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Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

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

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To cite this Article Swayze, Eric E. , Bhat, Balkrishen , Peoc'h, Didier and Sanghvi, Yogesh S.(1997) 'The Synthesis of the Sixteen Possible 2'-O-Methyl MMI Dimer Phosphoramidites: Building Blocks for the Synthesis of Novel Antisense Oligonucleotides', *Nucleosides, Nucleotides and Nucleic Acids*, 16: 7, 971 — 972

To link to this Article: DOI: 10.1080/07328319708006118

URL: <http://dx.doi.org/10.1080/07328319708006118>

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THE SYNTHESIS OF THE SIXTEEN POSSIBLE 2'-O-METHYL MMI DIMER PHOSPHORAMIDITES: BUILDING BLOCKS FOR THE SYNTHESIS OF NOVEL ANTISENSE OLIGONUCLEOTIDES

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Abstract: The synthesis of Methylene(methylimino) or MMI linked nucleoside dimers *in all sixteen possible configurations* has been accomplished *via* a reductive coupling of a nucleosidic aldehyde with an hydroxylamine. This has allowed us to prepare all of the necessary 2'-O-methyl MMI dimer building blocks necessary for use in an antisense motif.

We have previously described¹ the ability of the MMI backbone to act as a replacement for the natural phosphodiester backbone in an antisense construct, and have discovered that dimers having 2'-O-methyl ribofuranosides as the sugar units (**1**) show superior properties as antisense agents.² Herein we describe the synthesis of nucleoside dimers **1** in all sixteen possible configurations from precursors **2** and **3**.³ The key reaction in this sequence is the reductive coupling of aldehydes **2** with hydroxylamines **3** to provide dimers **4** utilizing 1 eq. of borane-pyridine complex and 1 eq. of pyridinium *para*-toluenesulfonate in methanol. The coupling reaction proceeds in good to excellent yield (45-80%), and gives predominantly a single dimeric product in 1-2 hours at room temperature. This method is general, and has been shown to be tolerant of both 5'-O-dimethoxytrityl and amide base protection except on 5-methylcytosine (MeC), which can be selectively benzoylated using benzoic anhydride in DMF after coupling. Removal of the silyl protecting group afforded dimers **5**, which were then converted to the phosphoramidites **1** in excellent yield. We also prepared derivatized solid supports **7** containing these dimeric nucleosides. Standard procedures gave poor loadings of **5** onto solid support (CPG), however, an oxidation/reduction technique⁴ employing the corresponding succinates gave excellent loadings of functionalized support. In this manner, we have prepared of all of the sixteen possible mixed base 2'-O-methyl MMI dimer phosphoramidites **1** and supports **7** necessary for the synthesis of *any* oligonucleotide sequence containing MMI dimers for use in an antisense motif.

¹Morvan, F.; Sanghvi, Y. S.; Perbost, M.; Vasseur, J-J.; Bellon, L. *J. Am. Chem. Soc.* **1996**, *118*, 255-256, and references cited therein.

²Pcoe'h, D.; Swayze, E. E.; Bhat, B.; Dimock, S.; Sanghvi, Y. S. *Nucleosides Nucleotides* **1997**, *16*, in this issue.

³Dimock, S.; Bhat, B.; Pcoe'h, D.; Sanghvi, Y. S.; Swayze, E. E. *Nucleosides Nucleotides* **1997** *16*, in this issue.

⁴Kumar, P.; Sharma, A. K.; Sharma, P.; Garg, B. S.; Gupta, K. C. *Nucleosides Nucleotides* **1996** *15*, 879-888.