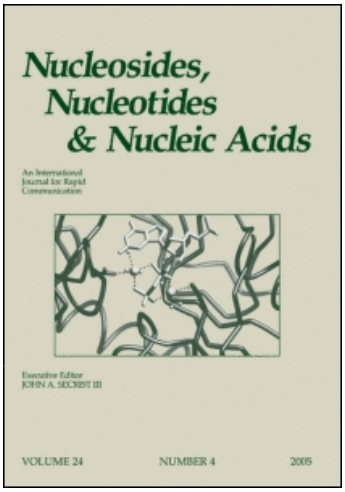

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4'-Thio-β-D-oligoribonucleotides: Nuclease Resistance and Hydrogen Bonding Properties

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4'-THIO-β-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-β-D-oligoribonucleotides (4'-S-RNA), are reported.

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

Results and discussion : 4'-Thio-ß-D-oligoribonucleotides (**4'-S-RNA**) (Figure 1) can be obtained by solid support assembling of the 4'-thio-ß-D-ribonucleosides building block using phosphoramidite methodology [1]. 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 [2, 3]. 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-β-D-ribonucleosides of the three bases (Ad, Cy, Ur) (Figure 3) was performed using appropriate glycosylation reactions [4, 5]. The β 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 [6-8] Finally, the

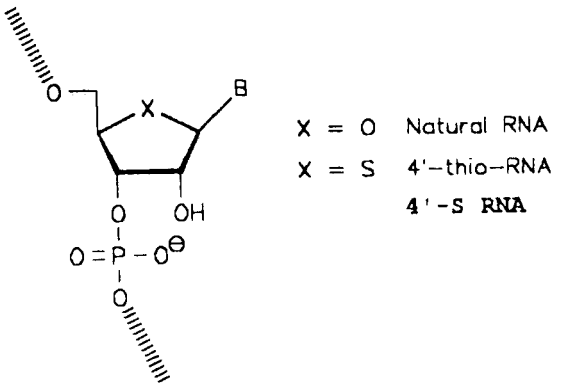
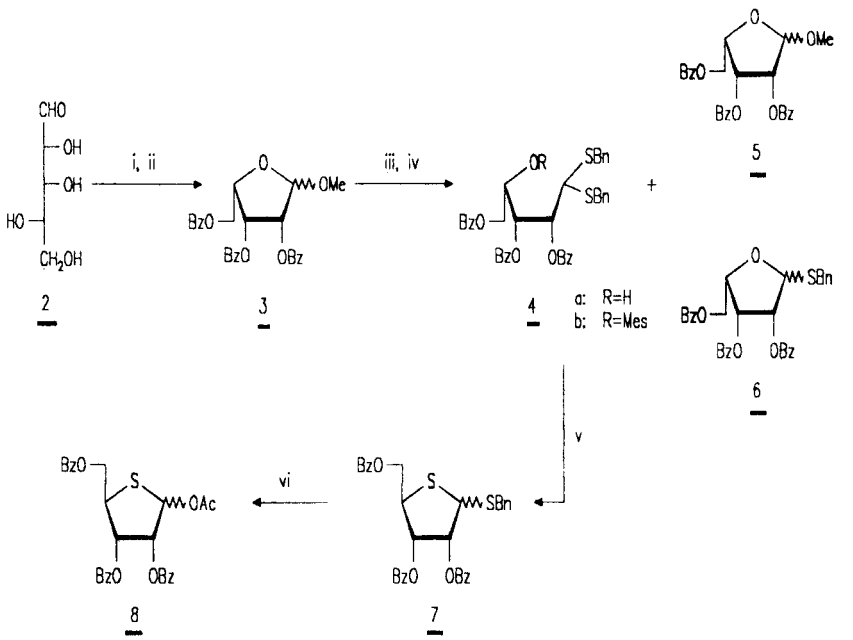
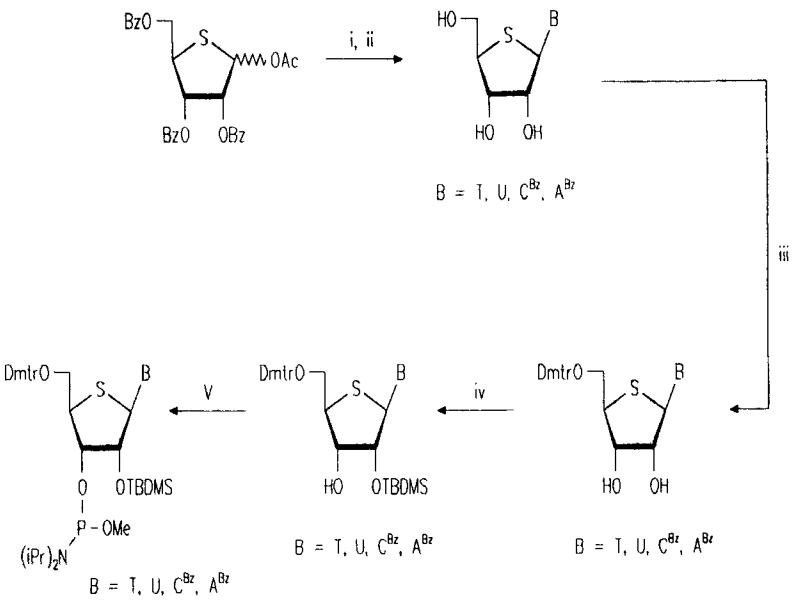


Figure 1.



i = MeOH, H_2SO_4; ii = BzCl, Pyr.; iii = Ph-CH_2SH, BF_3 , Et_2O; iv = MsCL, Pyr.; v = NBu_4I, $BaCO_3$
vi = Ac_2O, BF_3, Et_2O, CH_2Cl_2.

Figure 2.



i = Base, Coupling Agents ; ii = NaOH 2N, EtOH, Pyr.; iii = DmTrCl, pyr. ; iv = TBDMSCl, pyr.
v = $ClP(OMe)N(iPr)_2$, CH_2Cl_2.

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. Tm data clearly indicated an important stability of triple helix formed by this 4'-S-ARN.

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