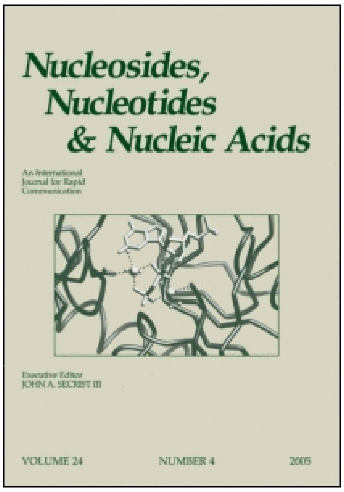

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Improvements in the Synthesis of L-Ribonucleosides for the Preparation of Mirror-Image Oligoribonucleotides

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IMPROVEMENTS IN THE SYNTHESIS OF L-RIBONUCLEOSIDES FOR THE PREPARATION OF MIRROR-IMAGE OLIGORIBONUCLEOTIDES

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ABSTRACT: Different improvements are described for the chemical synthesis of L-ribonucleosides corresponding to the four natural bases. These nucleosides properly protected were used to synthesize successfully a 27-base long L-oligoribonucleotide.

The so called "mirror-image" oligonucleotides are probably the most nuclease-resistant oligonucleotide analogs which still retain the natural 3'-5' phosphodiester internucleoside links. These analogs are also called enantio- or L-oligonucleotides since they contain, in place of the natural D-ribose, its enantiomer L-ribose. Although, their potential as antisense agents was found poor because they weakly anneal to natural nucleic acids, Nolte *et al* reported an elegant application of the SELEX method, which led to the identification of L-oligoribonucleotides that interact with L-arginine[1,2]. More recently, an L-oligoribonucleotide, corresponding to the Tat interactive top half of HIV-1 TAR-RNA stem-loop was shown to selectively inhibit TAR-Tat protein binding[3].

Here, we report several improvements in the chemical synthesis of L-ribonucleosides corresponding to the four natural bases.

2',3',5'-Tri-O-benzoyl-L-uridine was used as precursor in the synthesis of L-cytidine and L-adenosine building block, whereas L-guanosine building block was obtained by glycosylation reaction using fully-protected L-ribofuranose.

One key-step in the synthesis of 2',3',5'-tri-O-benzoyl-L-uridine is the BF_3-promoted hydrolysis of 3',5'-di-O-benzoyl-2,2'-anhydro-L-uridine according to Holy's procedure[4].

We found that water content of the reaction mixture is very important in the outcome of the reaction. In anhydrous conditions, a complex mixture was obtained which corresponds to a partial O-debenzoylation and other unidentified compounds. In contrast, when the reaction was carried out in presence of water (1%) we obtained almost exclusively a mixture of isomeric 2'(3'),5'-di-O-benzoyl-L-uridine.

N6-Benzoyl-L-adenosine was obtained in 61% yield by transglycosylation reaction from 2',3',5'-tri-O-benzoyl-L-uridine used as a glycosyl donor, in presence of trimethylsilyl-triflate.

N2-Isobutyryl-L-guanosine was obtained by glycosylation reaction according to a modified Robins's procedure[5]. In these conditions, no formation of N7-isomer was observed.

The corresponding 2'-O-*tertio*butyldimethylsilyl ribonucleosides phosphoramidites were used successfully in combination with solid phase chemistry to synthesize 27-base long oligoribonucleotide corresponding to the top half of the HIV-1 TAR-RNA stem-loop.

REFERENCES

1.Nolte, A.; Klubmann, S.; Bald, R.; Erdmann, V. A.;Fürste, J. P. *Nature Biotech.*, **1996,** *14*, 1116-1119.

2.Klubmann, S.; Nolte, A.; Erdmann, V. A.;Fürste, J. P. *Nature Biotech.*, **1996,** *14*, 1112-1115.

3.Garbesi, A.; Hamy, F.; Maffini, M.; Albrecht, G.;Klimkait, T. *Nucleic Acids Res.*, **1998,** *26*, 2886-2890.

4.Holy, A., *Collect. Czech. Chem. Commun.* **1973,** *38*, 423-427.

5.Robins, M. J.; Zou, R.; Guo, Z.;Wnuk, S., *J. Org. Chem.* **1996,** *61*, 9207-9212.