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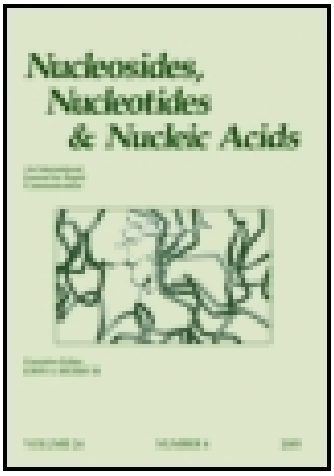

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The Synthesis of the Sixteen Possible 2′-O-Methyl MMI Dimer Phosphoramidites: Building Blocks for the Synthesis of Novel Antisense Oligonucleotides

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NUCLEOSIDES & NUCLEOTIDES, 16(7-9), 971-972 (1997)

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.

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We have previously described[1] 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 (^{Me}C), 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 technique[4] 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.

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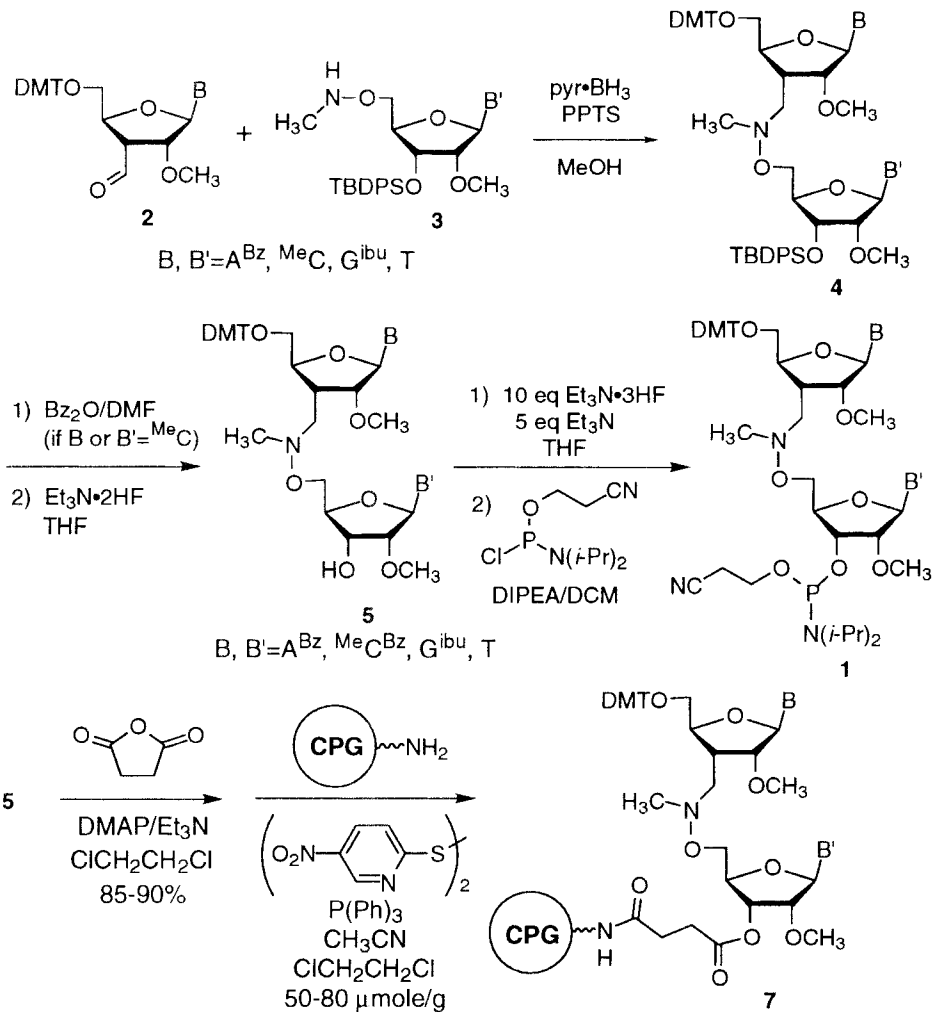

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