

The studies on chemoenzymatic method of synthesis of enantiomerically pure 3-aryl-4-pentenoic acids

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The aim of this study was to develop a new chemoenzymatic method for the synthesis of enantiomerically pure 3-aryl-4-pentenoic acids. These compounds are valuable building blocks in the synthesis of substances with documented biological activity. This activity is closely related to the absolute configuration of stereogenic centers, located in their structure. Therefore, it is extremely important to develop methods of synthesis of enantiomerically pure 3-aryl-4-pentenoic acids and their derivatives.

In this thesis, the studies on enzymatic kinetic resolution and dynamic kinetic resolution of selected 3-aryl-4-pentenoic acids were presented. To achieve these goals, the optimization of these processes in terms of the applied solvent, an alkoxy group donor, an enzyme and a racemization catalyst (for dynamic kinetic resolution) was performed.

Based on obtained results, kinetic resolution of 3-aryl-4-pentenoic acids was developed. This method is based on the enzymatic esterification of racemic carboxylic acids with applied novel alkoxy group donors (orthoesters, acetals, ketals and orthocarbonates). Under optimal conditions the corresponding enantiomerically pure esters were obtained with the highest possible yields for kinetic resolution (50%). After hydrolysis, the corresponding 3-aryl-4-pentenoic acids were obtained with identical optical purity.

In a next step, dynamic kinetic resolution of 3-aryl-4-pentenoic acids was developed. This methodology combines enzymatic kinetic resolution with *in situ* racemization of the substrate catalyzed by the transition metal complexes. After optimization, the corresponding enantiomerically pure esters (after hydrolysis - carboxylic acids) were obtained with quantitative yields. The developed methodology is the first example of the chemoenzymatic synthesis of enantiomerically pure carboxylic acids.

The initial studies were also performed to explain the plausible mechanism of enzymatic kinetic resolution of 3-aryl-4-pentenoic acids with applied alkoxy group donors. The obtained results indicate that the product formation may be a result of promiscuous activity of applied hydrolases.

Moreover, the studies on development of dynamic kinetic resolution of racemic cyclic acids and 3-alkyl-4-pentenoic acid were performed. The initial results of these studies turned out to be very promising regarding the synthesis of this challenging class of compounds.

The major advantages of developed procedures are the simplicity, low cost of the process, high efficiency and excellent enantioselectivity. In addition, the processes are environmentally friendly, which is crucial for the synthesis of the compounds for pharmaceutical application.