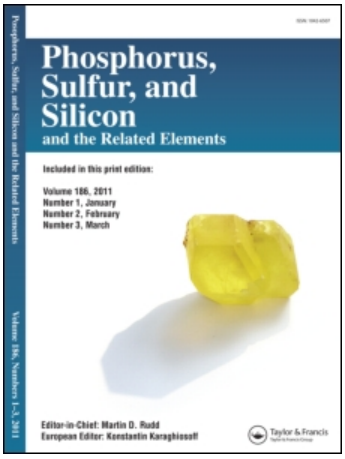

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Stereospecific synthesis of dinucleoside monophosphate aryl esters by using new condensing reagents

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To cite this Article Ohtsuka, Eiko , Shiraishi, Masahiko and Ikehara, Morio(1983) 'Stereospecific synthesis of dinucleoside monophosphate aryl esters by using new condensing reagents', Phosphorus, Sulfur, and Silicon and the Related Elements, 18: 1, 365 — 368
To link to this Article: DOI: 10.1080/03086648308076041
URL: http://dx.doi.org/10.1080/03086648308076041

Phosphorus and Sulfur, 1983, Vol. 18 pp. 365-368
0308-664X/83/1801-0365/$18.50/0

STEREOSPECIFIC SYNTHESIS OF DINUCLEOSIDE MONOPHOSPHATE ARYL ESTERS BY USING NEW CONDENSING REAGENTS

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Abstract New condensing reagents, arenesulfonyl 5-(pyridin-2-yl)tetrazoles have been synthesized and used for stereospecific synthesis of dinucleoside monophosphate aryl esters.

INTRODUCTION

The phosphotriester method has become a method of choice for the synthesis of oligonucleotides, since separation techniques for intermediates and activating reagents for phosphodiesters became available.[1] Synthetic oligonucleotides are required for physicochemical and biochemical studies on nucleic acids.

We have previously reported that new condensing reagents, 2,4,6-isopropylbenzenesulfonyl or mesitylenesulfonyl 5-(pyridin-2-yl) tetrazoles gave one of stereoisomers when they were used to condense 5'-dimethoxytrityldeoxynucleoside 3'-o-chlorophenyl phosphates with 3'-O-benzoyldeoxynucleosides.[2] Preparation of these condensing reagents, TPSPy and MSPy (Chart 1) and use in the solid phase synthesis were also reported.[3] Bulkiness of the pyridine residue was not considered to affect the stereospecific activation of the phosphodiester, since another new reagent mesitylenesulfonyl-5-phenyl tetrazole (MSPh) (Chartl) did give two stereoisomers. The mechanism of this stereospecific synthesis was proposed as illustrated in Chart 2.

RESULTS

To investigate the configuration of the phosphotriester, two diastereoisomers of deoxyadenylyl-(3'-5')(o-chlorophenyl)-deoxyadenosine (11, Chart 3) were synthesized by using a conventional condensing

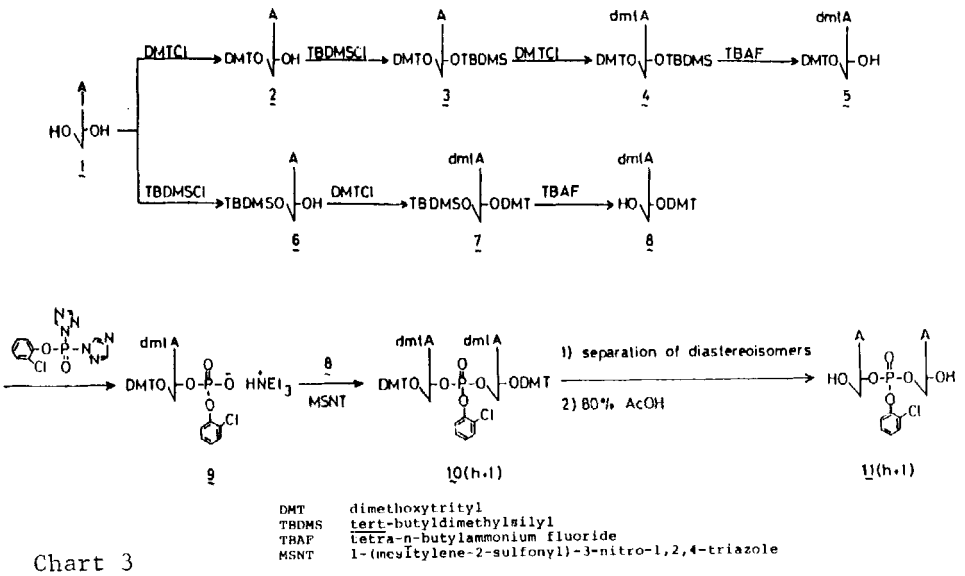

Chart 3

reagent mesitylenesulfonyl 3-nitrotriazolide.[4] Schemes for the synthesis are shown in Chart 3. Condensation of 8 and 9 with TPSPy or MSPy gave the lower isomer of 11.

Phosphorus and proton NMR of these isomers were investigated. Chemical shift of ^{31}P of 11-l was lower than that of 11-h. Overhauser effect in proton NMR suggested that the lower isomer had a contact between phenyl protons and the ribose C-H1' and C-H4' protons of 5'-adenosine. CD spectra of 11-h and 11-l at different temperature suggested that the lower isomer had a stacked conformation at low temperature. The higher isomer showed almost the same spectra at lower and higher temperature, which suggested an unstacked form. From these evidences, the lower isomer was considered to have Sp configuration. The product obtained by the stereospecific synthesis was presumably Sp configuration.

Mechanism of activation of phosphodiesters can be investigated by using derivatives of substituted tetrazoles or triazoles.

Stereospecific synthesis of phosphotriesters is useful in preparation of protected oligonucleotide triester blocks which are

Condensing reagents
for the phosphotriester method

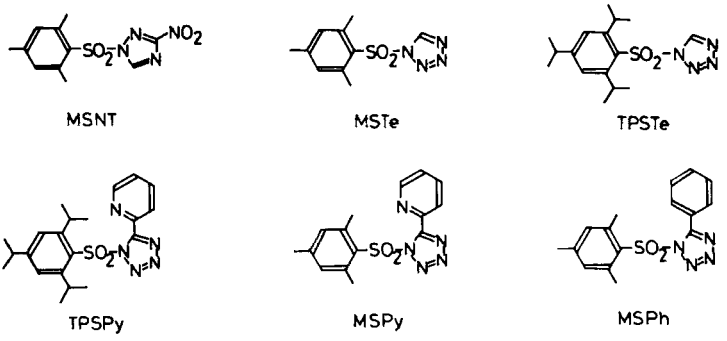

Chart 1

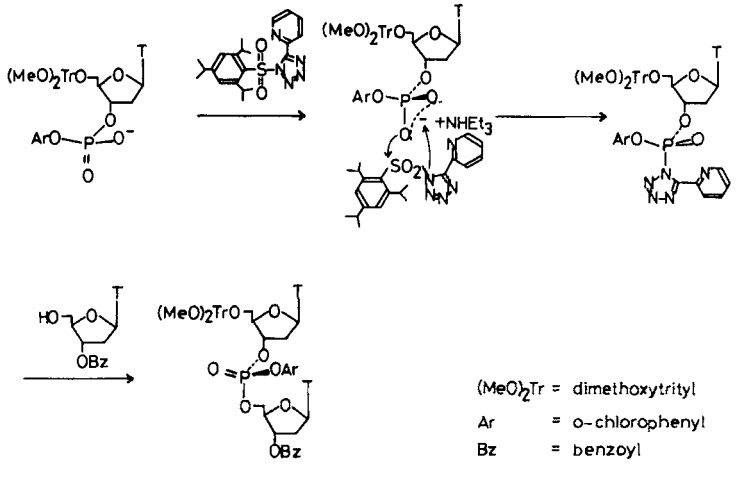

Chart 2

key intermediates for polynucleotide synthesis and are mostly synthesized in liquid phase, in which separation of products is performed by chromatography on silica gel or alkylated silica gel. Stereospecific synthesis reducing diastereoisomers should facilitate separation and purification of phosphotriesters.

REFERENCES

1. C.B. Reese, Tetrahedron, 34, 3143 (1978); M. Ikehara, E. Ohtsuka and A.F. Markham, Adv. Carbhydr. Chem. Biochem., 36, 135 (1979); E. Ohtsuka, M. Ikehara and D. Söll, Nucleic Acids Res., 10, 6553 (1982).
2. E. Ohtsuka, Z. Tozuka and M. Ikehara, Tetrahedron Lett., 22, 4483 (1981).
3. E. Ohtsuka, Z. Tozuka, S. Iwai and M. Ikehara, Nucleic Acids Res., 10, 6235 (1982).
4. C.B. Reese, R. Titmus and L. Yau, Tetrahedron Lett., 2727 (1978).