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Enzymatic Resolution of *cis*-Dimethyl-1-acetylpiperidine-2,3-dicarboxylate for the Preparation of a Moxifloxacin Building Block

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This work presents the enantioselective resolution of a water-soluble racemic mixture of *cis*-dimethyl 1-acetylpiperidine-2,3-dicarboxylate catalyzed by *Candida antarctica* lipase B. The separation of the carboxylic acid product in its (2*R*,3*S*) configuration from non-reacted substrate in the (2*S*,3*R*) configuration was easily obtained by organic phase extraction. The latter molecule can be used as an enantiomerically pure precursor in the synthesis of (4aS,7aS)-octahydro-1H-pyrrolo[3,4-b]pyridine, an expensive building block in the production of the antibiotic Moxifloxacin. On the other hand, the hydrolyzed product in the (2*R*,3*S*) configuration can be used for the preparation of a neuromediator analogue. The lipase demonstrated enantioselectivity towards the (2*R*,3*S*) substrate enantiomer and regioselectivity towards the ester in position 3 of the molecule. Studies of hydrolysis kinetics and the use of the immobilized enzyme were performed to evaluate its industrial application.

Introduction

Pharmacological activity is often linked to only one of the two possible enantiomers of a drug, or to a portion of it, due to the different affinity of the two molecules for the biological target. Indeed, control authorities generally allow chiral drugs to be put on the market only in their optically pure and active forms because of possible side effects of inactive enantiomers. Therefore, large scale production of pure stereoisomers is strictly necessary and is usually obtained starting from prochiral molecules by using asymmetric synthesis or by racemate resolution achieved by crystallization, liquid chromatography or enzymatic resolution.

Lipase or esterase enzymes can be exploited in biocatalytic processes to obtain enantiomeric pure compounds of interest starting from racemic mixtures of esters.[1] The appropriately chosen enzyme selectively hydrolyses the ester bond of one of the two ester enantiomers, resulting in the resolution of the racemic mixture. The required enantiomer can be then separated and subsequently used. Many enzymatic resolutions have been proposed to produce useful Active Pharmaceutical Ingredients (API).[2,3]

Moxifloxacin is a third generation quinolonic antibacterial molecule. It is chemically synthesized and it is active, in particular, against gram-negative and gram-positive bacteria that cause respiratory diseases. It is successfully employed for the treatment of infections of the respiratory system (pneumonia, chronic sinusitis and chronic bronchitis), skin, soft tissues, and it is also used at low doses for the treatment of ophthalmic diseases. Clinical trials where Moxifloxacin is used in the treatment of tuberculosis are also being carried out. Its bactericidal activity is mediated by the inhibition of topoisomerase II and IV, which are involved in the replication of bacterial DNA.[4–8]

The Moxifloxacin molecule is characterized by a fluoroquinolonic skeleton, in common with two other antibiotics of the same category (Gatifloxacin and Balofloxacin), and by an (*S*,*S*)-2,8-diazabicyclo[4.3.0]nonane side chain. The synthesis of the latter compound is the most critical, since it has two stereocenters, both in the S configuration, providing levorotatory optical activity. To the best of our knowledge, its preparation is obtained by resolving racemates of its intermediates. For instance, it can be obtained starting from pyridine-2,3-dicarboxylic acid through several chemical steps, that give the precursor 8-benzyl-*cis*-2,8-diazabycyclo[4.3.0]nonane racemate, then resolved using natural (*R*,*R*)-(+)-tartaric acid.[9] Another recently reported method is based on a quick procedure that involves the preparation of a sulfonamide derivative and its resolution with mandelic acid.[10] Before our study, a single chemo-enzymatic approach was reported, exploiting selective acetylation and resulting in an unsatisfactory process.[11]

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Here, we propose a new biocatalytic pathway for the preparation of (*S*,*S*)-2,8-diazabycyclo[4.3.0]nonane, a chiral building block for Moxifloxacin synthesis. Starting from N-substituted esters of pyridine 2,3 dicarboxylic acid, reduction of the pyridine ring using hydrogen and Pd/C can easily produce the two *cis* isomers of the dialkyl piperidine-2,3-dicarboxylate in the (2*S*,3*R*) and (2*R*,3*S*) configurations. Our idea was that of separating the two *cis* enantiomers resulting from the enzymatic hydrolysis of one of them and then using the (2*S*,3*R*) enantiomer for the preparation of the desired building block.

We searched in the literature for several commercially available hydrolytic enzymes (esterases, lipases, proteases) able to resolve racemates of analogue compounds. Some of them demonstrated interesting selectivity among pipecolate esters. Kinetic resolution of methyl pipecolate using *Aspergillus niger* lipase with an E = 20 in favor of the *S* enantiomer was reported.[12] *Candida antarctica* lipases A and B (Cal B) were also used to perform resolution of methyl pipecolinate by selective N-acylation and transesterification, respectively.[13] Pig liver esterase was extensively studied to perform racemic resolution; some preliminary results were obtained using N-acetylated 2- or 3-methyl pipecolinate as substrates.[14] Two lipases from *Candida cylindracea* were successfully used together with Cal B and pig liver esterase for the preparation of 3,5-dicarboxylic acid monomethyl ester,[15] while analogue-selective reactions were also designed using porcine pancreatic lipase.[16] Finally, both amidase[17] and protease[18] were proposed for the racemic resolution of esters.

A library of the enzymes mentioned above, with the addition of Subtilisin Carlsberg protease and *Citrus sinensis* amidase, was set up and used to screen the racemic substrates in order to identify a suitable enzyme-substrate combination able to resolve the racemate.

Results and Discussion

Preliminary screening

To identify the best substrate for subsequent enzymatic hydrolysis, three racemic mixtures of *cis* esters were prepared to be used as substrate: *cis*-dimethyl piperidine-2,3-dicarboxylate (**1**), *cis*-diethyl piperidine-2,3-dicarboxylate (**2**) and *cis*-dimethyl 1-acetylpiperidine-2,3-dicarboxylate (**3**) (Figure 1).

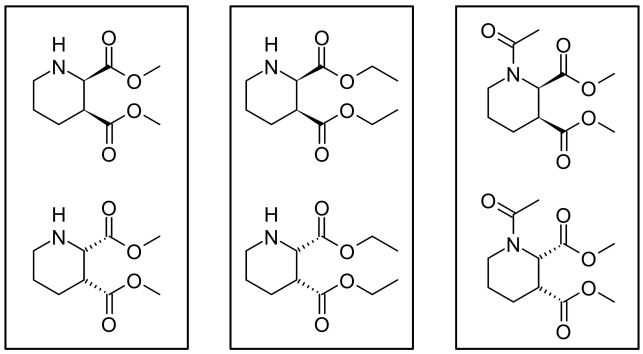

Figure 1. Compounds used as substrates for enzymatic screening. Racemate is intended as mixture of *cis*-enantiomers: **1**, *cis*-dimethyl piperidine-2,3-dicarboxylate; **2**, *cis*-diethyl piperidine-2,3-dicarboxylate; **3**, *cis*-dimethyl 1-acetylpiperidine-2,3-dicarboxylate.

All of them could be obtained from the cheap pyridine-2,3-dicarboxylic acid molecule and easily transformed into the desired (*S*,*S*)-2,8-diazabicyclo[4.3.0]nonane synthon after racemate resolution. These racemic mixtures were used as substrates for the screening of the following enzymes: *Candida antarctica* lipase A, *Candida antarctica* lipase B (either free or immobilized), *Aspergillus niger* lipase, *Candida cylindracea* lipase, *Citrus sinensis* Amidase, pig liver esterase, porcine pancreatic lipase and Subtilisin Carlsberg. The esterase activity reported for the purchased enzymes referred to different substrates, not exclusively esters, as summarized in Table 1.

In order to set up reactions with the same enzyme units, their activity was normalized using PNPA as the common ester substrate.[12] According to the relative activity measured with PNPA (Table 1), we performed a preliminary screening of the reactivity of the enzymes (at 0.1–2 mg/ml concentration) towards the piperidine diester substrates **1**, **2** and **3** (used at 10 mM concentration). After a one-day incubation, all mixtures were analyzed by ^{1}H-NMR and HPLC-MS. In the case the enzyme would act with absolute enantiomeric preference, we expected the reaction to proceed until hydrolysis of half of the initial substrate. A single enzyme-substrate combination was shown to be promising, *Candida antarctica* lipase B and

Table 1. Esterase activity of enzymes used for initial screening, as declared by suppliers and referring to different substrates (second column), or referring to ester p-nitrophenyl-acetate.[12]

Enzyme	Declared substrate	Declared specific activity	Activity with PNPA[a] (mU/mg)
Aspergillus niger lipase	Triolein	4 U/g	10,27
Candida antarctica lipase A	Trybutirin	30 U/mg	72,5
Candida antarctica lipase B	Trybutirin	34 U/mg	98,3
Candida cilyndacea lipase	Triolein	15–25 U/mg	131,3
Citrus sinensis amidase	Z-gly-tyr-NH_2	2 U/ml	0,33[b]
Pig liver esterase	Ethyl valerate	> 130 U/mg	28,2
Porcine pancreatic lipase	Olive oil	27,4 U/mg	2,39
Subtilisin Carlsberg protease	Casein	12 U/mg	8,78

[a] PNPA: p-nitrophenyl acetate. [b] (mU/μL)

substrate *cis*-**3**. This combination was therefore selected for further investigation.

Investigation of hydrolysis of substrate 3 by Cal B

In the preliminary screening, Cal B was shown to be able to partially hydrolyze the racemic mixture of *cis*-dimethyl 1-acetylpiperidine-2,3-dicarboxylate (*cis*-**3**). In particular, ^{1}H-NMR analysis detected the formation of methanol after reaction with the enzyme, while HPLC-MS analysis showed that the initial racemic mixture, characterized by an m/e value of 244.1, was partially hydrolyzed to give a product of m/e 231.1, corresponding to the mono-ester form.

To evaluate if the reaction was enantioselective, an experiment was performed using 1 g of racemic substrate **3** and 0.1 g of enzyme in 10 ml of 0.1 mM phosphate buffer at pH 6, in a controlled stirred reactor. Progress of the hydrolysis was monitored by HPLC equipped with a chiral column, analyzing samples drawn from the reaction mixture at different times (Figure 2).

The results clearly showed the high enantiomeric selectivity of Cal B, which catalyzed the hydrolysis of a single enantiomer of the racemic mixture. Prolonged reaction times progressively raised the yield of the reaction. The other enantiomer remained non-reacted. Configurations of the hydrolyzed product and the non-reacted substrate were determined after their separation and respective transformation to 2,8-diazabicyclo[4.3.0]nonane, as described in Experimental Section. Resulting synthons were compared in a GC chiral column with the molecular standard (*S*,*S*)-2,8-diazabicyclo[4.3.0]nonane, allowing assignment of the enantiomeric configuration to the starting molecules. These transformations allowed us to attribute the enantiomeric configuration to the hydrolyzed enantiomer, which was in the (2*R*,3*S*) form, and to the non-reacted one, which was in the (2*S*,3*R*) configuration.

Concerning the methyl ester position, HPLC-MS analysis confirmed that one of the two ester groups was hydrolyzed. In order to verify if the hydrolysis had occurred with regioselectivity, and to unambiguously identify the position of the hydrolyzed ester, ^{1}H one-dimensional and two-dimensional (^{1}H-^{1}H DQF-COSY, ^{1}H-^{13}C HMQC and ^{1}H-^{13}C HMBC) NMR experiments were performed on the racemic substrate **3**. The same experiments were repeated on a parallel Cal B-treated sample, where the reaction had reached more than 40% of conversion. The first series of experiments allowed us to achieve the assignment of the initial substrate **3**; by comparison, the second series allowed the NMR carbon and proton assignment for the mono-hydrolyzed product (Figure S1). The resulting assignment is summarized in Table S1.

Two possible structural configurations, chair and boat, were observed for both substrate **3** and the mono-hydrolyzed product, as deduced from the presence of lower intensity peaks, generally assigned to the less stable boat configuration of the molecule.

The results of the NMR analysis showed that hydrolysis occurs at position 3. Figure S1 shows a strip of the HMBC spectra, before (b) and after (d) enzymatic treatment of the

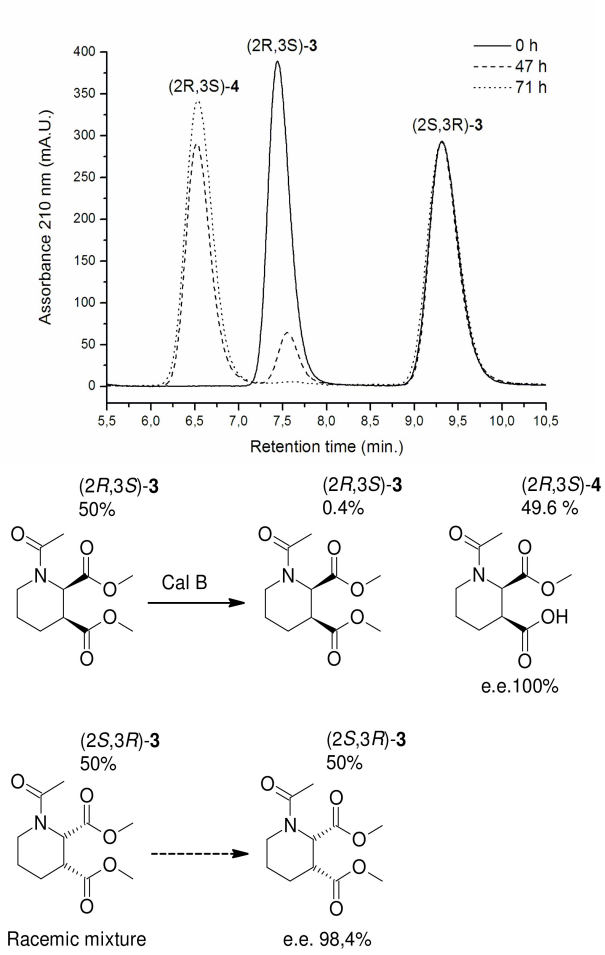

Figure 2. On the top, time course chiral HPLC analysis performed on the reaction mixture, as described in the text. The peaks were assigned after characterization of products (see Results section): peaks at 6.52, 7.55 and 9.3 minute retention time correspond to (2*R*,3*S*)-**4** monoacid, (2*S*,3*R*)-**3** diester and to (2*R*,3*S*)-**3** diester, respectively. Below, schematic summary of relative quantities of substrate and product molecules, and relative e.e. of main species, before and after 71 hours reaction catalyzed by Cal B.

racemic substrate **3**, corresponding to the region of correlations of carbonyl carbons. Referring to the structures presented in Table S1, the C^{11} of the hydrolyzed form displays a shift to higher ppm values according to the formation of a free carboxylic acid carbon. These experiments confirmed the assignment of the new carbonylic peak observed in the mono-hydrolyzed form: similarly to the C^{11} of the racemic substrate **3**, C^{11} of the product shows cross peaks with H^{2}, H^{3}, H^{4} and $H^{4'}$ protons of the new compound in the mixture.

These case studies showed that Cal B hydrolyses, with enantiospecificity and regioselectivity, the racemic mixture of *cis*-dimethyl 1-acetylpiperidine-2,3-dicarboxylate, producing (2*R*,3*S*)-1-acetyl-(2-methoxycarbonyl)piperidine-3-carboxylc acid ((2*R*,3*S*)-**4**) and leaving the 2S,3R-**3** substrate non-reacted. The whole reaction catalyzed by Cal B is summarized in Figure 2, where the relative quantities and e.e. values refer to a reaction time of 71 hours. At that time, the original racemate reached

49.6% conversion, the (2*S*,3*R*)-**3** substrate remained in 98.4% e.e. while the (2*R*,3*S*)-**4** product was present in 100% e.e.

Kinetic characterization of reaction

Before scaling up the kinetic resolution protocol, we sought to define the optimal conditions for the reaction to proceed to the maximum yield, that is a minimum non-hydrolyzed fraction of enantiomer (2*R*,3*S*)-**3**. To this aim, we performed a series of experiments for analyzing reaction kinetics and to determine kinetic constants. These were estimated by using ^{1}H-NMR equipment, measuring the rate of methanol formation as product of hydrolysis at different substrate concentrations and constant concentration of the enzyme. Obtained values were 11.2 ± 1.2 mM and 0.0159 ± 0.0008 s^{-1}, for K_M and K_{cat} respectively, referring to the dimethyl *cis*-1-acetylpiperidine-2*R*,3*S*-dicarboxylate enantiomer and determining the enzyme amount by Bradford assay. Such values showed that the reaction proceeds quite slowly (see K_{cat}); moreover, once the racemate concentration had lowered to ≤ 5 g/l (i.e., 2.5 g/l, 11 mM, for the reacting enantiomer), the reaction rate was practically halved, possibly because of a low affinity of the enzyme for the substrate. We inferred that a high initial concentration of racemate **3** was necessary in order to speed up the resolution reaction in the industrial scaling up.

Furthermore, the absolute enantioselectivity of reaction was verified by incubating pure (2*S*,3*R*)-**3** with free Cal B in phosphate buffer, pH 6.0, at different temperatures (20-35 °C). The substrate resulted to be stable, and no product of hydrolysis was identified after 45 days of incubation (data not shown). In the light of this observation, constant rate values for the kinetic resolution were defined as $K_S = 0$ and $K_R = K_{cat} = 0.0159 +/- 0.0008$ s^{-1}.

Large scale racemate resolution

The new discovered method for enzymatic resolution was then considered for its application in the preparation of a Moxifloxacin building block precursor at a higher scale. To this aim, we proceeded with experimental tests where quantities of initial substrate, enzyme and buffer were increased (Table 2).

By monitoring the time necessary to reach an e.e > 99% of desired enantiomer (2*S*,3*R*)-**3**, we observed that the reaction could be easily scaled up without notable reduction of catalytic efficiency. At the laboratory scale, (2*S*,3*R*)-**3**. was finally obtained in a reaction time of 100 hours, starting from 50 g of racemic substrate and 3 g of Cal B, in a volume of 250 ml.

Subsequently, because of the relatively low catalytic rate, we considered the possibility of re-utilizing the enzyme after a first round of resolution, making the process more convenient. For this reason, free Cal B was replaced with covalently immobilized Cal B on polyacrylic beads that, after proper enzymatic conversion, could be recovered from the reaction mixture by filtration, allowing recovery of the fixed enzyme, which was used in a new batch. Recycling trials demonstrated that the immobilized enzyme preserved its activity if used at 20 °C. At this temperature, however, the reaction proceeded too slowly; e.g., 240 hours were necessary to reach 49% conversion. On the other hand, we observed that at a working temperature favorable for the industrial process, the immobilized enzyme gradually lost activity. For example, 48% conversion was obtained in 80 hours in a first run at 40 °C; in the following two cycles, final conversion was 47% and 45%, respectively, in the same reaction times. This suggested that the immobilized enzyme may be reused for a very limited number of cycles at that temperature.

The third step was to find a way to separate the two molecules obtained after the hydrolysis, in a mixture of diester **3** (the non-reacted substrate, i.e., the desired (2*S*,3*R*)-enantiomer of the diester **3** in very large e.e.) and monoacid (2*R*,3*S*)-**4** (see Figure 3).

We hypothesized that the two molecules could be easily separated by solvent extraction at slightly basic pH. In this condition, the non-reacted diester was expected to remain in the organic solvent while the monoacid (as sodium carboxylate) should have been water soluble. We performed a solubility study on the diester to determine the best solvent to use. The screening revealed that the solvent of choice was

Table 2. Scale-up of reactions. All experiments were performed at controlled temperature (20 °C), pH 6.0 and 150–300 rpm agitation. Final reaction time refers to > 99,5% conversion of the reactive 2*S*,3*R* enantiomer.

Trial	Buffer (ml)	Free Cal B (mg)	Substrate (g)	Reaction time (h)
1	50	50	0.5	150
2	10	100	1	90
3	10	200	3	80
4	50	800	10	85
5	250	3000	50	100

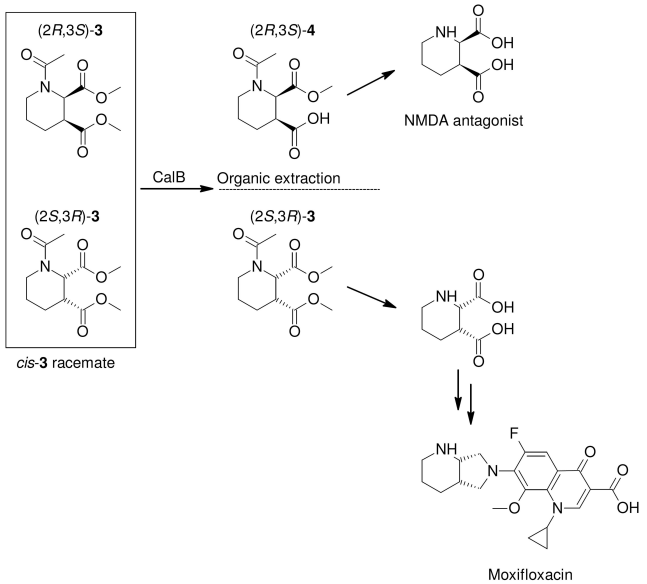

Figure 3. Scheme of deracemization of *cis*-**3** mixture by Cal B, with production of easily separable compounds, precursor of molecule of pharmaceutical interest.

ethyl acetate (100% p/v), while other solvents were required in larger volumes. Indeed, by using ethyl acetate, we were able to recover the desired non-reacted diester (2*S*,3*R*)-**3** with an optical purity sufficient to subsequently transform it into the final (*S*,*S*)-2,8-diazabicyclo[4.3.0]nonane with an e.e. > 99.9%.

After having applied all described modifications to the protocol, the reaction was productively scaled up to 160 g of the initial racemate *cis*-**3**, performed in two consecutive batches of 80 g. The substrate was dissolved in 400 ml of buffer solution maintained at 35 °C and pH 6 by adding 0.1 NaOH solution using an automatic titrator. The kinetic resolution was started with 40 g of immobilized Cal B, and its progress was monitored by HPLC and GC analysis. After 140 hours, the reaction was considered completed, and the solution was filtered. The recovered enzyme was recycled in a second batch, using the same conditions. The filtration was repeated at the end of the second round of reaction to remove the immobilized enzyme. Water mixtures remaining from the two batches were mixed, concentrated to 350 ml, and the pH was shifted to 8 to ensure complete ionization of the carboxylic acid (2*R*,3*S*)-**4**. The non-reacted substrate **3** was recovered by three subsequent extractions using 500 ml ethyl acetate each. At the end, the non-reacted (2*S*,3*R*)-**3** was found in the organic fraction with an e.e. of 98% and yield of 47% (relative to the initial quantity of racemate **3**), while the product of hydrolysis (2*R*,3*S*)-**4** remained 98% pure in the aqueous fraction. This high scale enzymatic deracemization by kinetic resolution demonstrates the industrial applicability of the developed process.

Conclusion

In the present article, we describe a very efficient biocatalytic method for the preparation of (*S*,*S*)-2,8-diazabicyclo[4.3.0]nonane, a building block in the synthesis of the antibacterial agent Moxifloxacin, starting from a precursor easily obtained by chemical synthesis. From a racemic mixture of *cis*-dimethyl 1-acetylpiperidine-2,3-dicarboxylate (**3**) in water buffer, resolution was achieved by using free or immobilized Cal B. This lipase hydrolyzed the (2*R*,3*S*)-**3** substrate enantiomer in position 3 with high regio- and stereo-selectivity, producing (2*R*,3*S*)-1-acetyl-(2-methoxycarbonyl)piperidine-3-carboxylic acid (**4**) and leaving the (2*S*,3*R*)-**3** enantiomer as non-reacted substrate. The monoacid product, obtained as a single enantiomer, could be easily separated from the non-reacted diester substrate by extraction of the latter using ethyl acetate.

We also demonstrated that the process is compatible with industrial application since the immobilized form of the enzyme could be recycled without significant loss of activity. In the light of the favorable experimental and economic conditions, we submitted this process for a patent.[19]

It is worth observing that racemate *cis*-**1** (*cis*-dimethyl piperidine-2,3-dicarboxylate) and *cis*-**2** (*cis*-diethyl piperidine-2,3-dicarboxylate) were not useful substrates for Cal B, while N-protection by an acetyl group made racemate *cis*-**3** a suitable substrate (Figure 1). This positive effect of the acetyl group was also observed by Kanerva and co-workers in lipase catalyzed resolution of amino acid esters by alcoholysis,[13,20,21] while the resolution of pipecolate ester racemate protection by the same group resulted in a decrease of the reaction rate.[13] Interestingly, in this latter work, alcoholysis proceeded on the ester in position 2, while in our work hydrolysis involves the ester in position 3. We think that the difference could be due to both different type of reaction (hydrolysis instead of alcoholysis) and steric hindrance to the ester in position 2 due to the presence of the bulky acetyl group.

The main limit of the enantiomeric resolution technique that we propose here is its low productivity, which is limited to half of the initial material. However, this problem may be circumvented by recycling the undesired enantiomeric product of the reaction; in principle, complete enzymatic conversion could be reached by designing and setting up a (semi-)continuous recycling system. We chose to recycle the monoester, product of hydrolysis, by regenerating the diester and the aromatic ring, followed by its reduction with Pd/C. Alternatively, we found that the discarded enantiomer, in the (2*R*,3*S*) configuration, could be exploited for the preparation of piperidine-2R,3S-dicarboxyl acid, which is used as an NMDA (N-methyl-D-aspartic acid) antagonist. The preparation of piperidine-2*R*,3*S*-dicarboxyl acid, as previously reported,[22] usually requires several steps from (2*S*)-2-phenylglycinol. We propose it could be prepared starting from the product of Cal B hydrolysis, the (2*R*,3*S*)-1-acetyl-(2-methoxycarbonyl)-piperidine-3-carboxylic acid (4), by chemical hydrolysis of its acetyl and methyl functions (Figure 3).

Patent originated from this work[19] served as a seed for several further investigation.[23–25] Moreover, the present paper corrects the wrong position of ester hydrolysis indicated in those works.

Supporting Information Summary

Supporting Information include detailed description of experimental procedures as well as ^{1}H one-dimensional NMR and HMBC spectra used for defining hydrolysis position of *cis*-**3** substrate.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Active pharmaceutical ingredients · Biocatalysis · *Candida antarctica* lipase B · Enzyme catalysis · Moxifloxacin

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