ENZYMATIC *N*-ALKOXYCARBONYLATION OF 1-SUBSTITUTED 6,7-DIMETHOXY-1,2,3,4-TETRAHYDROISOQUINOLINES. SUBSTRATE SPECIFICITY

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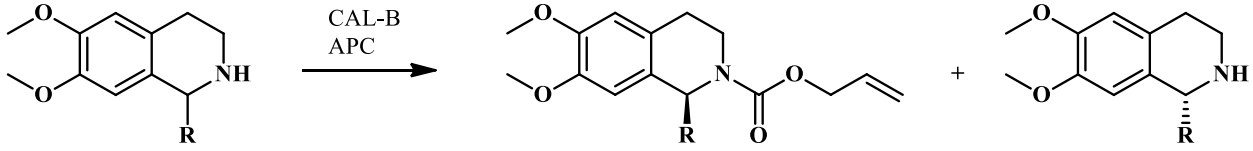
Abstract
In view of substrate specificity, CAL-B-catalysed asymmetric *N*-alkoxycarbonylations of 1-substituted 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (Et, Pr, *i*Pr, *t*-Bu, Ph) have been studied. High enantioselectivities (>200) were observed, when the reactions were performed from the substrates' HCl salts in triethylamine in the presence of allyl phenyl carbonate at 60°C using incubator shaker. The reaction time increased with increasing substituent size in position 1; however, the isopropyl- and *t*-buthyl-substituted compounds proved to be too bulky for the optimum activity of CAL-B.

Introduction
Isoquinoline alkaloids constitute one of the largest groups of natural substances. They possess a skeleton with various biological properties including analgesic effect (morphine), antibacterial activities (berberine), and antispasmodial activities (papaverine)[1]. Additionally, a novel effect of tetrahydroisoquinolines as phosphodiesterase type 4 (PDE4) inhibitor has recently been discovered, which led to the discovery of an effective antipsoriasis agent (skin disease)[2]. The class of isoquinolines are associated with pivotal pharmacological effects, which attracts increasing attention in medicinal and pharmaceutical research. In this work, we aimed to investigate lipase catalyzed kinetic resolution of a homolog series of 1-substituted tetrahydroisoquinolines (±)-**1-5**.

Experimental
Larger part of lipases (CAL-A, CAL-B, AY, AK, PPL) were from Sigma-Aldrich, the PS-IM was from Amano Pharmaceuticals. The substrates were synthetised according to the literature[3]. The aldehydes and the solvents were from Sigma-Aldrich and VWR. The selected acyldonor [allyl phenyl carbonate (APC)] was also from Sigma-Aldrich. For the substrates synthesis Discover CEM microwave reactor was applied. The enantiomeric excess (*ee*) values for the unreacted isoquinolines and the *N*-alkoxycarbonylated enantiomers were determined by Jasco HPLC with Chiralpack IA column after derivatization with acetic anhydride. (*n*-hexane/isopropyl alcohol 93/7 ratio, 1 ml/min flow rate). Optical rotations were measured with Perkin-Elmer 341 Polarimeter. NMR spectrograms were made by Bruker Avance DRX 400.

Results and discussion



(±)-**1-5** (*S*)-**6-10** (*R*)-**1-5**

R: ethyl, propyl, isopropyl, *terc*-buthyl, phenyl

Figure 1. Scheme of the reactions

Racemic 1-substituted 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines were synthetized with 45-65% yield, in microwave inducated Pictet-Spengler reactions, as described in the literature[3]. Next, an adequate analitical methot has been optimised to follow the enzymatic reactions. With the method all of the starting racemates such as the chemically prepared *N*-acylated poducts have ben baseline separated. Preliminary experiments were designed in order to establish the optimum conditions for the enzymatic resolution of model compound (R: ethyl)-**1**, the effects of enzyme, solvent, quantity of acyl donor and temperature on *E* and the reaction rate being examined. Finally, preparative-scale enzymatic reactions were carried out. When the alkoxycarbonylations of **(±)-2-5** compounds with 4 eq allyl phenyl carbonate performed under the optimized conditions: CAL-B, in triethylamine, 60°C in batch reactor, conversion of 50% was reached in 1-3 days for **(±)-1,2,5** which excelent E (>200). Unfortunately in case of resoluton of (±)-**3,4** no products formed geven after 7 days. On the bases of preliminary reactions, preparative scale resolutions were performed with (±)-**1,2,5** under the optimal conditions (CAL-B, APC, Et_3N, 60°C).

Conclusion

Kinetic resolution of 1-substituted-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines have been prepared through CAL-B catalyzed *N*-alkoxycarbonylation. Excellent enantioselectivity (E>200) when solvent was triethylamine, in presence of 4 eq APC, and the temperature was 60°C. The unreacted (*R*)-**1,2,5** and alkoxycarbonylated (*S*)-**6,7,10** products were isolated with *ee* 95-97, yield 32-42%. To follow the enzymatic reactions and determine conversion, enantioselectivities and enantiomeric excess an adequate analytical method was optimized with HPLC.

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