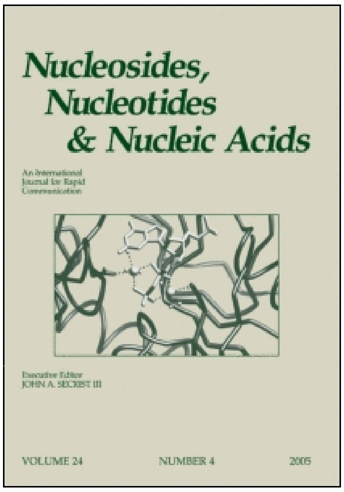

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High Stereoselectivity in the Formation of the Inter-Ribonucleotidic Phosphorothioate Bond

C. Battisthi[a]; M. G. Brasca[a]; S. Fustinoni[a]
[a] Farmitalia Carlo Erba (Erbamont Group) - R. & D., Milano, Italy

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HIGH STEREOSELECTIVITY IN THE FORMATION OF THE INTER-RIBONUCLEOTIDIC PHOSPHOROTHIOATE BOND.

C. Battistini*, M.G. Brasca and S. Fustinoni

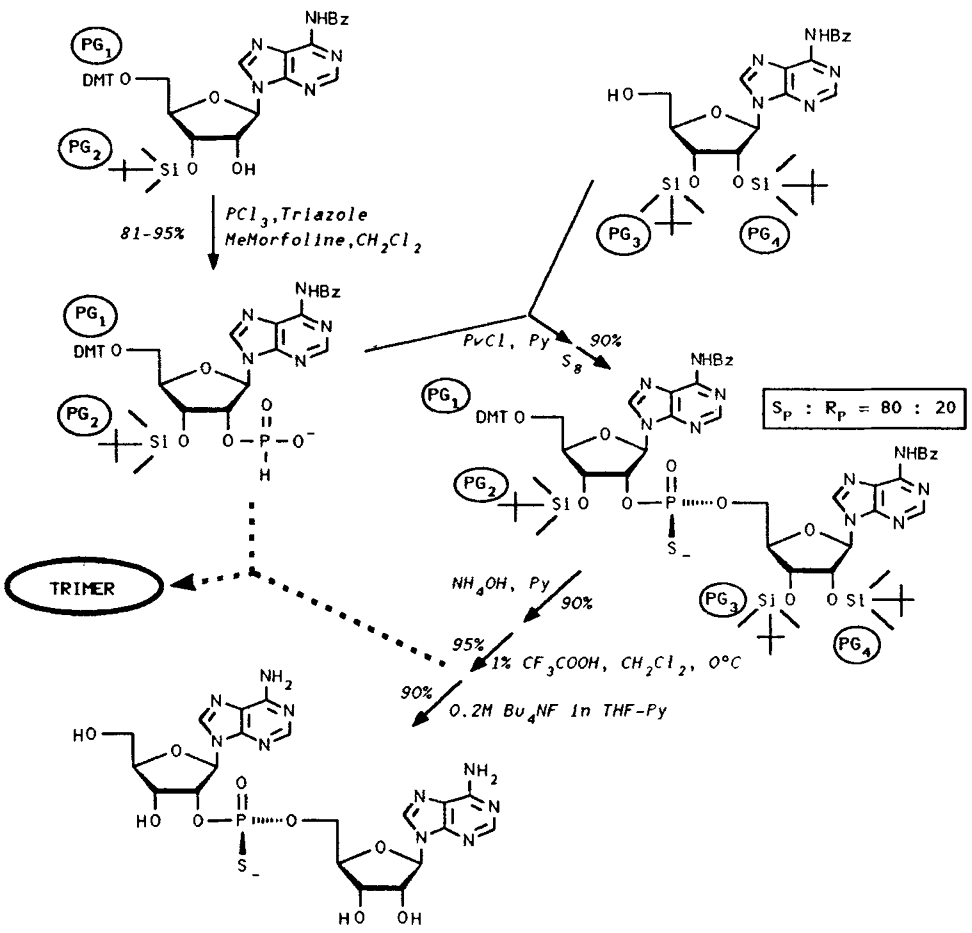
Farmitalia Carlo Erba (Erbamont Group) - R. & D.
Via dei Gracchi 35 - 20146 Milano - Italy

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.[1] and by Pfleiderer and Charubala[2] with non stereoselective methodologies. The only stereoselective synthesis of these compounds previously known is the enzymatic synthesis (from 2-5A synthetase and ATPαS)[3].

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 occurr in the further elongation to trimers. The configuration at the



SCHEME

TABLE

Protecting groups				COUPLING YIELDS	STEREOSELECTIVITY S_P : R_P
PG$_1$	PG$_2$	PG$_3$	PG$_4$		
DMT	t.BuMe$_2$Si	i.Pr$_2$Si-O-Sii.Pr$_2$		80 %	70 : 30
DMT	t.BuMe$_2$Si	t.BuMe$_2$Si	t.BuMe$_2$Si	90 %	80 : 20
i.Pr$_2$Si-O-Sii.Pr$_2$		i.Pr$_2$Si-O-Sii.Pr$_2$		85 %	> 99 : < 1

phosphorus atom has been assigned on the basis of the known higher susceptibility of R_P diastereomer to enzymatic hydrolysis and by comparison with the analitical data reported on the literature[2,4].

REFERENCES

1. Nelson, P.S.; Bach, C.T.; Verheiden, G.P.H. *J. Org. Chem.* **1984**, *49*, 2314.
2. Charubala, R.; Pfleiderer, W. *Nucleosides & Nucleotides* **1987**, *6*, 513.
3. Suhadolnik, R.J.; Lee, C. *Biochemistry* **1985**, *24*, 551.
4. Karikò, K.; Sobol, R.W.Jr.; Suhadolnik, L.; Li, S.W.;Reichenbach, N.L.; Suhadolnik, R.J Charubala, R.; Pfleiderer, W. *Biochemistry* **1987**, *26*, 7127.