

A practical synthesis of 4'-thioribonucleosides

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Abstract—A practical synthesis of 4'-thioribonucleosides starting from inexpensive L-arabinose is described. 1,4-Anhydro-2,3-O-isopropylidene-4-thioribitol, which was prepared by using a novel reductive ring-contraction reaction, was converted to the 5-O-silylated sulfoxides. The Pummerer-type thioglycosylation of the sulfoxides gave the 4'-thioribonucleosides stereoselectively.
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The replacement of the lactol oxygen of nucleosides with a sulfur atom proved to be an effective modification that permits the preparation of novel nucleoside antimetabolites. 4'-Thionucleosides are attractive candidates for use as both antiviral and antineoplastic agents¹ and, to date, a number of 4'-thionucleosides have been reported.^{1,2} We focused on the design and synthesis of 2'-modified 4'-thionucleosides and found that 4'-thioDMDC^{1g,h} (**1**) and 4'-thioFAC^{1h,3} (**2**, X = F, B = Cyt) had potent antineoplastic activities (Fig. 1).

In addition, we have shown that both 4'-thioarabino-nucleosides⁴ (**2**, X = OH) and 2'-deoxy-2'-fluoro-4'-thioarabinonucleosides⁵ (**2**, X = F) have potent antiherpes virus activities. Despite the unique biological activities of 4'-thionucleosides, the difficulties associated with the synthesis of these analogues have impeded investiga-

tions of structure–activity relationships. Thus, for the production of new 4'-thionucleoside analogues, the development of a suitable synthetic method would be highly desirable. This was the case for the synthesis of 4'-thioDMDC. To synthesize this compound, we explored two new methods: (1) a novel method for constructing the 4-thiosugar portion^{1g,h} and (2) a new coupling reaction of a sulfoxide of the 4-thiosugar portion with persilylated N⁴-acetylcytosine.^{1g,h} The latter thioglycosylation reaction was based on the sila-Pummerer-type reaction originally developed by Kita⁶ and would be applicable to the synthesis of a wide variety of 4'-thionucleoside derivatives including 4'-thioribonucleosides.⁷ This reaction was applied to the synthesis of 4'-thioribonucleosides (**3**). We also planned to synthesize the 4-thioribose moiety via a novel and practical method because the synthesis of the 4-thiosugar portion has often been met with various difficulties. Here, we report on a novel synthesis of the 4-thioribose moiety and the Pummerer-type thioglycosylation of the corresponding sulfoxide with persilylated nucleobases.

To construct the 4-thioribose portion, a novel reductive ring-contraction reaction was developed, in which 1,4-anhydro-4-thio-D-ribitol was synthesized from a 5-thioarabinose derivative: since the synthesis of the D-isomer of 5-thioarabinose **9** was reported by Hughes et al.⁸ We synthesized L-**9** by modifying this method.⁹ Commercially available L-arabinose was treated with acidic methanol to give the 1-methyl arabinoside **4**, and was

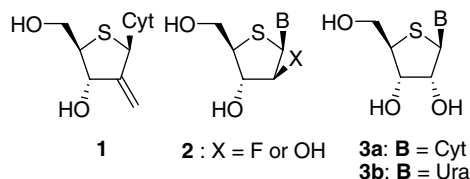


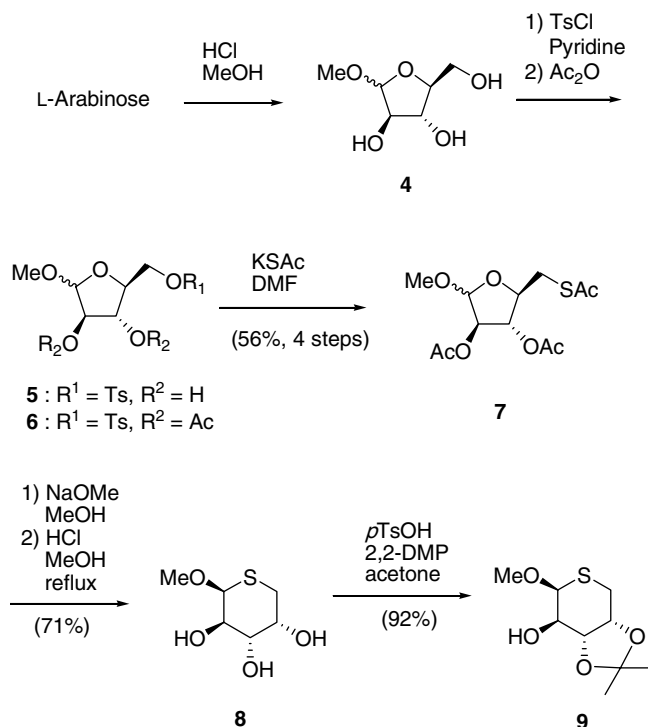
Figure 1.

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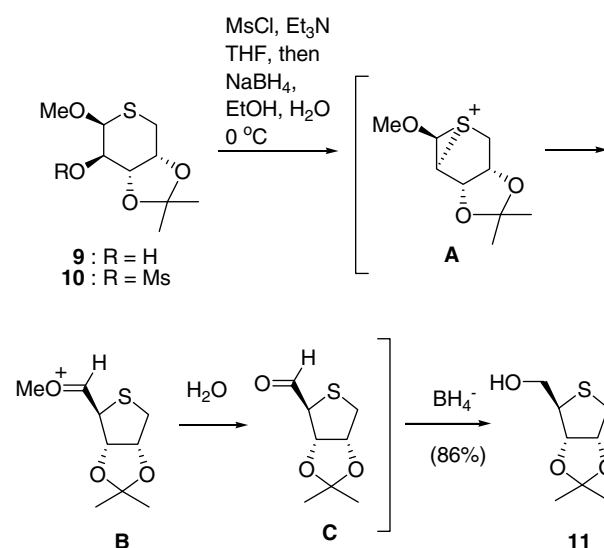
then tosylated at the primary hydroxyl group. The resulting 5-tosylate **5** was acetylated to give **6** in 56% yield from L-arabinose. Nucleophilic substitution of the 5-tosyloxy group of **6** with potassium thioacetate afforded the 5-thioacetate **7**, which was deacetylated by treatment with sodium methoxide and then with hydrochloric acid to give 5-thio-L-arabinose **8**. The *cis*-diol of 5-thio-L-arabinoside **8** was protected by an isopropylidene group to give **9** in good yield (Scheme 1).

To our knowledge, several ring-contraction reactions of 5-thiopyranose to 4-thiofuranose have been reported.^{8,10} Hughes et al. reported that the 2-mesylate of the L-enantiomer of **9** was transformed to the dimethyl acetal of 4-thiofurose 5-aldehyde under basic methanolysis conditions.⁸ This encouraged us to examine the direct conversion of the mesylate **10** to the desired 4-thioribose under reductive conditions. Compound **9** was converted to 2-mesylate **10**, which was used for the next reductive ring-contraction reaction without any purification, because of its instability. The reaction mixture containing **10** was treated with NaBH₄ in aqueous EtOH to give the ring contracted product **11** in 86% yield, as expected.¹¹ As shown in Scheme 2, the reaction proceeded via the following three steps: (1) the intramolecular nucleophilic attack of sulfur at the 5-position and the formation of an episulfonium ion **A**, (2) ring contraction and the generation of 5-aldehyde **C**, and (3) the hydride reduction of the resulting aldehyde **C**.

Although the synthesis of 1,4-anhydro-4-thio-D-ribitol was reported by Minakawa et al.,¹² it was necessary to remove undesired L-isomer by crystallization. Our method to access **11** is facile since some of the reaction steps can be done in one-flask and is highly stereospecific.



Scheme 1.

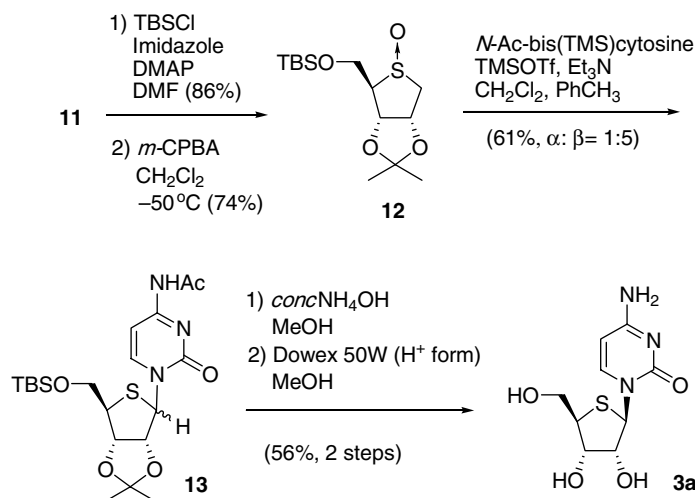


Scheme 2.

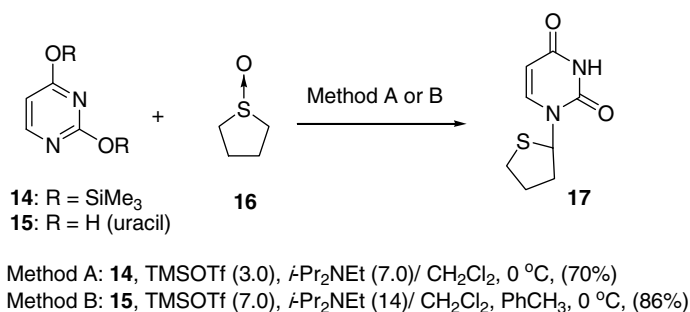
The 5-O-silylated sulfoxides **12**, prepared from **11** by 5-O-silylation and the subsequent MCPBA oxidation, was subjected to a Pummerer-type thioglycosylation. The reaction of **12** with persilylated *N*⁴-acetylcytosine in the presence of TMSOTf and triethylamine gave the desired 4'-thiocytidine derivatives **13** with the predominant formation of β-anomers (40%; α:β = 1:5). The yield of the reaction was improved slightly (61%) when the persilylated *N*⁴-acetylcytosine was premixed with TMSOTf (3 equiv) and triethylamine (3 equiv) prior to the addition of **12**.¹³ The reason as to why the premixing of the reagents improves the reaction yield is not clear. The deprotection of **13** was achieved by the treatment with aq NH₄OH/MeOH followed by an acidic resin (Dowex 50W H⁺ form) in MeOH. The resulting mixture was then purified by ODS column chromatography to give pure β-4'-thiocytidine **3a** in 56% yield (Scheme 3).

The reaction of **12** with the persilylated uracil gave the corresponding 4'-thiouridine derivative in poor yield (<33%). We attempted to optimize the conditions used in the Pummerer-type thioglycosylation for the 4'-thiouridine derivative using a model reaction. The reaction of persilylated uracil **14** or uracil **15** with tetramethylene sulfoxide **16** was investigated under various conditions. As a result, the reaction of persilylated uracil **14** with an excess of diisopropylethyamine at 0 °C gave **17** in 70% yield (Method A). In the proposed reaction mechanism, the sulfenium ion is formed from the reaction of the sulfoxide with TMSOTf. Our results suggest that the excess amine should facilitate abstraction of the α-proton of the O-silylated tetramethylene sulfoxide to generate the corresponding sulfenium ion. Indeed, the reaction of uracil **15** and **16** with an excess of TMSOTf (7 equiv) and diisopropylethyamine (14 equiv) also gave **17** in 86% yield (Method B) (Scheme 4).

Using the conditions mentioned above, the Pummerer-type thioglycosylation of uracil with **12** was investigated. Even though the model reaction using uracil afforded the corresponding thioglycosylated product in excellent



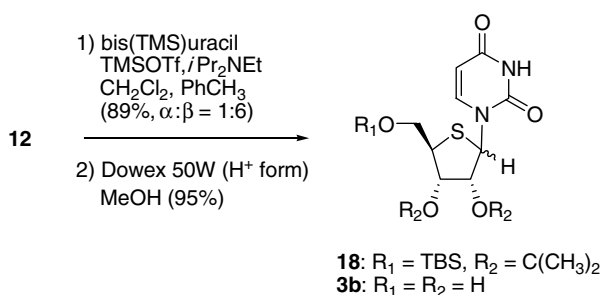
Scheme 3.



Scheme 4.

yield, the reaction of uracil **15** with **12**, under the same conditions as in Method B, gave a 4'-thiouridine derivative **18** only in 29% yield. Meanwhile, the reaction of persilylated uracil **14** with **12** as in Method A gave the 4'-thiouridine derivative **18** in 89% yield.¹⁴ The ratio of α - and β -anomers obtained, as determined by ¹H NMR, was 1:6 to α -**18**: β -**18**.¹⁵ Finally, the deprotection of **18** by the acid treatment furnished 4'-thiouridine **3b** in good yield (Scheme 5). However, separation of the α - and β -anomers of **3b** was unsuccessful.

The application of this reaction to the synthesis of purine 4'-thioribonucleosides is currently underway and will be reported in a future report.



Scheme 5.

Acknowledgments

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 - Compound β -**18**: ¹H NMR (600 MHz, CDCl₃) δ ppm 8.27 (1H, br), 7.99 (1H, d, *J* = 8.1 Hz), 6.13 (1H, d, *J* = 2.8 Hz), 5.75 (1H, dd, *J* = 2.1, 8.1 Hz), 4.73 (1H, dd, *J* = 2.6, 5.5 Hz), 4.70 (1H, dd, *J* = 2.9, 5.5 Hz), 3.93 (1H, dd, *J* = 4.9, 10.8 Hz), 3.87 (1H, dd, *J* = 3.9, 10.8 Hz), 3.74 (1H, dt, *J* = 2.6, 4.4 Hz), 1.59 (3H, s), 1.33 (3H, s), 0.92 (9H, s), 0.12 (3H, s), 0.10 (3H, s). HR-EI-MS *m/z* calcd for C₁₈H₃₀N₂O₅SSi 414.1645, found 414.1595.
 - The stereochemistry of the anomeric position of the thioglycosylated products was determined by NOE experiments.