

This article was downloaded by:

On: 26 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

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

F. Santamaria^a; B. Rayner^a

^a Laboratoire de Chimie Bio-Organique, Université de Montpellier II, Montpellier cedex, France

To cite this Article Santamaria, F. and Rayner, B.(1999) 'Improvements in the Synthesis of L-Ribonucleosides for the Preparation of Mirror-Image Oligoribonucleotides', *Nucleosides, Nucleotides and Nucleic Acids*, 18: 6, 1405 — 1406

To link to this Article: DOI: 10.1080/07328319908044733

URL: <http://dx.doi.org/10.1080/07328319908044733>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

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

F. Santamaria and B. Rayner*

Laboratoire de Chimie Bio-Organique, Université de Montpellier II, Place E. Bataillon,
34095 Montpellier cedex 5, France.

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 binding³.

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 BF₃-promoted hydrolysis of 3',5'-di-O-benzoyl-2,2'-anhydro-L-uridine according to Holy's procedure⁴.

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 procedure⁵. In these conditions, no formation of N7-isomer was observed.

The corresponding 2'-O-*tert*iobutyldimethylsilyl 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.