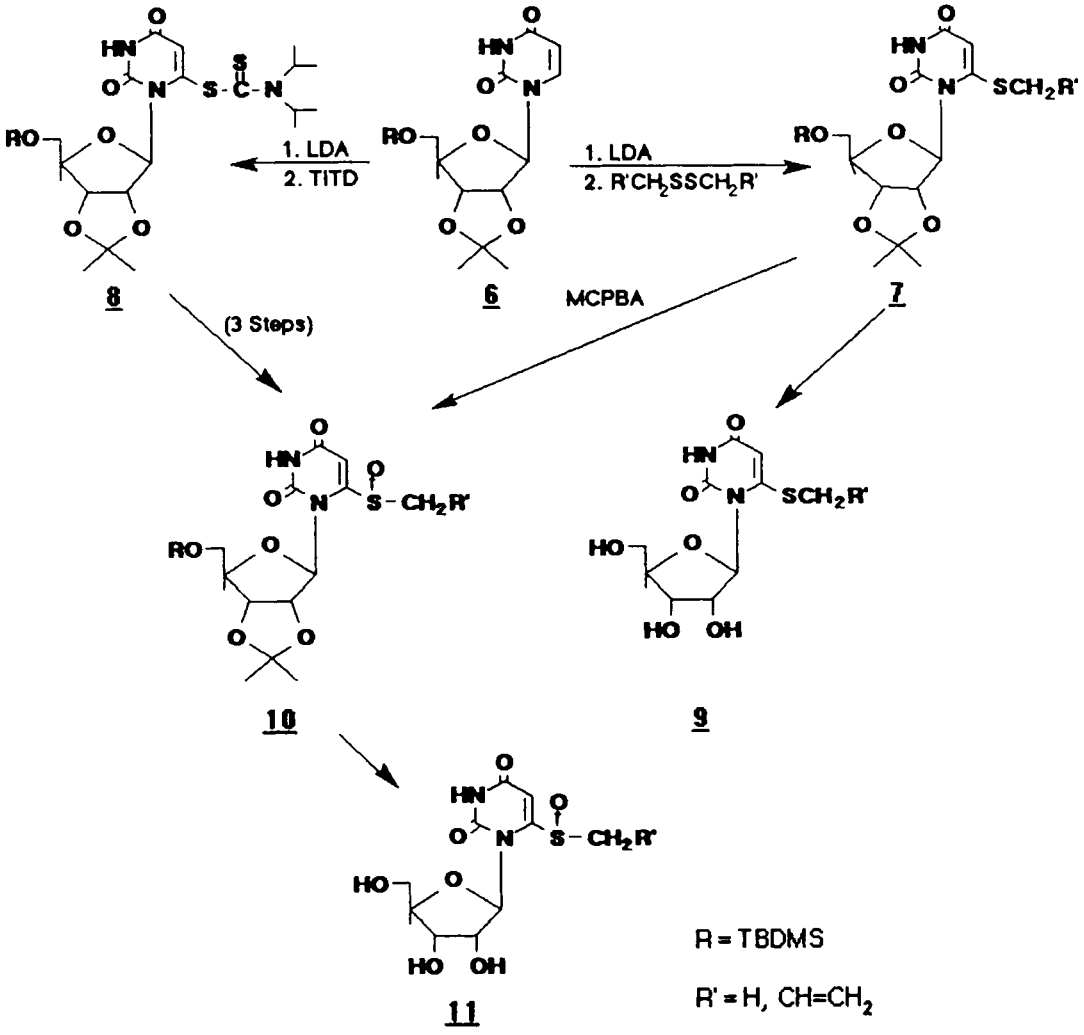
1 2 3

Scheme 1



4 5

Scheme 2



8 6 7 10 9 11

Scheme 3

furnished a 1:1 mixture of the C6 and C5 isomers 2 and 3 respectively[4]. 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 $^{\ominus}$SEt, afforded only the C5-substituted derivative[3]. Thus, a new synthetic approach was sought which would furnish only the desired C6-substituted isomer and in reasonable yield.

Tanaka and coworkers[5] have recently demonstrated that metallation of a protected uridine with LDA took place at the C6 position in a regiospecific 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-isopropylidine-5'-O-tert-butyldimethylsilyluridine (6, Scheme 3), a nucleoside conveniently prepared from uridine[6]. 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[4]. 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.

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