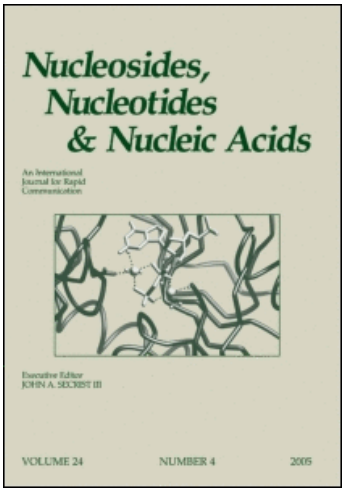

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Synthesis of Dinucleoside Boranophosphates by a Boranophosphotriester Approach

Takeshi Wada[ab]; Mamoru Shimizu[a]; Natsuhisa Oka[a]; Kazuhiko Saigo[a]
[a] Department of Integrated Biosciences, Graduate School of Frontier Sciences, The University of Tokyo, Chiba, Japan [b] Department of Integrated Biosciences, Graduate School of Frontier Sciences, The University of Tokyo, Kashiwa, Japan

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Synthesis of Dinucleoside Boranophosphates by a Boranophosphotriester Approach

Takeshi Wada,* Mamoru Shimizu, Natsuhisa Oka, and Kazuhiko Saigo

Department of Integrated Biosciences, Graduate School of Frontier Sciences, The University of Tokyo, Chiba, Japan

ABSTRACT

Dinucleoside boranophosphates including four kinds of nucleobases were synthesized by a boranophosphotriester method in good yields. In the present boranophosphotriester method, side-reactions at the nucleobases, which caused by a borane reagent, were completely avoided.

Oligodeoxyribonucleotides bearing internucleotidic boranophosphate linkages (boranophosphate DNA) are regarded as potentially useful antisense molecules.[1] The methods reported so far for the synthesis of this DNA analog are accomplished by the construction of an oligonucleotide chain via the phosphoroamidite or *H*-phosphonate method, followed by the boronation of the corresponding phosphite intermediate.[2–5] However, undesirable side reactions occur at the base moieties in the boronation step.[3,4,6,7] Therefore, in order to avoid the side reactions at the

*Correspondence: Takeshi Wada, Department of Integrated Biosciences, Graduate School of Frontier Sciences, The University of Tokyo, Bioscience Bldg. 702, 5-1-5 Kashiwanoha, 277-8562 Kashiwa, Japan; Fax: +81 47 136 36 152; E-mail: wada@k.u.tokyo.ac.jp.

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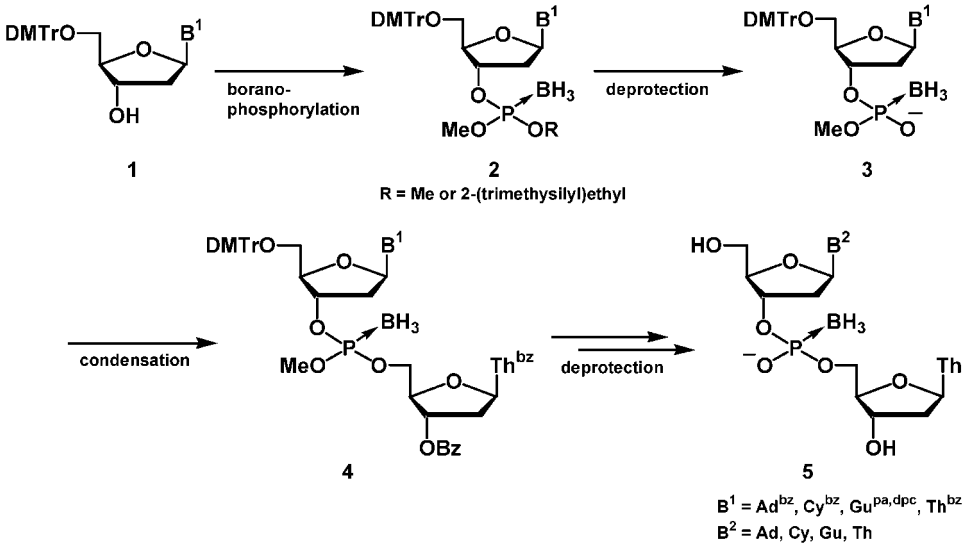
nucleobases caused by the borane reagent, we developed an alternative strategy for the synthesis of boranophosphate DNA by the use of a new boranophosphorylation reaction.



Four kinds of 5′-*O*-dimethoxytrityl nucleosides **1** (A, C, G, T), which have properly protected nucleobases, were condensed with a dialkyl boranophosphate in the presence of *N*,*N*′-bis(2-oxo-3-oxazolidinyl) phosphinyl chloride (Bop-Cl), 3-nitro-1,2,4-triazole (NT), and *i*-Pr_2NEt in THF. In all cases, the reactions proceeded quickly, and the desired nucleoside 3′-boranophsosphate triesters **2** were obtained in excellent yields.[8] One of the protecting groups in the boranophosphate triesters could be deprotected selectively, and the corresponding diesters **3** were obtained in excellent yields.[8] The resulting monomers were condensed with a 3′-*O*-protected thymidine to give the fully protected boranophosphate dimers **4**, AT, CT, GT, and TT in excellent yields.

Next, removal of the protecting groups was attempted. It is well known that the dimethoxytrityl cation ($DMTr^+$) reacts with borane groups to result the decomposition of internucleotidic linkages.[4,7] Therefore, we used Et_3SiH as a $DMTr^+$ scavenger for the deprotection of the DMTr group. First, the fully protected dimers **4** were treated with 3% DCA in CH_2Cl_2-Et_3SiH (1:1, v/v) to give the 5′-OH dimers, and all of other protecting groups were removed by a conventional procedure to yield the four kinds of dinucleoside boranophosphates **5**, AT, CT, GT, and TT in good yields.

In conclusion, the present so-called boranophosphotriester approach will be useful for the synthesis of boranophosphate DNA including all kinds of nucleobases. This strategy essentially eliminates troublesome side-reactions, caused by a borane reagent, which were unavoidable in the previously reported procedures. Therefore, our method will be useful for the synthesis of oligonucleotides bearing boranophosphate linkages. Solid-phase synthesis of oligomers is now in progress.

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