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"Synthesis of chiral cyclopropanes, as a key step in the synthesis of conformationally constrained amino acids with biological importance"

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Conformationally constrained amino acids have been the focus of both synthetic and medicinal chemistry; in particular the cyclopropane ring has served as a useful segment in peptidomimetic design. This system affects the chemical and biological properties of peptides through significant conformational restrictions in the amino acid residues. Because ring insertion is an effective way to improve pharmacological properties, intensive studies have been performed towards a stereoselective synthesis of this class of compounds.

The subject of my PhD thesis was to develop efficient methods of synthesis aminocyclopropanephosphonic acids starting from enantiomerically pure cyclopropyl sulfoxides obtained in asymmetric cyclopropanation reaction.

The key step of the synthesis was an asymmetric cyclopropanation reaction applying (*S*)-dimethylsulfoniom-(*p*-tolylsulfinyl)methylide designed and synthesized in our laboratory, performed on corresponding vinylic phosphonates. The additional electron-withdrawing group in α position in these olefins increases the reactivity, and also plays the role of the precursor of an amino moiety.

To obtain the desired biologically active products it was necessary to functionalize cyclopropane by introducing an additional substituent on the C2 or C3 carbon atom. At first, differentiation of the enantiotopic methylene groups was attained by the presence of two deuterium atoms on one of them. In other syntheses functionalization was based on the introduction of an additional substituent onto the cyclopropane ring in a methylation or acylation reaction at the α carbon atom to the sulfinyl group. Moreover, this functionalization had to ensure retention of the chirality of the cyclopropane molecule after removal of the chiral sulfinyl auxiliary in desulfinylation reaction. However, in some examples desulfinylation by *i*-PrMgCl led to

1,2-migration of the phosphoryl group. Elaborated procedures of desulfinylation in two cases allowed us to avoid rearrangement on the cyclopropane ring, either by lowering the temperature or by changing the configuration of the dominating diastereomer of cyclopropyl sulfoxide.

It was proposed that the rearrangement occurred as an internal process in a concerted manner. The feasibility of an intramolecular mechanism was supported by DFT calculations.

It was also discovered that the desulfinylation reaction occurred when $PhSiH_3$ in the presence of KOH was used.

The cyclopropylphosphonates with a retained structure and configuration were used in the synthesis of enantiopure 1-amino-2,2-dideuteriocyclopropanephosphonic acid, 1-amino-2-methylcyclopropanephosphonic acid and 1-carboxy-2-aminocyclopropanephosphonic acid. In the synthesis of a deutered analogue of aminocyclopropanephosphonic acid and phosphonic analogue of 2-aminocyclopropanecarboxylic acids, Curtius rearrangement was used to convert the ester group into an amino group. In the synthesis of a phosphonic analogue of norcoronamic acid, mediated oxidative Hoffmann rearrangement was used to transform amide into amino moiety.