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## Nucleosides, Nucleotides and Nucleic Acids

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### 4'-Thio- $\beta$ -D-oligoribonucleotides: Nuclease Resistance and Hydrogen Bonding Properties

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## 4'-THIO- $\beta$ -D-OLIGORIBONUCLEOTIDES : NUCLEASE RESISTANCE and HYDROGEN BONDING PROPERTIES

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**Abstract :** The syntheses and the study of nuclease resistance and hydrogen bonding of modified oligoribonucleotides, i.e. 4'-thio- $\beta$ -D-oligoribonucleotides (4'-S-RNA), are reported.

**Introduction :** To improve enzymatic stability and cellular uptake of synthetic oligonucleotides we propose an isosteric substitution (O  $\rightarrow$  S) on the sugar moiety of the monomeric nucleotide units **1**.

**Results and discussion :** 4'-Thio- $\beta$ -D-oligoribonucleotides (4'-S-RNA) (Figure 1) can be obtained by solid support assembling of the 4'-thio- $\beta$ -D-ribonucleosides building block using phosphoramidite methodology <sup>1</sup>. Our effort was focused on the design of a strategy to access to the desired 2,3,5-tri-O-benzoyl-4-thio-ribofuranose **8**. This synthetic route starting from L-lyxose **2** is based on the introduction of a sulfur atom at the C-1 position of a L-lyxose derivative intermediate **4**, followed by a nucleophilic displacement of the previously activated 4-hydroxyl group with inversion of configuration <sup>2, 3</sup>. As shown in Figure 2, the expected 1-O-acetyl-2,3,5-tri-O-benzoyl-4-thio-D-ribofuranose **8** can be obtained from L-lyxose **2** with 14% overall yield.

The synthesis of the necessary 4'-thio- $\beta$ -D-ribonucleosides of the three bases (Ad, Cy, Ur) (Figure 3) was performed using appropriate glycosylation reactions <sup>4, 5</sup>. The  $\beta$  anomer was obtained in 38% yield for Ur and Cy and 22% for Ad. The 5' and 3'-hydroxyl function of the different 4'-thioribonucleosides were protected respectively with DmTr and TBDMS groups as previously described <sup>6-8</sup>. Finally, the

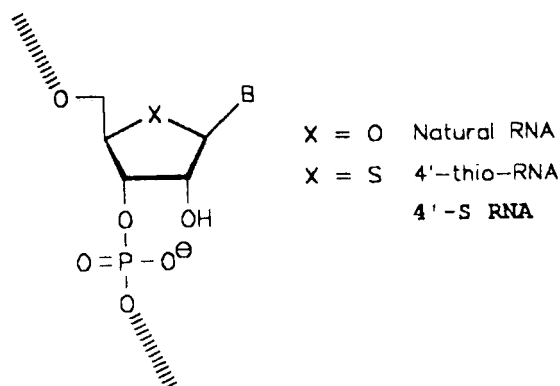


Figure 1.

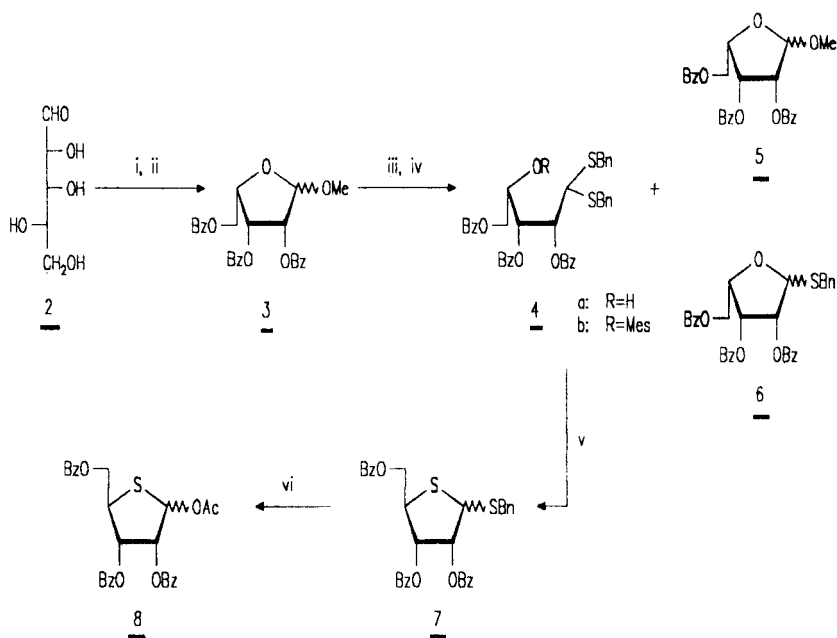
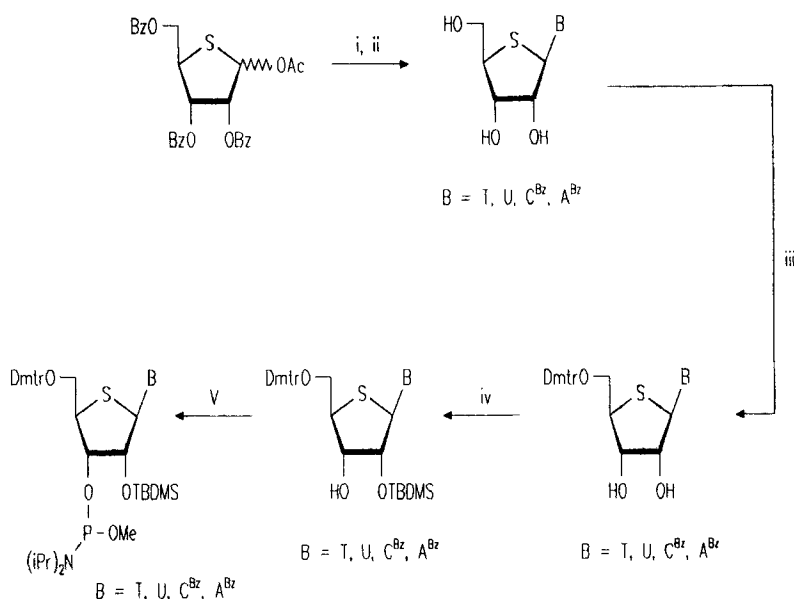


Figure 2.



i = Base, Coupling Agents ; ii = NaOH 2N, EtOH, Pyr.; iii = DmTrCl, pyr. ; iv = TBDMSCl, pyr.  
v = CIP(OMe)N(iPr)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>.

Figure 3.

corresponding 4'-thioribonucleosides derivatives were obtained according to a similar procedure as used in the oxygenated series.

The 4'-thio-β-D-oligoribonucleotide, 4'-S-(A C A C C C A A U U C U), **9**, complementary to the splicing acceptor site of the *tat* HIV gene was designed and evaluated for its nuclease resistance and hydrogen bonding properties. We found that **9**, possesses a high nuclease resistance as compared to other oligonucleotide derivatives. In addition, **9**, can form stable duplexes with RNA targets under near physiological conditions.

The 4'-thio-β-D-oligoribonucleotide, 4'-S-(U U U U C U U U U C C C C C C U), **10**, complementary to hairpin DNA structure of the polypurine track HIV gene was also synthesized. T<sub>m</sub> data clearly indicated an important stability of triple helix formed by this 4'-S-ARN.

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**REFERENCES :**

1. Beaucage, S. L. and Caruthers, M. H. *Tetrahedron Lett.*, **1981**, 22, 1859-1862.
2. Bellon, L.; Barascut, J.-L.; Imbach, J.-L. *Nucleosides Nucleotides*, **1992**, 11, 1467-1479.
3. Bellon, L.; Barascut, J.-L.; Imbach, J.-L. *Nucleosides Nucleotides*, **1993**, 12, 847-852.
4. Vorbruggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.*, **1981**, 114, 1234-1255.
5. Genu, C.; Gosselin, G.; Puech, F.; Henry, J.-C.; Aubertin, A. M.; Obert, G.; Kirn, A.; Imbach, J.-L. *Nucleosides Nucleotides*, **1991**, 10, 13459-1376.
6. Bellon, L.; Barascut, J.-L.; Maury, G.; Divita, G.; Goody, R. S.; Imbach, J.-L. *Nucleic Acids Res.*, **1993**, 21, 1587-1593.
7. Bellon, L.; Morvan, F.; Barascut, J.-L.; Imbach, J.-L. *Biochem. Biophys. Res. Comm.*, **1992**, 184, 779-803.
8. Bellon, L.; Leydier, C.; Barascut, J.-L.; Maury, G.; Imbach, J.-L. in *"Carbohydrate Synthetic Methods & Application in Antisens Therapeutics"*, Y. S. Sanghi and P. D. Cook Eds., **1994**, 000.