The utility of five-membered sugar-derived nitrones in the Kinugasa reaction.

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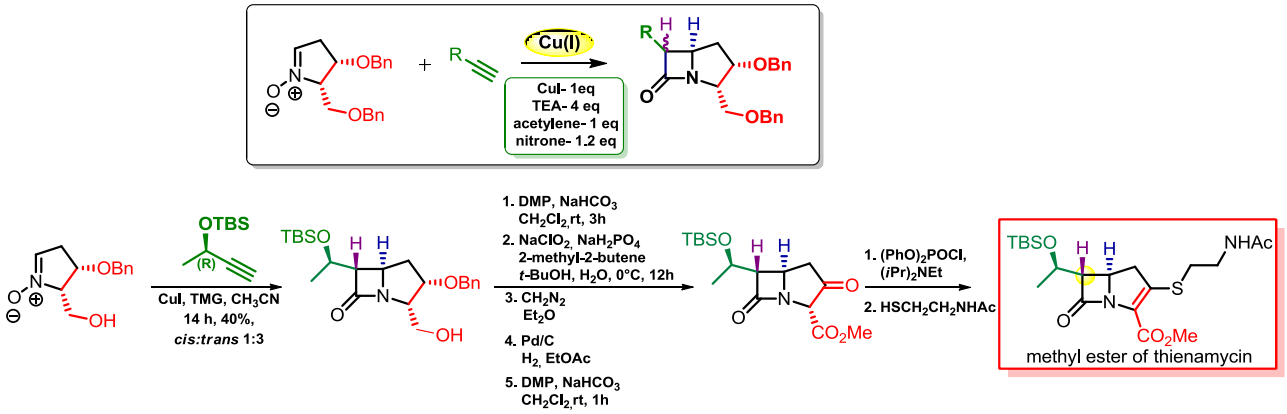
The aim of my PhD thesis was the elaboration and optimization of β-lactam formation based on the Cu(I)-catalyzed reaction of terminal acetylenes and sugar-derived nitrones (Kinugasa reaction). I demonstrated that cyclic nitrones easily available from 2-deoxy-D-ribose represent an attractive substrate for the stereocontrolled synthesis of thienamycin – an important natural carbapenem antibiotic (Scheme 1).



Scheme 1

The first task in my investigation was to develop a suitable and simple method of the synthesis of protected and partly deprotected cyclic nitrones obtained from pentafuranosides. Kinugasa reaction between the nitrone obtained from 2-deoxy-D-ribose and terminal acetylenes gives carbapenams with well defined configuration and moderate yield.

My investigation also showed that the best results in the reaction were obtained when a stoichiometric amount of copper iodide, three equivalents of tethylamine and acetonitrile as solvent were used. The asymmetric induction was found not to depend on the amount of Cu(I) salt employed. Moreover, a stereochemical model of the asymmetric induction was proposed in order to determine the influence of substrate structure on the yield and asymmetric induction.

In the second part of my research I demonstrated that a monoprotected nitrone obtained from 2-deoxy-D-ribose (L-*threo* configuration) guarantees the formation of the correct absolute configuration at the bridgehead carbon atom of the target molecule – thienamycin. Next I showed that the Kinugasa reaction between this nitrone and a terminal alkyne derived from D-lactic acid offers an attractive entry into carbapenems. When the reaction was performed in the presence of tetramethylguanidine (TMG) as a base, it led to the 5,6-*trans*-substituted carbapenam as the main product. The obtained carpapenam with (5*R*, 6*S*) configuration at the azetidinone ring was subsequently subjected to an oxidation/deprotection/oxidation reaction sequence to afford a β-keto ester which was directly transformed into *N*,*O*-protected methyl ester of thienamycin.