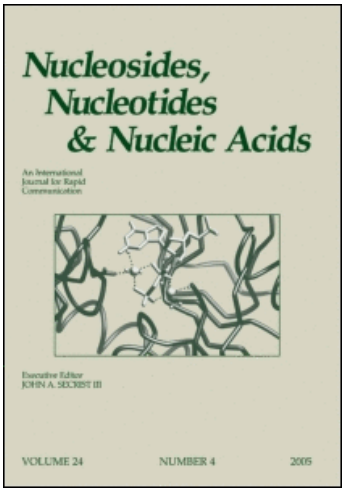

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Diastereoselective Synthesis of Thymidine-Methylphosphonate Dimers

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DIASTEREOSELECTIVE SYNTHESIS OF THYMIDINE-METHYLPHOSPHONATE DIMERS

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Abstract: A method of synthesizing predominantly the Rp isomers of dinucleoside methylphosphonates containing thymidine was recently introduced. Stereochemical assignments ascertained by nmr-experiments (ROESY) and experiments revealing the underlying reaction mechanism will be reported.

Diastereoselective synthesis of dinucleoside methylphosphonates can be achieved by the use of dichloromethylphoshine 2 as a phosphitylating agent and is accomplished in three steps[1]. The reaction of 2 with the 5'-protected first nucleoside 1 in THF at -80 °C yields the diastereomeric intermediates 3a and 3b. These are converted into 5a and 5b by the addition of the 3'-protected nucleoside 4. The resulting trivalent phosphodiesters are oxidised to the phosphonates 6a and 6b using t-butylhydroperoxide.

Stereochemical assignment of the resulting diastereomers was carried out using nuclear overhauser spectroscopy (ROESY[2]). In the Sp isomer only a NOE between $H_{3'}$ and P-Me should be measured while the Rp isomer shows two NOEs between $H_{3'}$ and P-Me and $H_{4'}$ and P-Me.

From ^{31}P-mnr studies it is known, that the diastereoselectivity occurs in the second step of the reaction and is due to steric hindrance caused by the 5'-triarylmethylprotection group of 1 in the kinetically controlled nucleophilic substitution of chloride in 3a and 3b by the second nucleoside 4. The steric hindrance depends on the conformation about the $C_{4'}$-$C_{5'}$-bond of 1. From measurement of the $^3J_{4'5'}$ coupling constants[4] two basic orientations of the 5'-protecting group, above (+sc) or away (ap, -sc) from the sugar ring, can be distinguished. A correlation beween these two basic conformations and the

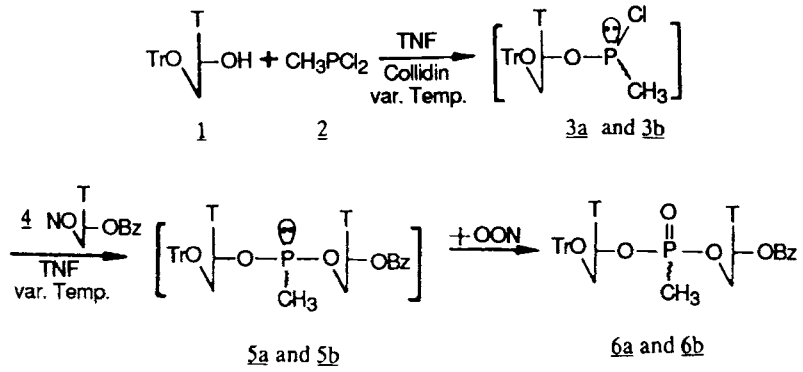

FIG. 1: Synthetic route for the preparation of the methylphosphonate dimers

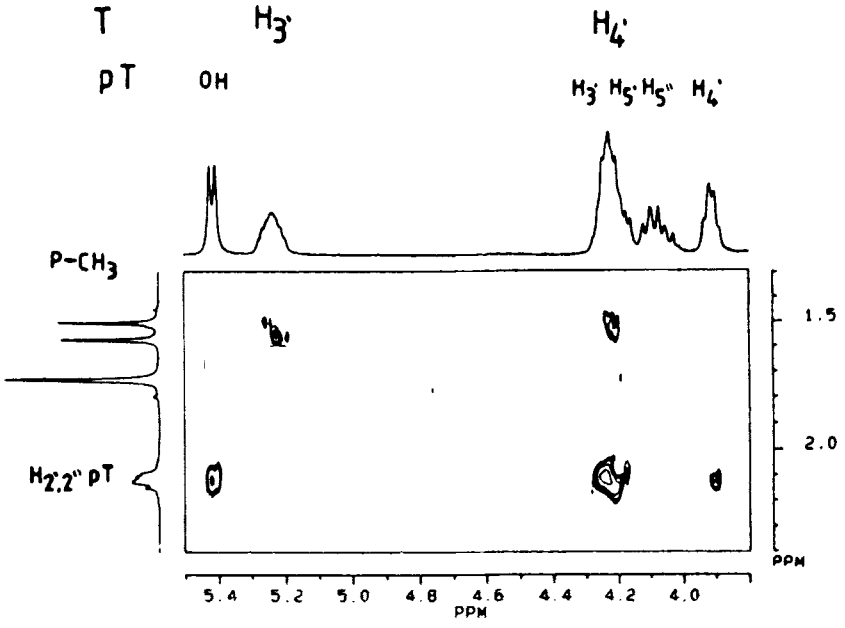

FIG. 2: Part of the ROESY-spectrum of the Rp-isomer of a fully protected TpT-dimer ($CDCl_3$)

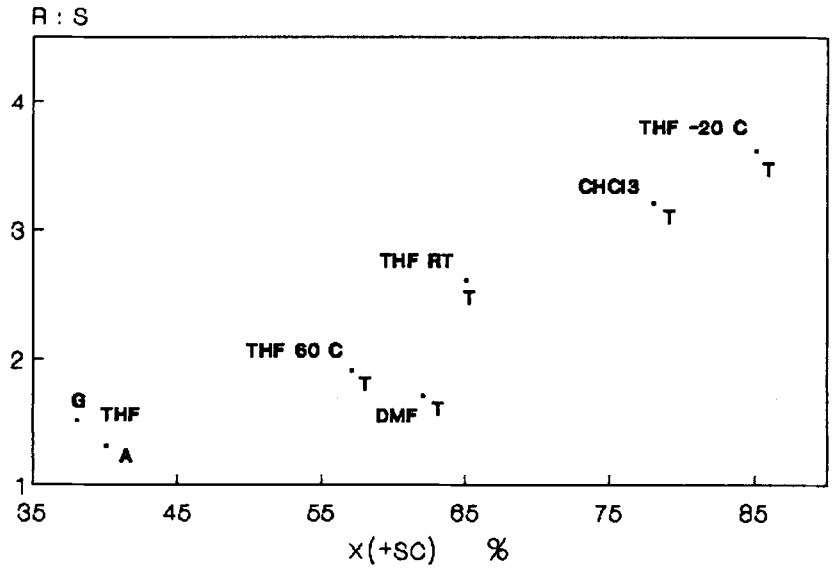

FIG. 3: Correlation of the R:S-ratio with the orientation about the C_4'-C_5' bond

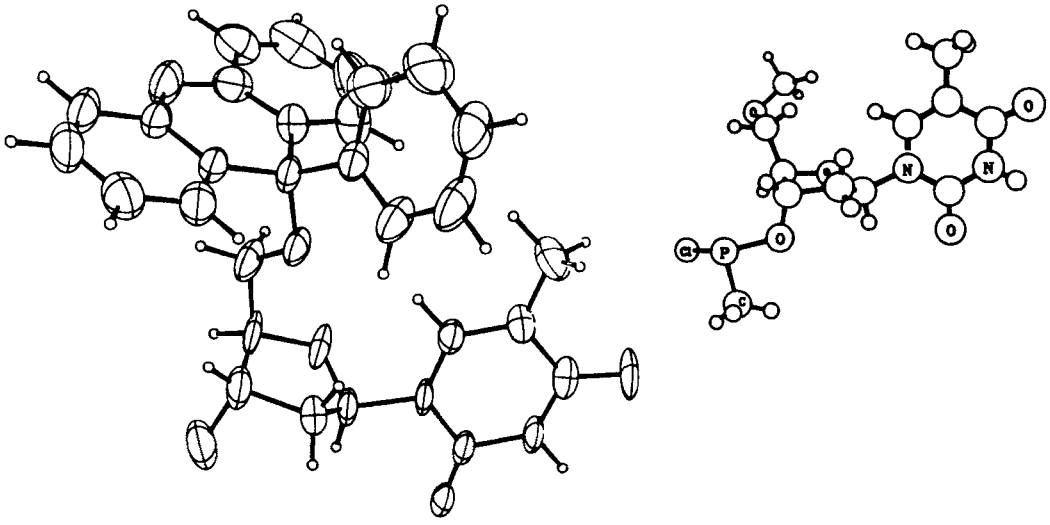

FIG. 4: Crystal structure of 5'-pixylthymidine (left)
AM1-calculated structure of intermediate (right)

R:S-ratio of the diastereomers can be shown. All factors reducing the +sc-population by disrupting intramolecular hydrogen bonds, like solvents with high dielectricity constants (DMF), high temperatures (RT, 60°C) or purine bases (A,G) in 1, cause low R:S-ratios.

During our attempts to get an insight into the reaction mechanism, 5'-protected nucleosides were crystallized, the conformation of the intermediates 3a and 3b were obtained by semiempirical calculations[5] using AM1. The crystal structure of 5'-pixylthymidine[6] shows the orientation of the protecting group. The smaller phenyl group is located above, the bigger xanthyl group away from the sugar ring, so preventing the attack of a nucleophile from the back of the molecule. From the calculated conformation at phosphorus it can be seen, that the attack from the front side (prefered) results in the R-isomer, the attack from the backside (hindered) in the S-isomer, after oxidation.

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