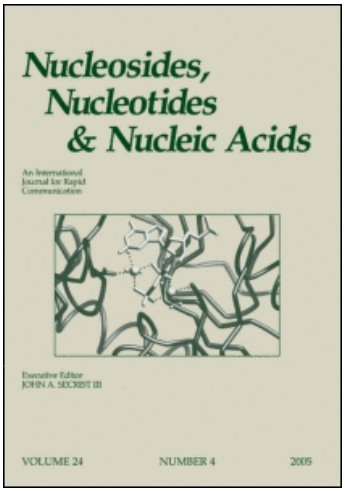

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Synthesis of 5, 6-Dichloro-Benzimidazole-(2', 5')-Nucleotide Trimer

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SYNTHESIS OF 5,6-DICHLORO-BENZIMIDAZOLE-(2',5')-NUCLEOTIDE TRIMER

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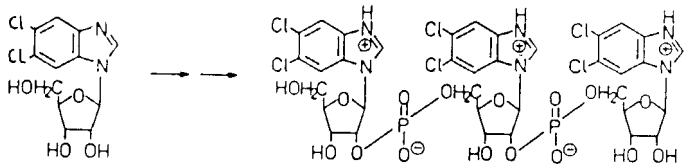
Summary: The chemical synthesis of the trimeric 5,6-dichloro-1-ß-D-ribofuranosylbenzimidazole-(2',5')-diphosphate using the phosphotriester approach is described.

Nucleosides of halo-substituted benzimidazoles in particular 5,6-dichloro-1-ß-D-ribofuranosylbenzimidazole (DRB) are regarded as specific and reversible inhibitors of nuclear hn RNA synthesis (1) as well as superinductors of interferon production in human fibroblasts (2). In order to answer the question whether DRB itself is the active component or a cell-transformed metabolite such as the 2',5'-DRB trimer we developed a synthetic approach to the latter oligonucleotide.



Starting from DRB the 5'-position was first protected by the p-methoxytrityl group followed by reaction of tert.butyldimethylsilyl-chloride to give a difficultly separable mixture of the two monosubstituted 2'- and 3'-isomers. Phosphorylation of the latter compound led to the 5,6-dichloro-3'-O-tert.butyldimethylsilyl-5'-O-p-methoxytrityl-benzimidazole-1-ß-D-ribofuranosid-2'-(2,5-dichlorophenyl, p-nitrophenyl-ethyl)-phosphate. DBU treatment formed the corresponding 2,5-dichlorophenylphosphodiester which on condensation with the 5,6-dichloro-2',3'-di-O-tert.butyldimethylsilylbenzimidazole-1-ß-D-ribofuranoside formed the dimer in 57 % yield. Deblocking of the p-methoxytrityl group afforded the necessary component for further condensation with the former phosphodiester to give the fully protected DRB-trimer in 55 % yield.

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Deprotection of the blocking groups was achieved in the usual manner but created a series of unexpected difficulties. Experimental details will be reported.

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