

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>

Novel Synthesis of 2'-O Modified Oligonucleotides by Solid Phase Fragment Condensation

Kotomi Sasaki^{ab}; Takanori Kubo^a; Ryoji Ueki^a; Mayuka Yano^a; Yosuke Anno^a; Hideki Ohba^c; Masayuki Fujii^{ad}

^a Department of Biological and Environmental Chemistry, Kyushu School of Engineering, Kinki University, Iizuka, Fukuoka, Japan ^b Department of Biological and Environmental Chemistry, Kyushu School of Engineering, Kinki University, Iizuka, Fukuoka, Japan ^c Kyushu National Industrial Research Institute, Agency of Industrial Science and Technology, Ministry of International Trade and Industry, Tosu, Saga, Japan ^d Molecular Engineering Institute, Kinki University, Iizuka, Fukuoka, Japan

Online publication date: 09 August 2003

To cite this Article Sasaki, Kotomi , Kubo, Takanori , Ueki, Ryoji , Yano, Mayuka , Anno, Yosuke , Ohba, Hideki and Fujii, Masayuki(2003) 'Novel Synthesis of 2'-O Modified Oligonucleotides by Solid Phase Fragment Condensation', *Nucleosides, Nucleotides and Nucleic Acids*, 22: 5, 1447 — 1449

To link to this Article: DOI: 10.1081/NCN-120023007

URL: <http://dx.doi.org/10.1081/NCN-120023007>

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.

Novel Synthesis of 2'-O Modified Oligonucleotides by Solid Phase Fragment Condensation

Kotomi Sasaki,^{1,*} Takanori Kubo,¹ Ryoji Ueki,¹ Mayuka Yano,¹
Yosuke Anno,¹ Hideki Ohba,² and Masayuki Fujii^{1,3}

¹Department of Biological and Environmental Chemistry, Kyushu School of Engineering, Kinki University, Iizuka, Fukuoka, Japan

²Kyushu National Industrial Research Institute, Agency of Industrial Science and Technology, Ministry of International Trade and Industry, Tosu, Saga, Japan

³Molecular Engineering Institute, Kinki University, Iizuka, Fukuoka, Japan

INTRODUCTION

Oligonucleotides modified at 2'-OH position have attracted much attention from a biological and medicinal point of view because they have a number of advantageous properties for their application to antisense and antigene medicines. For example, they can bind to complementary RNA with higher affinity than native oligoDNA, and they are more resistant to nuclease degradation. It has been shown by the researchers of ISIS Pharmaceuticals Ltd. that "gapmer technology" combining this type of modification and sulfurization of phosphate backbone of oligonucleotides makes it possible to apply chemically modified oligonucleotides to antisense therapy.^[1]

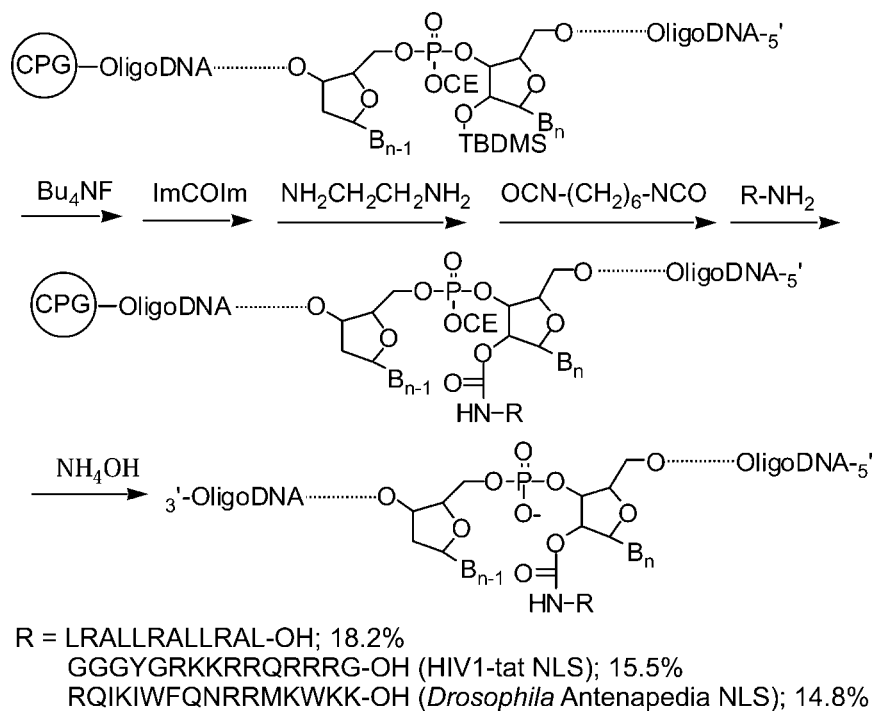
*Correspondence: Kotomi Sasaki, Department of Biological and Environmental Chemistry, Kyushu School of Engineering, Kinki University, 11-6 Kayanomori, 820-8555 Iizuka, Fukuoka, Japan; Fax: +81 94 823 0536; E-mail: ksasaki@iron.chem.fuk.kindai.ac.jp.



Almost of synthetic methods of them so far studied requires a preparation of phosphoramidite derivatives of the respective 2'-O modified nucleosides and the preparation sometimes includes complicated and prolonged steps. The present paper describes about the development of a novel method for the synthesis of 2'-O modified oligonucleotides by solid phase fragment condensation (SPFC).^[2]

RESULTS AND DISCUSSIONS

This method involves a coupling of an amine derivative to an oligonucleotide fragment at 2'-O position on solid phase. (Sch. 1) Oligonucleotides including ribonucleotides with 2'-OH groups protected by *t*-butyldimethylsilyl (TBDMS) groups assembled on CPG support by a standard cyanoethylphosphoramidite chemistry were treated with tetrabutylammonium fluoride (TBAF) to remove TBDMS and set 2'-OH groups free. The CPG linked oligonucleotides were then reacted with carbonyldiimidazole (CDI) and amine derivatives, sequentially. After treatment with aqueous ammonia at 50°C for 5 h, the modified oligonucleotides were purified by RPHPLC two times (DMT on and DMT off) to give 2'-O modified oligonucleotides in 15–30% yields. Protected peptide fragments bearing a free amino group, amino sugars, polyamines, and any other amine derivatives can be employed in the present



Scheme 1. Synthesis of 2'-O modified oligonucleotides by SPFC.

method. Since the present method requires only commercially available phosphoramidites and allows the modification of ribonucleotide moieties of any positions of oligonucleotides at one time, it can be applied to the synthesis of any types of 2'-O modified oligonucleotides.

REFERENCES

1. Cook, P.D. *Nucleosides & Nucleotides* **1999**, *18*, 1141–1162.
2. Takanori Kubo; Masayuki Fujii. *Nucleosides, Nucleotides and Nucleic Acids* **2001**, *20*, 1321–1324.



