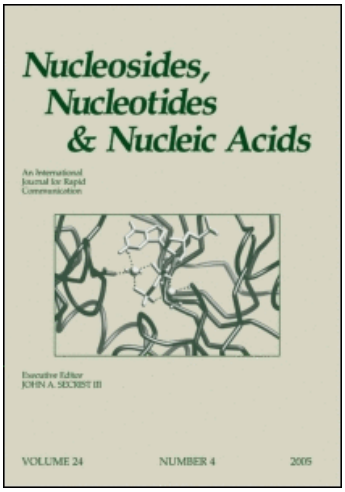

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Synthesis of 3'-Thioribouridine, 3'-Thioribocytidine, and Their Phosphoramidites

Sengen Sun[a]; Joseph A. Piccirilli[a]
[a] Howard Hughes Medical Institute, Department of Chemistry and Department of Biochemistry and Molecular Biology, The University of Chicago, Chicago, Illinois

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SYNTHESIS OF 3'-THIORIBOURIDINE, 3'-THIO-RIBOCYTIDINE, AND THEIR PHOSPHORAMIDITES

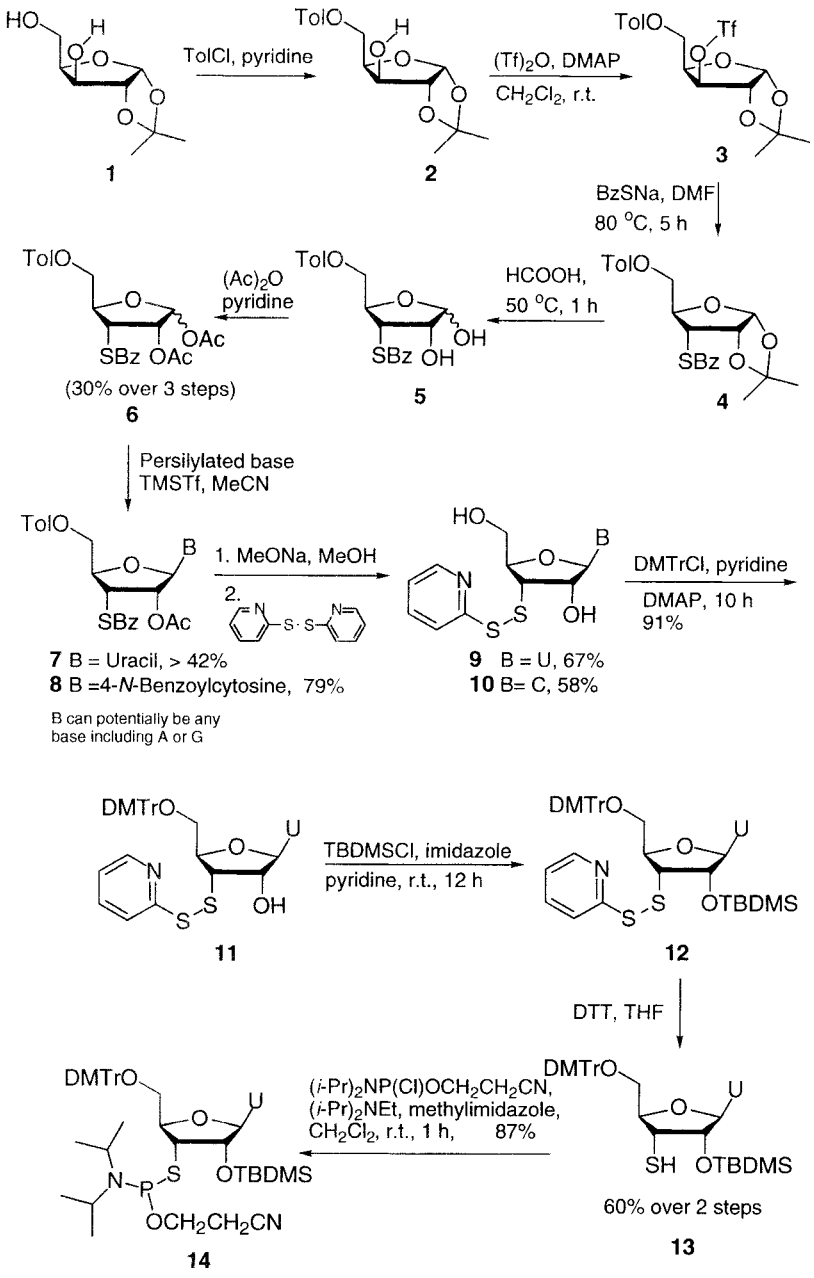
Sengen Sun and Joseph A. Piccirilli*

Howard Hughes Medical Institute, Department of Chemistry and Department of Biochemistry and Molecular Biology, The University of Chicago
5841 South Maryland Avenue, Room N101, Chicago, Illinois 60637

ABSTRACT: 3'-Thio-3'-deoxyribonucleosides (U and C) have been synthesized *via* Vorbruggen-type glycosylation with 3-*S*-benzoyl-5-*O*-toluoyl-1,2-*O*-diacetylfuranose, which was obtained from 1,2-*O*-isopropylidene-5-*O*-toluoyl-3-*O*-trifluoromethanesulfonyl-α-D-xylofuranose. 3'-Thio-3'-deoxyuridine has been converted to its phosphoramidite.

3'-Thionucleosides have proven useful as mechanistic probes in phosphoryl transfer reactions in both protein enzymes[1] and ribozymes.[2] However, studies have been restricted to 2'-deoxy versions of these molecules. The 3'-thiol derivatives of adenosine[3,4] and uridine[5] have been previously reported, but not get incorporated into oligonucleotides by solid phase synthesis.

We have recently synthesized 3'-thio-3'-deoxyriboinosine and incorporated it at the 3'-splice site of a nuclear premessenger RNA *via* phosphoramidite chemistry followed by enzymatic ligation.[6] Our interest in the mechanism of catalysis of RNA-mediated phosphoryl transfer reactions inspired us to develop a general procedure to access efficiently any of the 3'-thioribonucleoside analogs and their phosphoramidites (Scheme 1). The commercially available 1,2-*O*-isopropylidene-α-D-xylofuranose was transformed to 1,2-*O*-isopropylidene-5-*O*-toluoyl-3-*O*-trifluoromethanesulfonyl-α-D-xylofuranose.[7,8] The triflate group was easily displaced by thiobenzoate to give the 3-*S*-benoylfuranose derivative. Removal of the isopropylidene group followed by acetylation gave a product **6**, which was used successfully in Vorbruggen-type reactions to glycosylate uridine and 4-*N*-benzoylcytosine. Removal of the acyl protecting groups followed by protection of the sulfhydryl as the pyridyl disulfide allowed 5'-dimethoxytritylation and 3'-silylation. Reduction of the disulfide followed by phosphitylation gave the phosphoramidite in very good yield.[9]



SCHEME 1

In conclusion, we have developed a useful procedure to synthesize 3'-thioribonucleosides. We are working to extend the procedure to prepare the corresponding guanosine and cytidine analogs.

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9. Every new compound was characterized by ^{1}H- and ^{13}C-NMR, and either a satisfictory molecular weight from high resolution mass spectrometry or a satisfactory elemental analysis was obtained. For the final thiouridine phosphoramidite **14**, ^{31}P-NMR (90 MHz, in $CDCl_3$, using 85% H_3PO_4 as external standard): δ = 168.6, 157.4; Anal. calcd for $C_{45}H_{61}N_4O_8PSSi$: C, 61.64; H, 6.96; N, 6.39; S, 3.65. Found: : C, 61.38; H, 6.95; N, 6.62; S, 3.49.