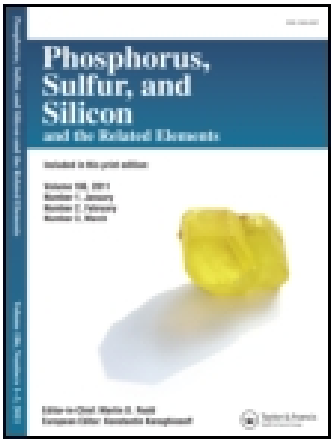

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Unusual Stereochemistry of Esterification of Uridine 3′-H-Phosphonothioate

Michał Sobkowski [a], Jadwiga Jankowska [a], Jacek Stawiński [a b] & Adam Kraszewski [a]

[a] Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznań, Poland

[b] Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, Sweden

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UNUSUAL STEREOCHEMISTRY OF ESTERIFICATION OF URIDINE 3′-*H*-PHOSPHONOTHIOATE

Michał Sobkowski,[1] Jadwiga Jankowska,[1] Jacek Stawiński,[1,2] and Adam Kraszewski[1]

[1]*Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznań, Poland*
[2]*Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, Sweden*

Abstract *According to ^{31}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_P (S_P) diastereomer of the product of type **3** is formed from the minor L_P (S_P) 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_P (S_P) configuration (Figure 1B).[1]

Ribonucleoside 3′-*H*-phosphonothioates **4** react with alcohols with high stereoselectivity with dominant formation of the expected D_P (S_P) 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_P (R_P) diastereomer of the mixed anhydride **5** (or of the aryl nucleoside *H*-phosphonothiate 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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Address correspondence to Michał Sobkowski, Institute of Bioorganic Chemistry, Polish Academy of Sciences, Noskowskiego 12/14, Poznań 61-704, Poland. E-mail: msob@ibch.poznan.pl

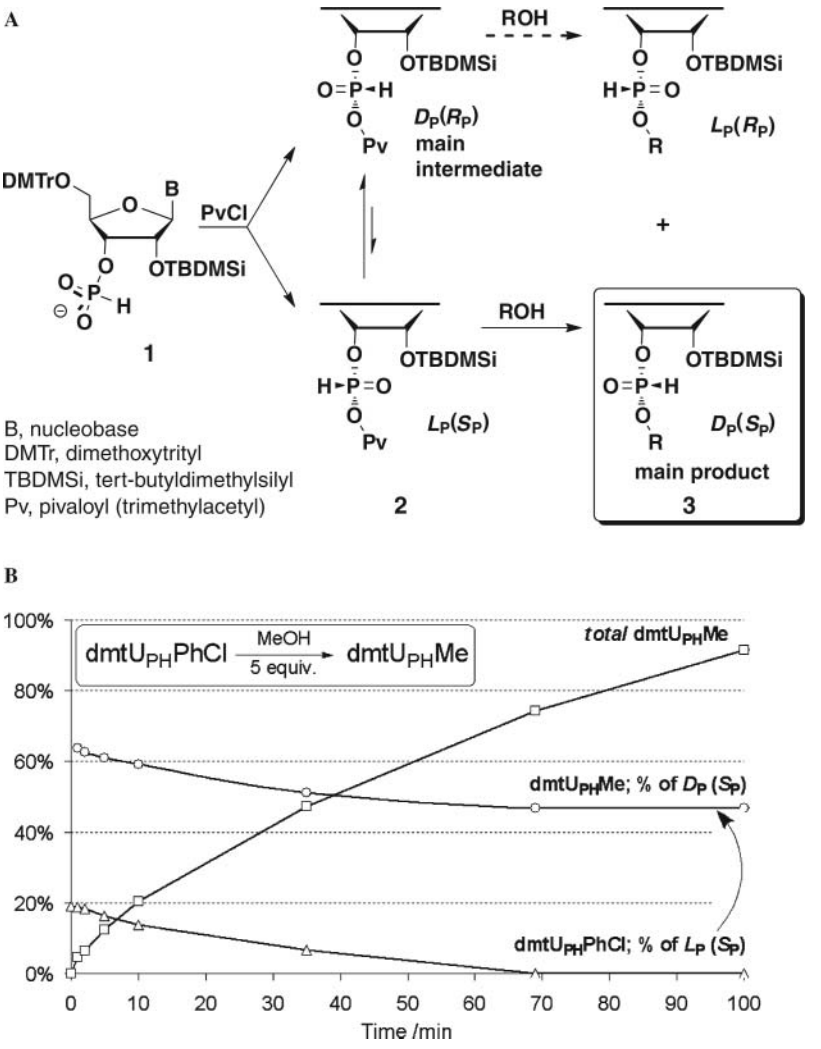

Figure 1 Stereochemistry of reactions of ribonucleoside 3′-*H*-phosphonates (OXO series). A. The dynamic kinetic asymmetric transformation scheme for asymmetric induction during condensation. B. Time course of transesterification of *p*-chlorophenyl uridine H-phosphonate with methanol.

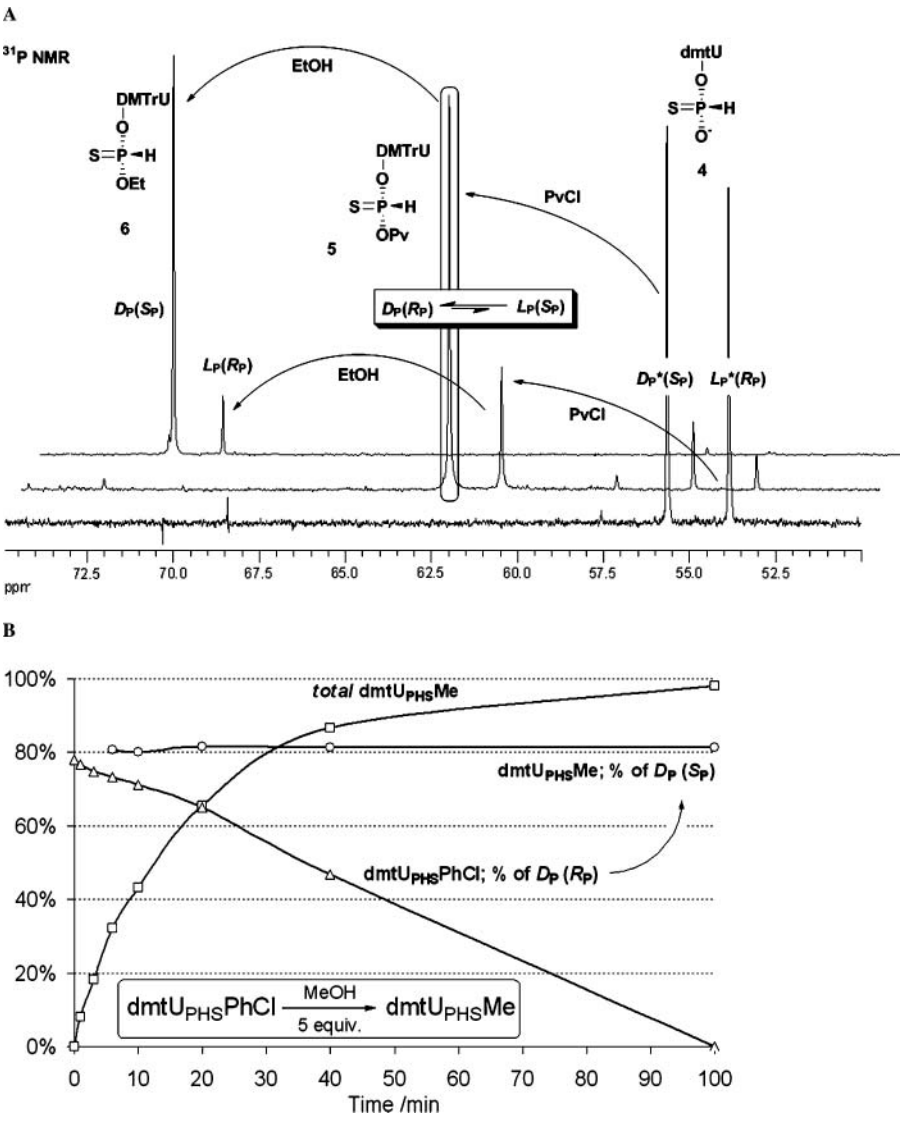

Figure 2 Stereochemistry of reactions of ribonucleoside 3′-*H*-phosphonothioates (THIO series). A. ^{31}P NMR spectra recorded during condensation of uridine H-phosphonothioate with EtOH. B. Time course of transesterification of *p*-chlorophenyl uridine H-phosphonothioate with methanol.

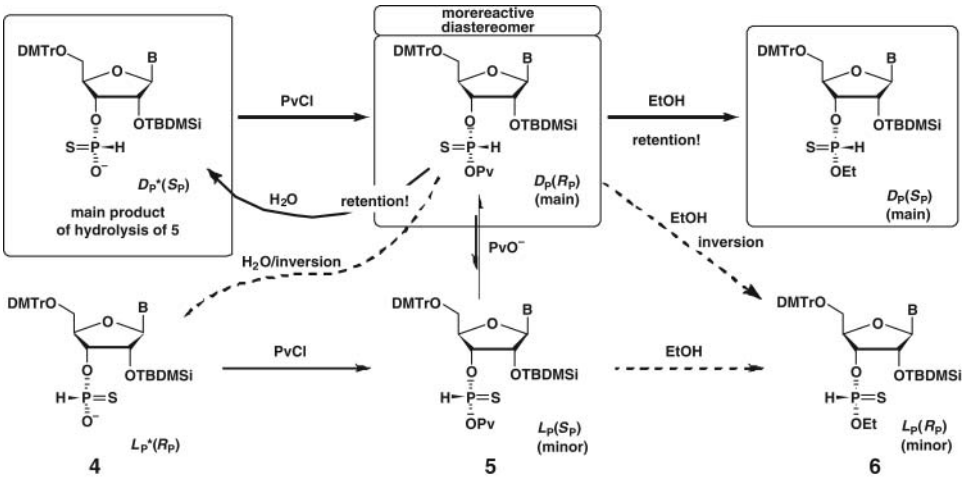

Figure 3 Putative mechanism for asymmetric induction during condensations of ribonucleoside 3′-*H*-phosphonothioates (solid arrows—main paths, dashed arrows—minor paths).

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