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### Unusual Stereochemistry of Esterification of Uridine 3'-H-Phosphonothioate

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## UNUSUAL STEREOCHEMISTRY OF ESTERIFICATION OF URIDINE 3'-H-PHOSPHONOTHIOATE

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**Abstract** According to <sup>31</sup>P-NMR correlation analysis, reactive derivatives of uridine 3'-H-phosphonothioate react with O-nucleophiles, probably with retention of configuration.

**Keywords** Nucleoside H-phosphonothioates; retention of configuration; stereochemistry

Condensation of ribonucleoside 3'-H-phosphonate monoesters **1** with nucleosides or alcohols owes its stereoselectivity to dynamic kinetic asymmetric transformation (DYKAT). The main *D<sub>P</sub>* (*S<sub>P</sub>*) diastereomer of the product of type **3** is formed from the minor *L<sub>P</sub>* (*S<sub>P</sub>*) diastereomer of a pivalic-H-phosphonic mixed anhydride **2** (Figure 1A). This was found, for example, in transesterifications of aryl nucleoside H-phosphonates, for which a correlation between the diastereomers of the reactant and the product implied that the minor diastereomer was more reactive and had an *L<sub>P</sub>* (*S<sub>P</sub>*) configuration (Figure 1B).<sup>1</sup>

Ribonucleoside 3'-H-phosphonothioates **4** react with alcohols with high stereoselectivity with dominant formation of the expected *D<sub>P</sub>* (*S<sub>P</sub>*) diastereomers of the products **6** (Figure 2A). However, transesterification of aryl nucleoside H-phosphonothioates with MeOH revealed a completely different stereochemical course of the reaction in comparison to the oxo series (Figure 2B). This indicated that in the thio series the major diastereomer of an intermediate involved is the more reactive one.

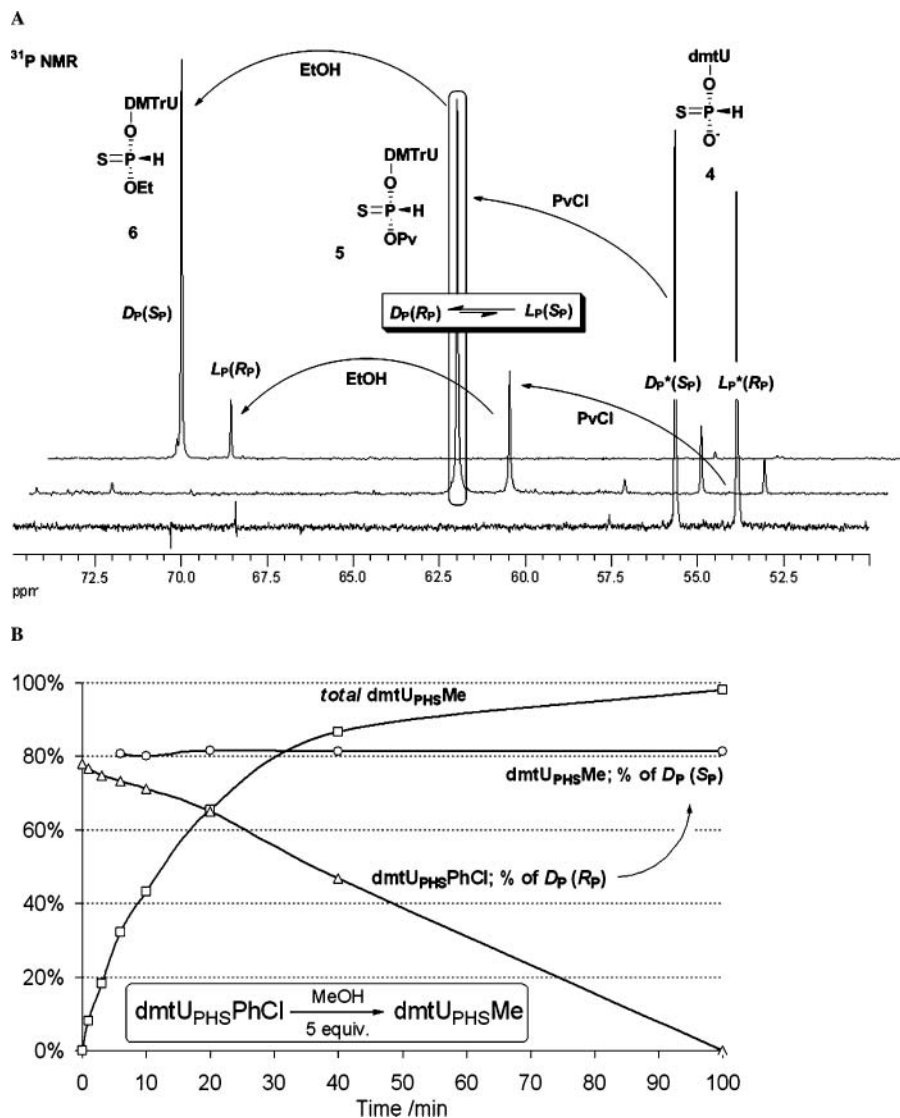
The results can be explained assuming that the major and more reactive *D<sub>P</sub>* (*R<sub>P</sub>*) diastereomer of the mixed anhydride **5** (or of the aryl nucleoside H-phosphonothioate diester) reacts with O-nucleophiles with unusual retention of configuration (Figure 3), probably due to the apical-equatorial geometry of the transition state or pseudorotation of an intermediate phosphorane.

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**Figure 2** Stereochemistry of reactions of ribonucleoside 3'-H-phosphonothioates (THIO series). A. <sup>31</sup>P NMR spectra recorded during condensation of uridine H-phosphonothioate with EtOH. B. Time course of transesterification of *p*-chlorophenyl uridine H-phosphonothioate with methanol.



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