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## DIASTEREOSELECTIVE SYNTHESIS OF THYMIDINE-METHYLPHOSPHONATE DIMERS

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**Abstract:** A method of synthesizing predominantly the *R<sub>p</sub>* 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 dichloromethylphosphine **2** as a phosphitylating agent and is accomplished in three steps<sup>1</sup>. 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 phosphodiester 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<sup>2</sup>). In the *S<sub>p</sub>* isomer only a NOE between H<sub>3'</sub> and P-Me should be measured while the *R<sub>p</sub>* isomer shows two NOEs between H<sub>3'</sub> and P-Me and H<sub>4'</sub> and P-Me.

From <sup>31</sup>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<sub>4'</sub>-C<sub>5'</sub>-bond of **1**. From measurement of the <sup>3</sup>J<sub>4'5'</sub> coupling constants<sup>4</sup> two basic orientations of the 5'-protecting group, above (+sc) or away (ap, -sc) from the sugar ring, can be distinguished. A correlation between these two basic conformations and the

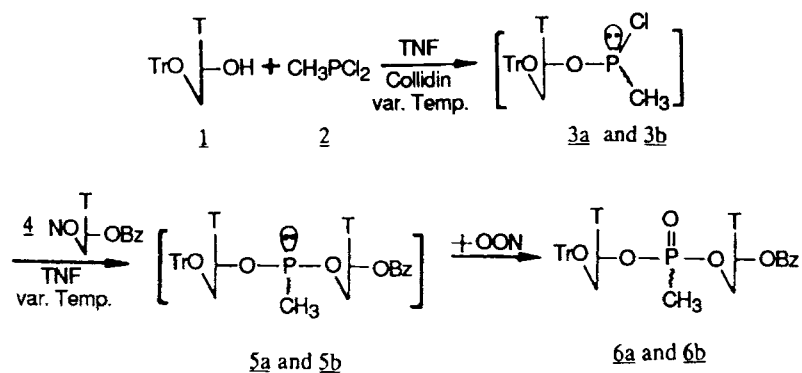
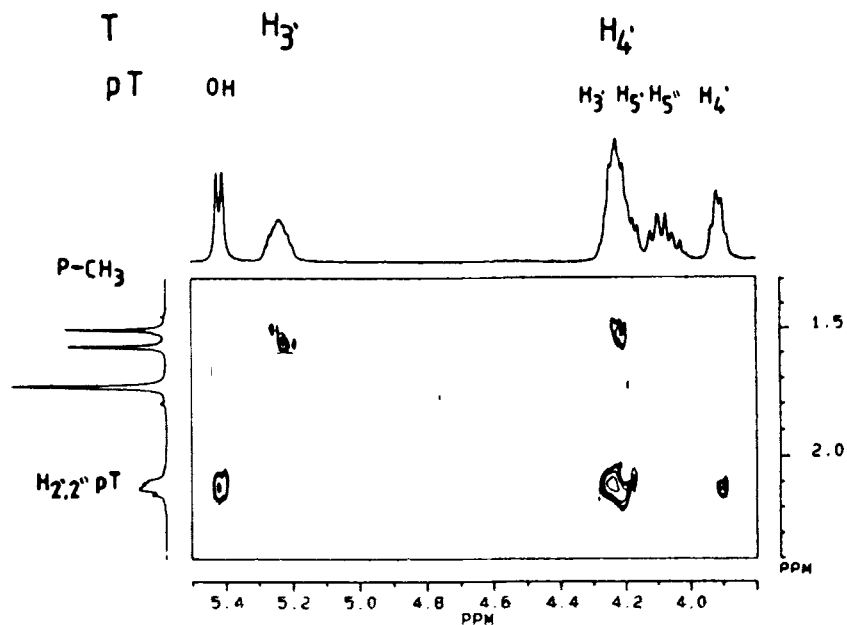


FIG. 1: Synthetic route for the preparation of the methylphosphonate dimers

FIG. 2: Part of the ROESY-spectrum of the Rp-isomer of a fully protected TpT-dimer (CDCl<sub>3</sub>)

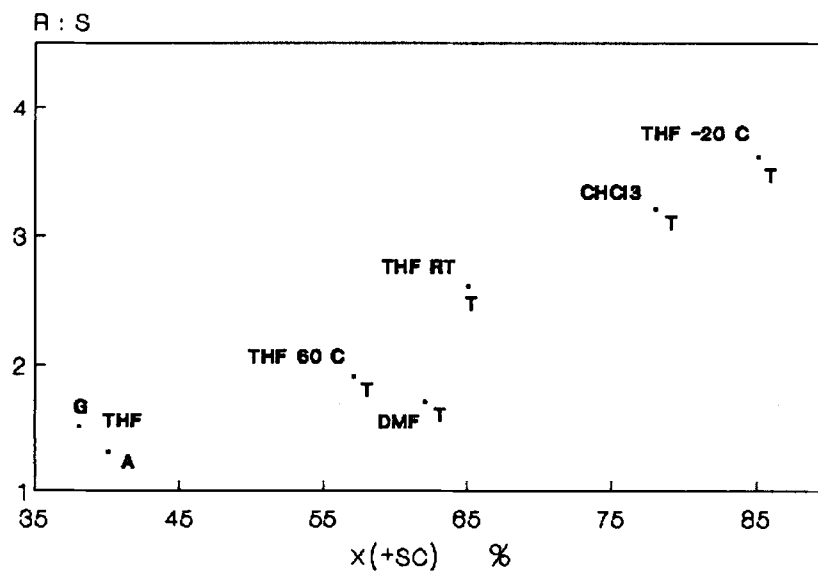


FIG. 3: Correlation of the R:S-ratio with the orientation about the C<sub>4</sub>'-C<sub>5</sub>' bond

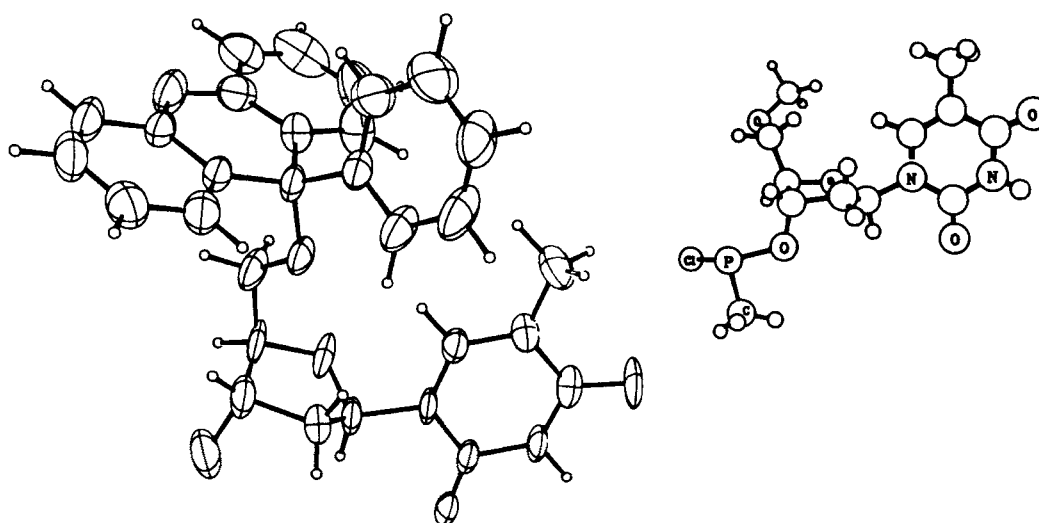


FIG. 4: Crystal structure of 5'-pixylthymidine (left)  
AM1-calculated structure of intermediate (right)

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<sup>5</sup> using AM1. The crystal structure of 5'-pitylthymidine<sup>6</sup> 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 (preferred) results in the R-isomer, the attack from the backside (hindered) in the S-isomer, after oxidation.

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