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### High Stereoselectivity in the Formation of the Inter-Ribonucleotidic Phosphorothioate Bond

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**HIGH STEREOSSELECTIVITY IN THE FORMATION OF THE  
INTER-RIBONUCLEOTIDIC PHOSPHOROTHIOATE BOND.**

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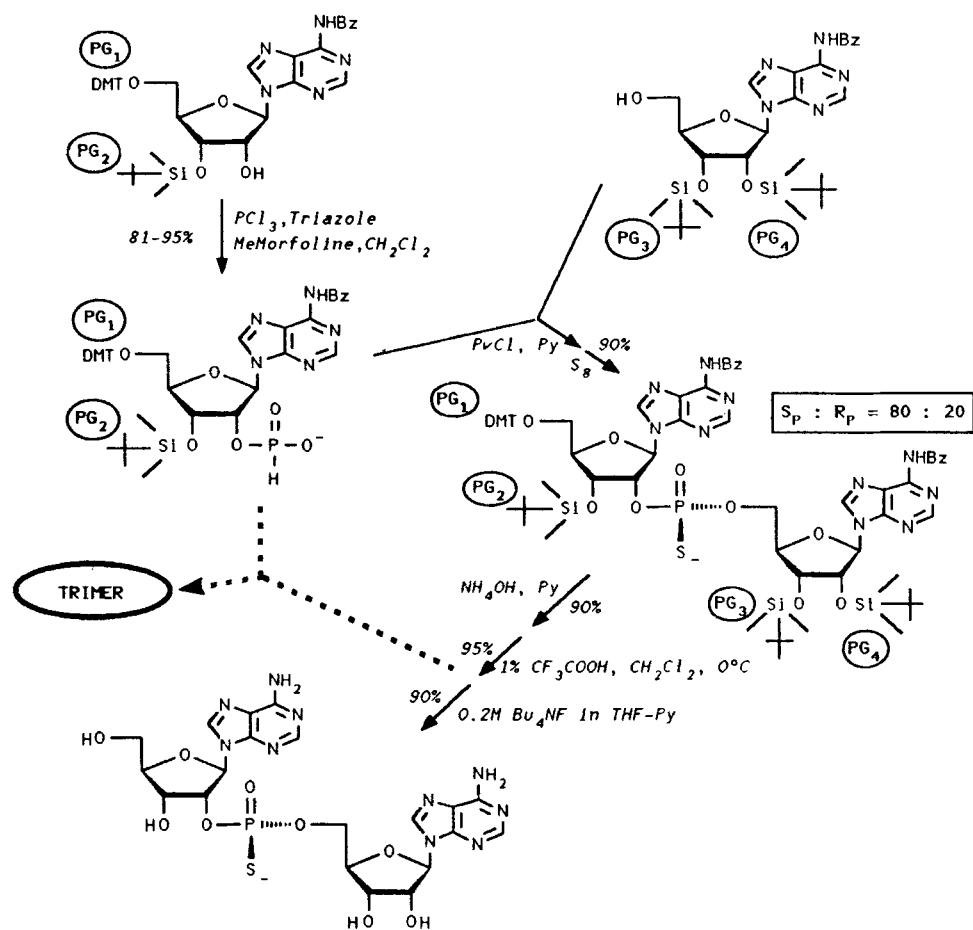
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**Abstract:** 2',5'-Phosphorothioates are synthesized with high  $S_P$ -stereoselectivity by H-phosphonate method and subsequent thio-oxidation.

Modified internucleoside moieties are often endowed with chirality at the phosphorus atom like in phosphorothioates leading to a high number of diastereomers in the case of the related modified oligomers. Efficiently stereocontrolled chemical syntheses of these oligomers are therefore highly attractive. Our interest on analogs of 2',5'-oligoadenylates led us to synthesize 2-5A dimer and trimer phosphorothioates as intermediates for further synthetic utilizations, being particularly interest to the stereochemical aspect.

2',5'-Di- and triadenylates phosphorothioates have been previously prepared by Nelson et al.<sup>1</sup> and by Pfleiderer and Charubala<sup>2</sup> with non stereoselective methodologies. The only stereoselective synthesis of these compounds previously known is the enzymatic synthesis (from 2-5A synthetase and ATP $\alpha$ S)<sup>3</sup>.

The new application to the 2-5A case of a recently well established methodology namely the "H-phosphonate method" followed by thio-oxidation gave a high degree of stereoselectivity in the phosphorothioate formation. Three cases differing for the protective groups at the proper ribosidic hydroxyl groups showed a marked prevalence of the  $S_P$  diastereomer, the ratio of  $S_P$  to  $R_P$  diastereomers being 7:3, 8:2 and only  $S_P$  respectively. This stereoselectivity showed also to occur in the further elongation to trimers. The configuration at the



SCHEME

TABLE

Protecting groups				COUPLING YIELDS	STEREOSELECTIVITY $S_p : R_p$
$\text{PG}_1$	$\text{PG}_2$	$\text{PG}_3$	$\text{PG}_4$		
DMT	$t\text{-BuMe}_2\text{Si}$	$1\text{-Pr}_2\text{Si-O-Si-1-Pr}_2$		80 %	70 : 30
DMT	$t\text{-BuMe}_2\text{Si}$	$t\text{-BuMe}_2\text{Si}$	$t\text{-BuMe}_2\text{Si}$	90 %	80 : 20
$1\text{-Pr}_2\text{Si-O-Si-1-Pr}_2$		$1\text{-Pr}_2\text{Si-O-Si-1-Pr}_2$		85 %	> 99 : < 1

phosphorus atom has been assigned on the basis of the known higher susceptibility of R<sub>p</sub> diastereomer to enzymatic hydrolysis and by comparison with the analytical data reported on the literature<sup>2,4</sup>.

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