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Chemoenzymatic synthesis of rasagiline mesylate using lipases

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ABSTRACT

A straightforward chemoenzymatic synthesis of rasagiline mesylate has been developed. The key steps for the introduction of chirality involved kinetic enzymatic resolution with lipases via acetylation of *rac*-indanol and an inversion configuration Mitsunobu reaction of the produced (*S*)-indanol. Immobilized lipase from *Thermomyces lanuginosus* proved to be a robust biocatalyst in the kinetic resolution, leading to (*S*)-indanol with high selectivity (*e.e.* > 99%, *E* > 200) in just 15 min, at 35 °C, in hexane, being reused for ten-times without significant loss of the activity and selectivity.

1. Introduction

Rasagiline mesylate (***R*-7**) (Fig. 1), also known as *R*-(+)-*N*-propargyl-1-aminoindan mesylate, is a commercially marketed pharmaceutically active substance, under the brand name Azilect®, indicated for treatment of Parkinson's disease (PD) being effective both as monotherapy in early PD and as adjunctive in patients with advancing PD and motor fluctuations [1–9]. This chiral compound is a potent second-generation propargylamine pharmacophore that selectively and irreversibly inhibits the B-form of the monoamine oxidase enzyme (MAO-B) over type A by a factor of fourteen [3–10]. European drug-regulatory authorities approved this potent MAO-B inhibitor in February 2005 and the US FDA in May 2006 [11]. Although the *S*-(−)-enantiomer of *N*-propargyl-1-aminoindane still exerts some neuroprotective properties, the potency of *R*-(+)-enantiomer against the MAO-B enzyme is approximately 1000-fold higher [12].

In the last years, many efforts have been focused on developing procedures to introduce chirality in the target molecule (***R*-7**) by the synthesis of *R*-1-aminoindan or *R*-*N*-propargyl-1-aminoindan (***R*-6**). Some examples are the strategies based on classical kinetic resolution with chiral acids [4,12–22], hydrosilylation in the presence of chiral rhodium [23] or ruthenium [24] catalysts, asymmetric synthesis using chiral auxiliaries [25–28] or asymmetric induction using chiral oxazaborolidine [29]. Biocatalytic routes include deracemization with cyclohexylamine oxidase (CHAO) [30], kinetic enzymatic resolution in the presence of subtilisin [31,32], ω-transaminase [33], lipase from *Candida antarctica* B [34] and more recently dynamic kinetic resolution by *C. antarctica* B and Pd nanocatalyst [35]. Although less employed, an alternative approach to the introduction of chirality in rasagiline mesylate (***R*-7**) is the synthesis of the intermediate (*S*)-indanol followed by conversion of the hydroxyl group into a leaving group, and subsequent reaction with an appropriate nucleophile to promote inversion of configuration [36,37].

Chemists have found great difficulties in the kinetic resolution of small molecules via nonenzymatic systems, *rac*-indanol being historically one of the most challenging alcohols to enrich via the aforementioned methodology [38–41]. On the other hand, enzymatic processes have been utilized successfully in resolving both enantiomers of *rac*-indanol with high selectivity, especially in the presence of lipases [42–50].

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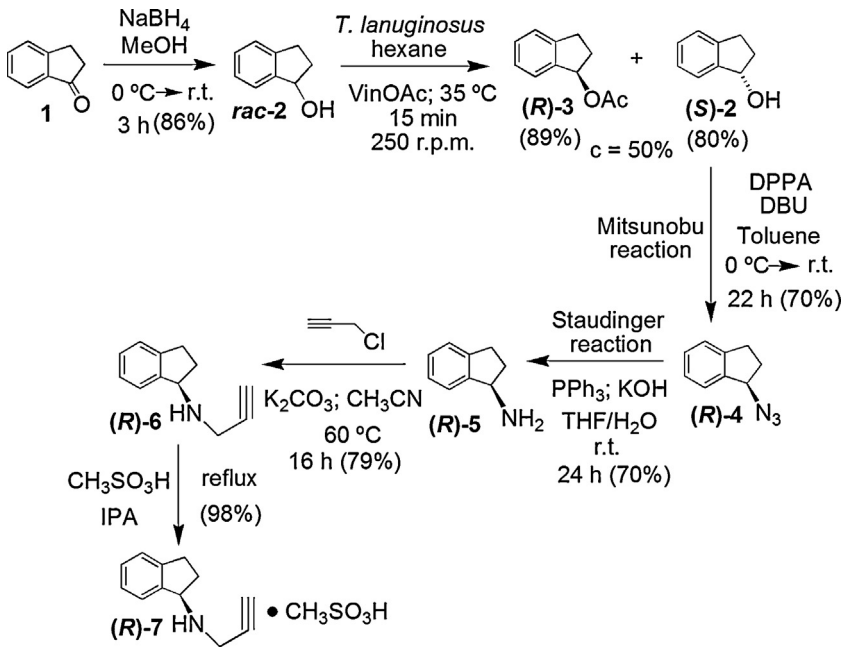

Fig. 1. Chemoenzymatic synthesis of rasagiline mesylate.

Particularly, lipases (EC 3.1.1.3) have largely demonstrated their powerful utility as a versatile tool for the synthesis of enantiomerically pure compounds of great importance, and are the most employed enzymes in the industrial process in the last three decades. This fact is mainly based on their wide availability in nature, their broad substrate acceptance and low cost, besides the maintenance of high activity and selectivity in organic solvents, and the fact of not requiring the addition of cofactors during the biocatalytic process [51,52].

Herein, we wish to report the chemoenzymatic synthesis of rasagiline mesylate (***R*-7**) which had the introduction of the chirality in the target molecule achieved by lipase-mediated kinetic resolution of *rac*-indanol (***rac*-2**) followed by Mitsunobu reaction. We have especially focused on the optimization of the reaction conditions including the enzymes recycling outcome.

2. Experimental

2.1. Enzymes

(i) Immobilized lipases: *C. antarctica* lipase type B immobilized on acrylic resin (CAL-B, Novozym 435, 7300.0 U/g) and *Rhizomucor miehei* lipase immobilized on anionic resin (RML, 150.0 U/g) were purchased from Novozymes®. *Thermomyces lanuginosus* lipase immobilized on immobead-150 (TLL, 250.0 U/g) and *Rhizopus oryzae* lipase immobilized on immobead-150 (ROL, 340.0 U/g) were acquired from Sigma-Aldrich®. (ii) Free lipases: *Pseudomonas fluorescens* lipase (AK, 22,100.0 U/g), *Penicillium camemberti* lipase (G, 50.0 U/g), *Aspergillus melleus* lipase (Acylase I, 200.0 U/g) were acquired from Sigma-Aldrich®. Porcine pancreas lipase (PPL, 46.0 U/g solid), and *Candida rugosa* lipase (CRL, 1.4 U/g) were obtained from Sigma®.

2.2. Chemical materials

Chemical reagents were purchased from different commercial sources and used without further purification. Methanol, hexane, ethyl acetate and dichloromethane were acquired from Synth®. Toluene and diethyl ether were obtained from Vetec®. Acetonitrile and hexane, HPLC grade, were purchased from TEDIA® and tetrahydrofuran was acquired from Sigma-Aldrich®. Solvents used in the reaction of biocatalysis were distilled over an adequate desiccant under nitrogen. Analytical TLC analyses were performed on aluminum sheets pre-coated with silica gel 60 F254 (0.2-mm thick) from Merck®. Flash chromatographies were performed using silica gel 60 (230–240 mesh).

2.3. Analysis

Melting points of the *rac*-indanol (***rac*-2**) and (*R*)-*Rasagiline Mesylate* (***R*-7**) were determined in open capillary tube Mettler Toledo model FP62 and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1720-X F7 using NaCl plates or KBr pellets in. ^{1}H, ^{13}C NMR, and DEPT were obtained using Spectrometers Bruker model Avance DPX 300 and Avance DRX-500, operating at frequencies of 300 and 500 MHz for hydrogen and frequencies of 75 and 125 MHz for carbon, respectively. The chemical shifts are given in delta (δ) values and the coupling constants (J) in Hertz (Hz). Measurement of the optical rotation was done in a Perkin-Elmer 241 polarimeter. Gas chromatograph (GC) analysis were carried out in a Shimadzu chromatograph model GC 2010 with a flame ionization detector using a chiral column CP-chirasil-dex (25 m × 0.25 mm × 0.25 μm, 0.5 bar N_2). For the following of the reaction time courses: 110 °C; 0.5 °C/min 130 °C (hold 15 min); 5.0 °C/min 140 °C (hold 5 min). Retention times were: (*S*)-acetate (***S*-3**) 32.68 min; (*R*)-acetate (***R*-3**) 33.17 min; (*S*)-alcohol (***S*-2**) 37.95 min; (*R*)-alcohol (***R*-2**) 38.98 min.

2.4. Calculation of enantiomeric excess, conversion and enantiomeric ratio

The efficiency of kinetic resolution was evaluated based on the optical purity of the compounds, expressed in terms of enantiomeric excess of the substrate ($e.e._s$) and product ($e.e._p$), using the following Eqs. (1) and (2):

$$e.e._s = \frac{A-B}{A+B} \quad (1)$$

$$e.e._p = \frac{A-B}{A+B} \quad (2)$$