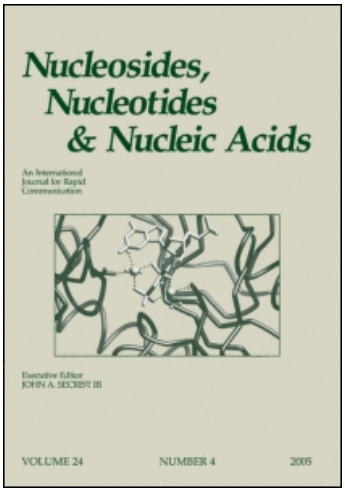

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SYNTHESIS OF 2′-*C*-METHYL-4′-THIO RIBONUCLEOSIDES

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▫ *Starting from 2-C-methyl-ribonolactone, 1,2,3,5-tetra-O-acetyl-2-C-methyl-4-thioribofuranose was synthesized and condensed with heterocyclic bases to afford 2′-C-methyl-4′-thioribonucleosides.*

Keywords 4-Thiosugar, 4′-Thionucleosides, 2′-*C*-Methyl Branched 4′-Thionucleosides

INTRODUCTION

Recently, several 2′-*C*-methyl branched ribonucleosides, including 2′-*C*-methylcytidine **1** (Scheme 1), were discovered to be potent and selective inhibitors in cell culture of a number of RNA viruses, like bovine viral diarrhea virus (BVDV), yellow fever virus (YFV), and West Nile virus (WNV).[1–3] As many key nucleosides in the field of antiviral and antitumor chemotherapies have been converted into their 4′-thio derivatives,[4–8] we decided to combine these two kinds of modifications by synthesizing 2′-*C*-methyl-4′-thio-ribonucleosides in order to assess their biological activity.

CHEMISTRY

2-*C*-Methyl-D-ribonolactone **3**[9] was converted into its 2,3-*O*-isopropylidene derivative, and then the 5-hydroxyl group was mesylated to give **4** in quantitative yield. Subsequent treatment of **4** with aqueous potassium hydroxide yielded the L-lyxonic acid intermediate, and direct acidification of the reaction mixture afforded

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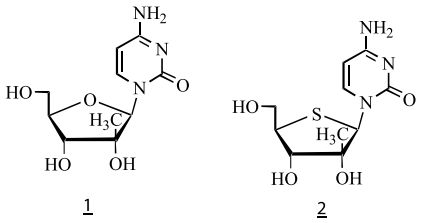
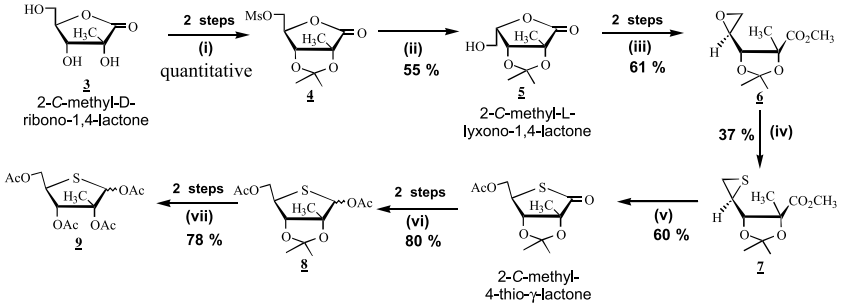


SCHEME 1 Structures of 2′-*C*-methylcytidine **1** and its 4′-thio counterpart **2**.

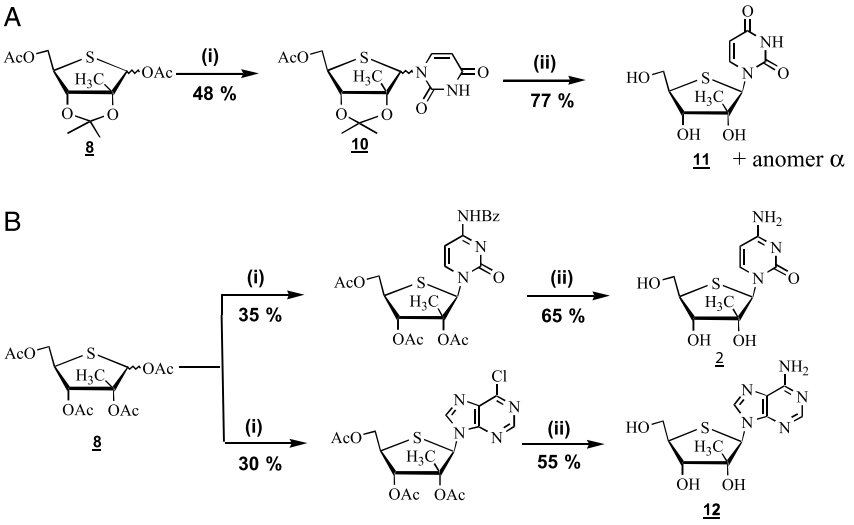
the 2-*C*-methyl-2,3-*O*-isopropylidene-L-lyxonolactone **5**.[10] Compound **5** was converted in two steps into the 4,5-epoxide derivative **6**. Reaction of **6** with thiourea resulted in the thiirane **7** formation, with inversion of the C-4 configuration. Thiolactonization was accomplished by heating **7** with AcONa in acetic acid.[12] Reduction of the thiolactone with sodium borohydride, followed by acetylation led to the protected lactol **8**. Finally, removal of the isopropylidene, followed by peracetylation afforded 1,2,3,5-tetra-*O*-acetyl-2-*C*-methyl-4-thio-D-ribofuranose **9** (Scheme 2).

Both the 1-*O*-acetyl-2,3-isopropylidene **8** and the peracetylated **9** sugars were used in glycosylation reactions. When **8** was condensed with silylated uracil, an inseparable mixture of α and β anomers **10** (50/50) of fully protected 2′-*C*-methyl-4′-thiouridine was obtained. After removal of the 5′-acetyl and 2′,3′-isopropylidene groups, 2′-*C*-methyl-4′-thiouridine **11** and its corresponding α anomer were separated and isolated.

Using Vorbrüggen's methodology, condensation of the 2-*C*-methyl-4-thio–peracetylated sugar **9** with N4-benzoylcytosine, followed by removal of the acetyl groups under basic conditions, led to the single β anomer 2′-*C*-methyl-4′-thiocytidine **2**. A similar route using **9** and the commercially available 6-chloropurine as starting material afforded 2′-*C*-methyl-4′-thioadenosine **12** (Scheme 3).



SCHEME 2 Synthesis of 1,2,3,5-tetra-*O*-acetyl-2-*C*-methyl-4-thio-D-ribofuranose **9**. (i): a) Acetone, H_2SO_4; b) MsCl, pyr/CH_2Cl_2; (ii) a) KOH, H_2O b) HCl/H_2O; (iii) a) TsCl, pyr/CH_2Cl_2; b) NaOMe, MeOH; (iv) Thiourea, MeOH; (v) Ac_2O, AcONa, AcOH; (vi) a) $NaBH_4$, MeOH, b) Ac_2O, pyr (vii) AcOH/H_2O; c) Ac_2O, pyr.



SCHEME 3 Synthesis of 2′-*C*-methyl-4′-thio-uridine **11**, -cytidine **2**, and -adenosine **12**. (A) (i) bis(trimethylsilyl) acetamide, uracil, TMSOTf, CH_3CN, reflux; (ii) a) TFA/H_2O, 4/1 v/v; b) CH_3ONa, CH_3OH, room temperature (rt). (B) (i) bis(trimethylsilyl)acetamide, N^4-benzoylcytosine or 6-chloropurine, TMSOTf, CH_3CN, reflux; (ii) CH_3ONa, CH_3OH, room temperature (rt); (iii) NH_3/CH_3OH, 100°C.

CONCLUSION

We have developed a convenient approach for the synthesis of 1,2,3,5-tetra-*O*-acetyl-2-*C*-methyl-4-thioribofuranose **9**, which enabled us to prepare 2′-*C*-methyl-4′-thio-ribonucleosides using Vorbrüggen's methodology.

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