

Review

Lipase-Catalyzed Strategies for the Preparation of Enantiomeric THIQ and TH β C Derivatives: Green Aspects

György Orsy  and Enikő Forró * 

Institute of Pharmaceutical Chemistry, University of Szeged, Eötvös u. 6, H-6720 Szeged, Hungary; orsy.gyorgy@szte.hu

* Correspondence: forro.eniko@szte.hu; Tel.: +36-62-544964

Abstract: This report reviews the most important lipase-catalyzed strategies for the preparation of pharmaceutically and chemically important tetrahydroisoquinoline and tetrahydro- β -carboline enantiomers through *O*-acylation of the primary hydroxy group, *N*-acylation of the secondary amino group, and COOEt hydrolysis of the corresponding racemic compounds with simple molecular structure, which have been reported during the last decade. A brief *introduction* describes the importance and synthesis of tetrahydroisoquinoline and tetrahydro- β -carboline derivatives, and it formulates the objectives of this compilation. The strategies are presented in chronological order, classified according to function of the reaction type, as kinetic and dynamic kinetic resolutions, in the *main text*. These reactions result in the desired products with excellent *ee* values. The pharmacological importance of the products together with their synthesis is given in the *main text*. The enzymatic hydrolysis of the hydrochloride salts as racemates of the starting amino carboxylic esters furnished the desired enantiomeric amino carboxylic acids quantitatively. The enzymatic reactions, performed in *t*BuOMe or H₂O as usable solvents, and the transformations carried out in a continuous-flow system, indicate clear advantages, including atom economy, reproducibility, safer solvents, short reaction time, rapid heating and compression vs. shaker reactions. These features are highlighted in the *main text*.

Keywords: continuous-flow reactions; enzymatic *O*-acylation; enzymatic *N*-acylation; enzymatic COOEt hydrolysis; green solvents; primary hydroxy group; secondary amino group; TH β C; THIQ



Citation: Orsy, G.; Forró, E.

Lipase-Catalyzed Strategies for the Preparation of Enantiomeric THIQ and TH β C Derivatives: Green Aspects. *Molecules* **2023**, *28*, 6362. <https://doi.org/10.3390/molecules28176362>

Academic Editor: Hua Zhao

Received: 26 July 2023

Revised: 19 August 2023

Accepted: 28 August 2023

Published: 30 August 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Derivatives containing a tetrahydroisoquinoline (THIQ) or tetrahydro- β -carboline (TH β C) core are important from both biological and chemical aspects. A large number of naturally occurring THIQs have significant pharmacological activity [1,2]. For example, (*R*)-salsolidine (*Genista pungens*) has MAO A inhibitory effect [3], whereas expectorant emetine, (*Ipecacuanha*) [4], antitussive noscapine (*Papaver somniferum*) [5], and Trabectedine, approved as Yondelis[®] (*Ecteinascidia turbinata*) [6], show anticancer effect. Saframycin (*Myxococcus xanthus*) [7] and liensinine (*Nelumbo nucifera*) [8] exhibit pharmaceutical activities toward HIV and cancer. Some synthetic THIQ alkaloid analogues, such as Zalypsis[®] [9], possess anticancer activity. The use of TH β C-containing compounds in medicine is as important as in the case of the abovementioned THIQ derivatives. For instance, vincristine, vinblastine [10], and reserpine [11] show antihypertensive and/or antitumor activity. Harmicine (*Kopsia griffithii*) [12] has antinociceptive activity, whereas (+)-7-bromotypargine (*Ancorina* sp.) [13] shows antimalarial activity. Synthetic TH β Cs are used in drug research. For instance, Tadalafil (Cialis[®]) [14] was successfully applied in the treatment of erectile dysfunction. MK-4256 [15] is an antagonist of somatostatin subtype receptor 3 and it was a promising preclinical candidate for the medication of type II diabetes mellitus. Significant proliferation inhibitor effect of pyridoxal TH β C derivatives against *Plasmodium falciparum* was also reported [16]. In addition, synthetic 1-substituted *N*-acylated TH β Cs exhibits inhibitory

effect against the Breast Cancer Resistance Protein (ABCG2) [17]. The protected form of (S)-1-isopropyl-TH β C was used in the synthesis of (S)-quinolactacin-B with activity against tumor necrosis factor [18].

Therefore, it is not surprising that a large number of publications describing the preparation of important THIQ and TH β C derivatives have appeared and most of them reviewed [1,2,19–23]. Indeed, only very few articles describe the lipase-catalyzed synthesis of THIQ and TH β C enantiomers, with simple molecular structures.

Lipases (triacylglycerol hydrolases E.C. 3.1. 1.3) are versatile enzymes, widely used for various kinds of biocatalyzed reactions, performed in both aqueous and nonaqueous media. They can catalyze chemical transformations with high catalytic efficiency and specificity as chemo-, regio-, and enantio-selectivities. Lipase-catalyzed enantioselective acylation of alcohols and amines together with the hydrolysis of esters and amides are among the most utilized biocatalytic methods for the preparation of enantiomerically pure alcohols, esters, amines, amides, and acids. The reason is that lipases are highly active and robust enzymes with broad substrate specificities.

From a green chemistry perspective, the best solvent for reactions is no solvent [24–28]. The solvent-free reactions are not always achievable and the selection of another more efficient solvent becomes critical. Water has increasing popularity, because it is inexpensive, nontoxic, nonflammable, and safe for use. In addition, to ensure high activity and selectivity, water allows easy product isolation by filtration.

Green solvents play a crucial role in lipase-catalyzed reactions, offering numerous advantages over traditional solvents in terms of environmental sustainability, safety, and efficiency [29–35]. Lipase-catalyzed reactions are widely employed in various industries, including the production of pharmaceuticals, food, and biofuels, due to their ability to produce enantiopure compounds and minimize unwanted side reactions. The choice of solvent significantly influences the overall performance of the enzymatic reaction, and the use of green solvents has emerged as a preferred option for several reasons. First, green solvents are available from renewable resources, making them inherently more sustainable compared to conventional solvents obtained from petroleum-based sources. This is in accordance with the growing global emphasis on reducing the carbon footprint and moving toward ecofriendly practices in chemical processes. Furthermore, green solvents are nontoxic and biodegradable, minimizing environmental hazards and reducing health risks for both workers and consumers. Their low toxicity is also beneficial for the stability and activity of enzymes during catalysis leading to enhanced reaction rates and product yields. Moreover, the use of green solvents promotes improved enzymatic selectivity. They typically have lower polarity, which can reduce nonspecific interactions between the enzyme and the substrate, resulting in higher enantioselectivity and regioselectivity. This is particularly important in the synthesis of pharmaceutical intermediates and fine chemicals, where chirality is of utmost significance. Green solvents also contribute to overcome mass transfer limitations. They possess lower viscosities compared to conventional solvents, facilitating better diffusion of substrates to the active site of the enzyme and faster product release. These properties can lead to shorter reactions and increased productivity. Furthermore, green solvents are often compatible with a wide range of substrates and enzyme types. Their ecofriendly nature, reduced toxicity, improved selectivity, and enhanced mass transfer properties make them invaluable tools for sustainable and efficient enzymatic processes. Although there are some greener organic solvents, for example, cyclopentyl methyl ether (CPME), a promising ecofriendly solvent without any handling difficulties, and *t*BuOMe, which is one of the most widely used solvents for lipase-catalyzed transformations. Note, however, that according to the green solvent selection guide [36], there are some unfavorable issues and substitution is advisable.

The majority of lipase-catalyzed reactions have been performed as batch reactions. However, enzymatic continuous-flow processes, because of their numerous advantages, have gained significant attention in recent years as promising alternatives to traditional batch reactions [37–42]. For example, continuous flow systems allow controlled flow

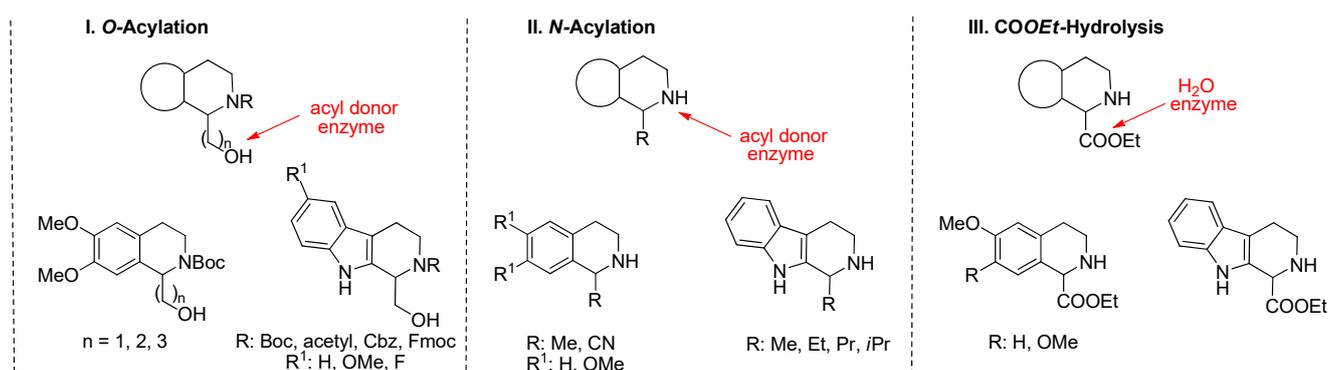
of reactants, ensuring a constant supply of substrates to the enzyme, which improves the overall reaction efficiency, leading to higher productivity and increased yield of the desired products. Enzyme-catalyzed reactions in continuous flow can be finely tuned by adjusting residence times, temperature, and enzyme concentration, enabling better selectivity in product formation, minimizing unwanted byproducts, and reducing the need for downstream purification steps. Continuous-flow reactors can handle hazardous materials more safely than traditional batch reactors. The smaller reaction volumes in continuous flow reduce the risk of accidental spills and exposure to toxic or reactive substances, enhancing overall operator safety. The continuous flow of reactants ensures that they spend less time in the reactor, leading to shorter reaction times. This is of particular significance when working with unstable substrates or sensitive enzymes that may degrade over prolonged exposure. Enzymatic continuous-flow processes are readily scalable, making it easier to transition from laboratory-scale to industrial-scale production. Additionally, continuous-flow setups can be easily integrated into automated systems, allowing precise control and reproducibility.

Although lipase-catalyzed kinetic resolution (KR) methods have been developed for the enantioselective acylation in a large number of primary and especially secondary alcohols or the hydrolysis of their corresponding esters, the first chemoenzymatic method for the preparation of optically active alcohols and esters possessing the 1,2,3,4-tetrahydroquinoline (THQ) moiety was published only recently [43]. The enantioselective transesterification (E values > 328) of racemic 1,2,3,4-THQ-propan-2-ols was performed with vinyl acetate (VA) in the presence of immobilized *Candida antarctica* lipase B (CALB) or *Burkholderia cepacia* lipase (BCL) or engineered acyltransferase variants from *Mycobacterium smegmatis* (MsAcT). These reactions furnished (S)-alcohols and the corresponding (R)-acetates with excellent optical purities ($ee > 99\%$).

Candida rugosa lipase (AY)-catalyzed KR of 1-methyl THIQ through N -alkoxycarbonylation with 3-methoxyphenyl allyl carbonate in water-saturated toluene at 30 °C, resulting in the desired (R)-1-methyl THIQ (ee 98% and yield 47%) and (S)-amide (ee 99% and yield 46%) has been described [44].

DKR of 6,7-dihydroxy-1-methyl-1,2,3,4-THIQ by $[\text{IrCp}^*\text{I}_2]_2$ and lipase AY in the presence of 3-methoxyphenyl propyl carbonate in toluene at 40 °C, resulting in (R)-carbamate (ee 96%, conversion 90% after 23 h) was described [45].

The aim of this compilation is to present the most important lipase-catalyzed routes devised for the preparation of pharmaceutically and chemically important THIQ and TH β C enantiomers (simple molecular structures) with the appropriate absolute configuration of the asymmetric center (Scheme 1) over the last decade. The transformations through O -acylation (I), N -acylation (II), and COOEt hydrolysis (III) of the corresponding racemates (Scheme 1) are classified as KR (a maximum yield of 50% enantiopure product is obtainable from asymmetric acylation, hydrolysis, etc.) and DKR (this theoretically allows 100% conversion), and they are discussed in chronological order. The reactions, performed under environmentally benign green conditions, are highlighted in the *main text*.



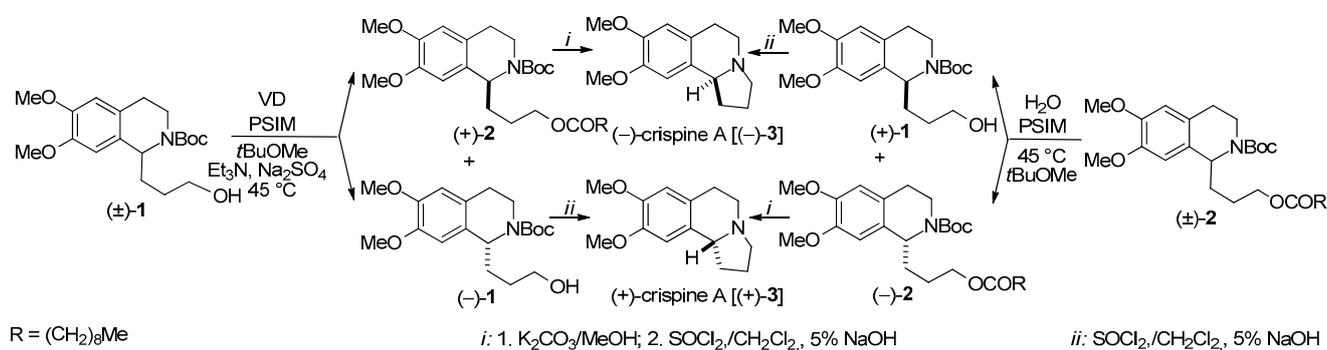
Scheme 1. Lipase-catalyzed routes to THIQ and TH β C enantiomers.

2. Enzymatic Strategies for the Synthesis of THIQ and TH β C Enantiomers

2.1. KR through O-Acylation

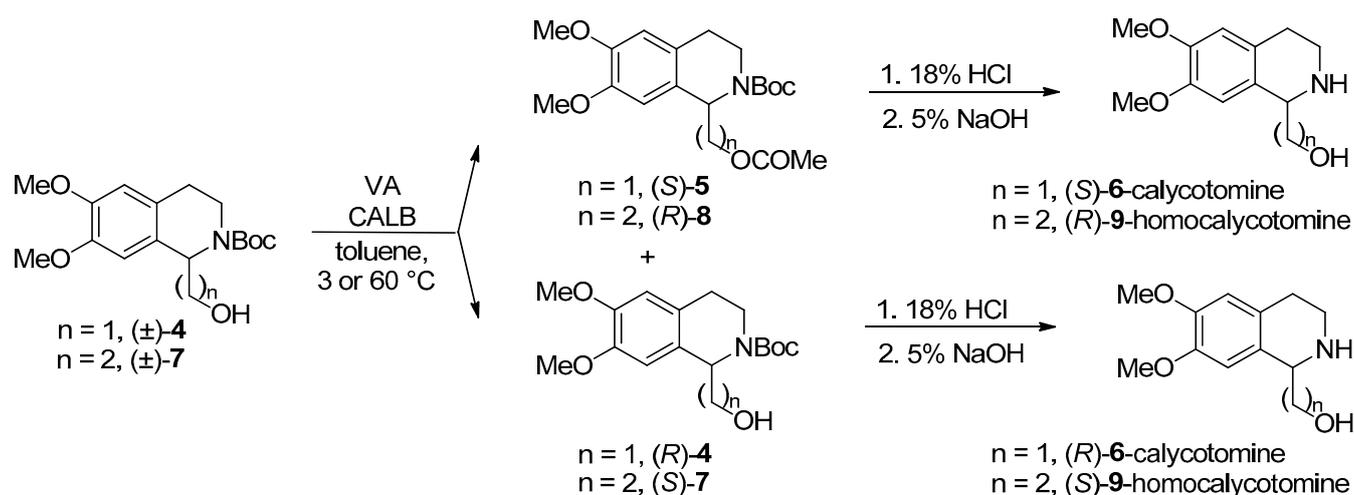
Successful lipase-catalyzed methods for the asymmetric O-acylation of the primary hydroxy group of several 1,2,3,4-THIQ and 1,2,3,4-TH β C racemates were developed. Efficient enzymatic resolution processes of racemates, bearing a stereogenic center separated from the functional group by a larger nonchiral moiety, were also developed. In general, good yields accompanied by high enantioselectivities were obtained, thus underlining the potential of enzymes to recognize and transform enantiomers of racemates with ‘remote’ stereogenic centers in an enantioselective manner. The reactions were performed in an organic solvent either in a continuous-flow system or as a batch reaction.

The total synthesis of the antitumor-active alkaloid crispine A [46] enantiomers ($ee \geq 94\%$) has been performed [47] through *Burkholderia cepacia* lipase (PSIM)-catalyzed S-selective O-acylation of the primary hydroxy group of N-Boc-protected 1-(3-hydroxypropyl)-6,7-bis(methoxy)-1,2,3,4-THIQ ((\pm)-1) (vinyl decanoate (VD), Et₃N, Na₂SO₄, tBuOMe as a green solvent, 45 °C) ($E = 68$) or the R-selective hydrolysis of the corresponding racemic O-decanoate ((\pm)-2, R = (CH₂)₈Me, H₂O, tBuOMe, 45 °C) ($E = 52$)) (Scheme 2). The enzymatic resolutions, performed in two steps, afforded key alcohol (+)-1 and (–)-1 and ester (+)-2 and (–)-2 enantiomers with high ee ($\geq 94\%$, yields $\geq 21\%$). Ring-closure reactions of these enantiomers with thionyl chloride afforded the desired crispine A enantiomers (+)-3 and (–)-3 ($ee \geq 95\%$, yield $\geq 78\%$). It was mentioned that (+)-1 and (–)-1 can also serve as starting enantiomers for the synthesis of enantiomerically pure crispine E [48]. The authors also noted that, ‘although crispine A enantiomers have been prepared by asymmetric routes, to the best of our knowledge, they have not yet been obtained via a strategy involving enzyme-catalyzed kinetic resolution’ [47].



Scheme 2. Synthesis of the crispine A enantiomers.

Both enantiomers of calycotomine ((*R*)-6 and (*S*)-6) were prepared [49] through *Candida antarctica* lipase B (CALB)-catalyzed asymmetric O-acylation of N-Boc-protected (6,7-dimethoxy-1,2,3,4-THIQ-1-yl)methanol ((\pm)-4). Taking advantage of the continuous-flow technique (atom economy, reproducibility, safer solvents, short reaction time, rapid heating and compression), the authors carried out the preliminary experiments in a continuous-flow system (an H-Cube system in ‘No H₂’ mode, equipped with a stainless-steel enzyme-charged cartridge, under laboratory conditions). The preparative-scale resolution of (\pm)-4 was performed as a batch reaction, in an incubator shaker with VA in toluene at 60 °C (Scheme 3) ($E > 200$). The resulting (*R*)-4 amino alcohol and (*S*)-5 amino ester, obtained with high enantiomeric excess ($ee = 99\%$) were separated by column chromatography (silica, elution with *n*-hexane:EtOAc (5:1)) (yields $\geq 43\%$), and then transformed into the desired calycotomine (*R*)-6 and (*S*)-6 ($ee = 99\%$, yields $\geq 73\%$).

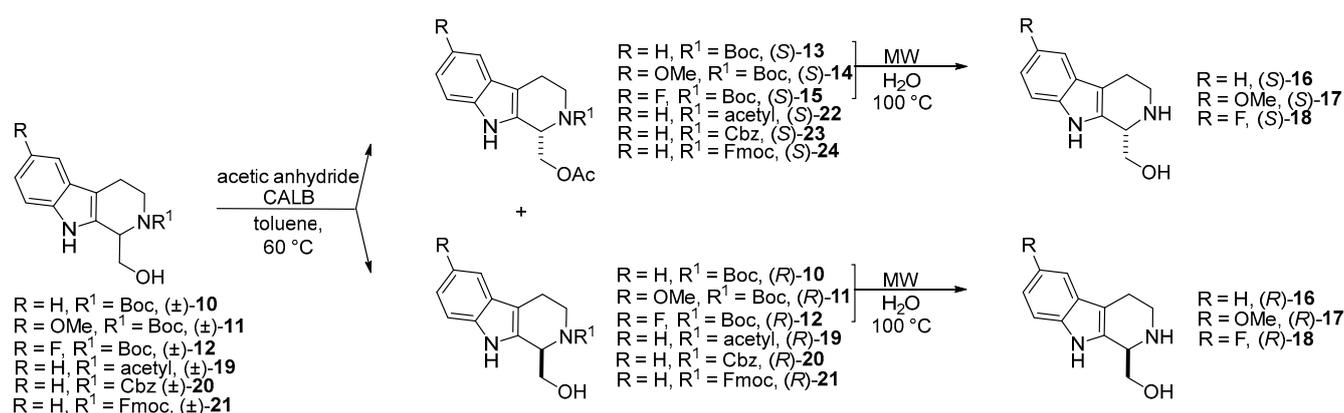


Scheme 3. Synthesis of the calycotomine and homocalycotomine enantiomers.

CALB-catalyzed *O*-acylation of *N*-Boc-protected (6,7-dimethoxy-1,2,3,4-THIQ-1-yl)-ethanol ((±)-7) has also been described [50]. Preliminary experiments were performed either in a continuous-flow system or as batch reactions, while the preparative-scale resolution was carried out in two steps with VA, Et₃N, and Na₂SO₄ in toluene at 3 °C, as a batch reaction (Scheme 3). The furnished amino alcohol (*S*)-7 and amino ester (*R*)-8 (*ee* ≥ 94%) were separated by column chromatography (silica, elution with *n*-hexane:EtOAc (2:1) (yields ≥ 32%) and they were then transformed (treatment with 18% HCl, followed by 5% NaOH) into the desired homocalycotomine (*S*)-9 (the intermediate of emetine [51]) and (*R*)-9 (*ee* ≥ 94%, yields ≥ 71%).

A systematic study was carried out in a continuous-flow system on the *O*-acylation of THIQ amino alcohol homologues ((±)-1, (±)-4, and (±)-7) containing a remote stereogenic center (VA, CALB, toluene, 80 bar, 60 °C, 0.1 mL min⁻¹ flow) [50]. The authors found that the enantioselectivity decreased from 200 to 1, when the distance between the hydroxy group and the stereogenic center increased from one carbon atom ((±)-4) to three carbon atoms ((±)-1).

Enantiomeric *N*-Boc-protected amino alcohols ((*R*)-10–(*R*)-12) and amino esters ((*S*)-13–(*S*)-15) were prepared through CALB-catalyzed *O*-acylation of the hydroxy group of THβC ((±)-10, (±)-11, and (±)-12 [52]. The optimization reactions were carried out in a continuous-flow system, while preparative-scale resolutions were performed as batch reactions (incubator shaker). Excellent *E* values (>200) were obtained when CALB and acetic anhydride were used in toluene at 60 °C (Scheme 4). The amino alcohols and esters were separated by column chromatography (silica, elution with *n*-hexane:EtOAc 3:1 or 2:1) with high *ee* (≥96%) and good yields (≥43%). Enantiomers (*S*)-13–(*S*)-15 were transformed via methanolysis (in K₂CO₃/MeOH at 60 °C) to the corresponding amino alcohols (*S*)-10–(*S*)-12 without a loss in *ee* values (98%) (reactions not shown in the Scheme). MW-assisted Boc deprotection of these products (in water at 100 °C) resulted in the formation of the desired THβC amino alcohols ((*R*)-16–(*R*)-18 and (*S*)-16–(*S*)-18) without a drop in the *ee* values (≥96%).



Scheme 4. Synthesis of 1-hydroxyalkyl-TH β C enantiomers substituted in different manners.

In the frame of substrate engineering, the steric effect of different *N*-protecting groups (*N*-Boc, *N*-acetyl, *N*-Cbz, *N*-Fmoc) on the enantioselectivity and reaction rate of CALB-catalyzed *O*-acylation (acetic anhydride, toluene, 60 °C) of 1-hydroxymethyl-TH β Cs (±)-10, (±)-19, (±)-20, and (±)-21 has been investigated [53]. The reactions were carried out in batch mode, in an incubator shaker. Excellent enantioselectivities ($E > 200$) were observed for the acylation of (±)-10, (±)-20, and (±)-21 (Scheme 4, Table 1). The resolution of (±)-19 initially showed excellent E (>200), but as the reaction progressed, E started to decrease, because of *N/O* and *O/N* acyl migrations.

Table 1. *O*-acylation of (±)-10, (±)-20, and (±)-21.

Substrate	Reaction Time (min)	$ee_{\text{amino alcohol}}$ (%) ^b	ee_{ester} (%) ^b	Conv. (%)	E
(±)-10 *	15	86	99	47	>200
(±)-20 *	60	69	99	41	>200
(±)-21 *	60	79	98	45	>200

* 0.0125 mmol substrate; 30 mg mL⁻¹ CALB; 2 equiv. acetic anhydride; 1 mL toluene; 60 °C. ^b According to HPLC equipped with a Daicel Chiralpak IA or OD-H column.

Preparative-scale resolutions of (±)-20 and (±)-21 resulted in esters (S)-23 and (S)-24 and unreacted amino alcohols (R)-20 and (R)-21 with excellent enantiomeric excess values ($\geq 88\%$). The products were separated by column chromatography [silica, elution with *n*-hexane:EtOAc (2:1)] (yields $\geq 44\%$).

- A new total synthesis of crispine A enantiomers via *Burkholderia cepacia* lipase-catalyzed acylation of the primary hydroxy group of *N*-Boc-protected 1-(3-hydroxypropyl)-6,7-bis(methoxy)-1,2,3,4-THIQ [(±)-1] and enantioselective hydrolysis of the corresponding *O*-decanoate [(±)-2], with a remote, four-atom-distant stereogenic center was reported [47].
- Both enantiomers of calycotomine [49] and homocalycotomine [50] (one of them is the intermediate of emetine) through *Candida antarctica* lipase B-catalyzed asymmetric *O*-acylation of *N*-Boc-protected (6,7-dimethoxy-1,2,3,4-THIQ-1-yl)methanol ((±)-4)), with a remote, two-atom-distant stereogenic center and (6,7-dimethoxy-1,2,3,4-THIQ-1-yl)ethanol ((±)-7)), with a remote, three-atom-distant stereogenic center were described.
- A systematic study on the *Candida antarctica* lipase B-catalyzed *O*-acylation of THIQ amino alcohol homologues ((±)-1, (±)-4, and (±)-7) containing a remote stereogenic center was reported [50].
- The synthesis of new enantiomers of 1,2,3,4-TH β C derivatives through *Candida antarctica* lipase B-catalyzed *O*-acylation of *N*-Boc-protected 1-hydroxymethyl-1,2,3,4-TH β C

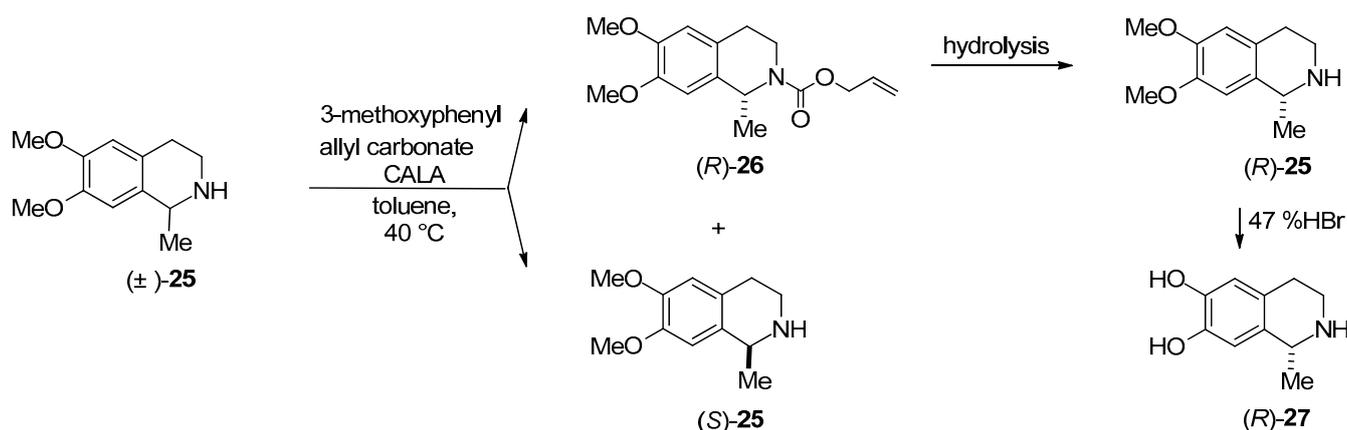
((±)-**10**), 1-hydroxymethyl-6-methoxy-1,2,3,4-TH β C ((±)-**11**), and 1-hydroxymethyl-6-fluoro-1,2,3,4-TH β C ((±)-**12**) was described [52].

- In the frame of substrate engineering, the steric effect of different *N*-protecting groups (*N*-Boc, *N*-acetyl, *N*-Cbz, *N*-Fmoc) on the enantioselectivity and reaction rate of *Candida antarctica* lipase B-catalyzed *O*-acylation of 1-hydroxymethyl-TH β Cs [(±)-**10**, (±)-**19**, (±)-**20**, and (±)-**21**] was investigated [53].

2.1.1. KR through *N*-Acylation

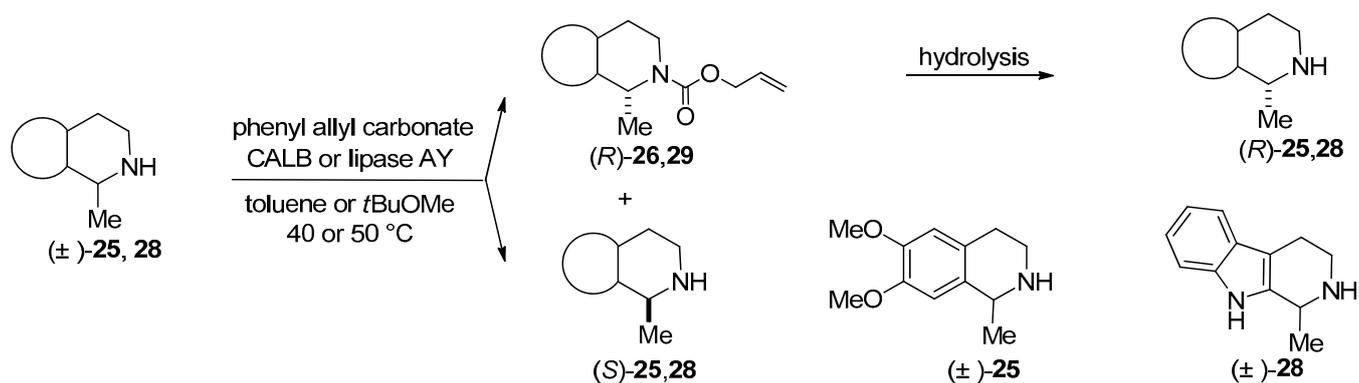
A number of racemic cyclic secondary amines bearing a stereogenic center such as 1-substituted 1,2,3,4-THIQs and 1,2,3,4-TH β Cs were resolved successfully through *N*-acylation/alkoxycarbonylation. In general, good yields accompanied by high enantioselectivities were obtained. The reactions were performed in an organic solvent either in a continuous-flow system or as a batch reaction.

An efficient chemoenzymatic route for the synthesis of (*R*)-salsolinol ((*R*)-**27**) has been described [54]. *Candida antarctica* lipase A (CALA) catalyzed the *N*-acylation (3-methoxyphenyl allyl carbonate, toluene, 40 °C) of 1-methyl-6,7-dimethoxy-1,2,3,4-THIQ (±)-**25** in an enantioselective manner (*E* > 200) resulting in carbamate (*R*)-**26** and unreacted amine (*S*)-**25** with an excellent enantiomeric excess value (98%) and good yield (50%) (Scheme 5). Base-catalyzed hydrolysis (triethanolamine in 50% aqueous NaOH solution at 120 °C) of (*R*)-**26**, followed by treatment with 47% HBr, furnished the desired (*R*)-salsolinol with excellent enantiomeric excess value (98%) and good yield (85%).



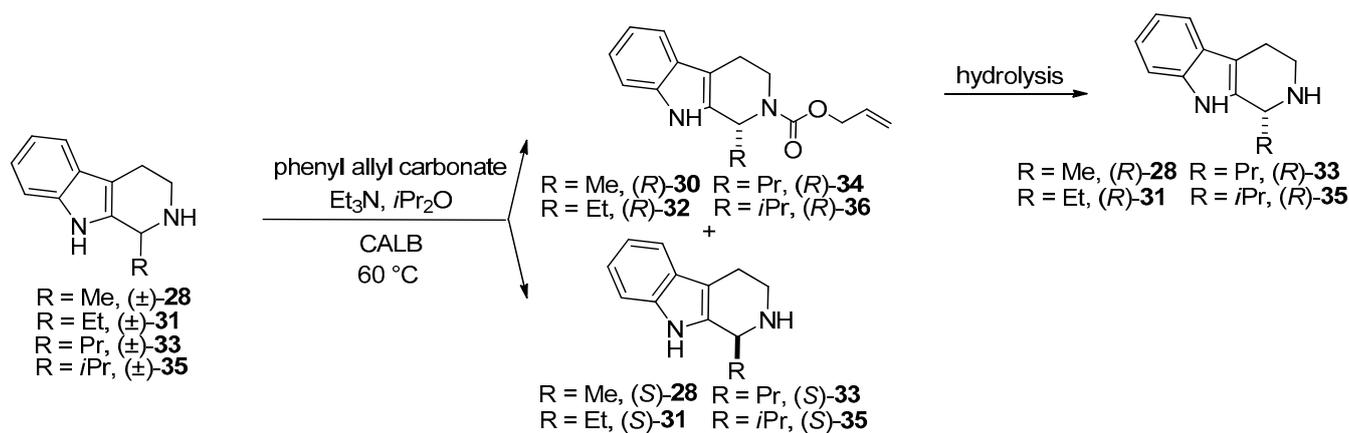
Scheme 5. Synthesis of salsolinol enantiomers.

Another enzymatic method for the resolution of salsolidine (±)-**25** and its analogue 1-methyl-1,2,3,4-TH β C (±)-**28** through *Candida rugosa* lipase (AY) and CALB-catalyzed enantioselective *N*-alkoxycarbonylation with phenyl allyl carbonate has been reported [55]. Excellent enantioselectivities (*E* > 200) were observed, when the acylation of (±)-**25** was performed in the presence of lipase AY in toluene at 40 °C or with CALB in *t*BuOMe at 50 °C (Scheme 6) in both batch mode and a continuous-flow system. The CALB-catalyzed acylation of (±)-**28**, carried out in the presence of Et₃N in *t*BuOMe at 50 °C, was also characterized with an excellent enantioselectivity (*E* > 200). The resulting unreacted amine and carbamate enantiomers (*ee* > 97%) were separated by column chromatography (silica, elution with CH₂Cl₂:MeOH (1:1) (yields ≥ 44%). The product (*R*)-carbamates [(*R*)-**26**,**29**] (*ee* > 97%) were hydrolyzed into the corresponding free amine (*R*)-enantiomers (*R*)-**25** and (*R*)-**28** (*ee* = 99%) with the use of Pd₂(dba)₃.CHCl₃ as the catalyst.



Scheme 6. Synthesis of salsolidine enantiomers.

In the frame of substrate specificity, CALB-catalyzed asymmetric *N*-alkoxycarbonylation of 1-substituted TH β Cs (Me, Et, Pr, *i*Pr) has been studied [56]. High enantioselectivities (>200) were observed when alkoxycarbonylations of racemic compounds (\pm)-28,31,33,35 were performed in *i*Pr₂O in the presence of phenyl allyl carbonate and Et₃N at 60 °C (Scheme 7) resulting in carbamates (*R*)-30,32,34,36 and unreacted amines (*S*)-28,31,33,35. The reaction time had to be increased considerably with increasing substituent size on C1; however, the isopropyl-substituted compound proved to be too bulky to have optimum activity of CALB (Table 2).



Scheme 7. Synthesis of 1-substituted (Me, Et, Pr, *i*Pr) TH β C enantiomers.

Table 2. *N*-alkoxycarbonylation of (\pm)-28, (\pm)-31, (\pm)-33, and (\pm)-35.

Substrate	Reaction Time (day)	<i>ee</i> _{amine} (%) ^b	<i>ee</i> _{carbamide} (%) ^b	Conv. (%)	<i>E</i>
(\pm)-28 *	1	99	97	50	>200
(\pm)-31 *	3	99	99	50	>200
(\pm)-33 *	5	99	99	50	>200
(\pm)-35 *	7	27	99	21	>200

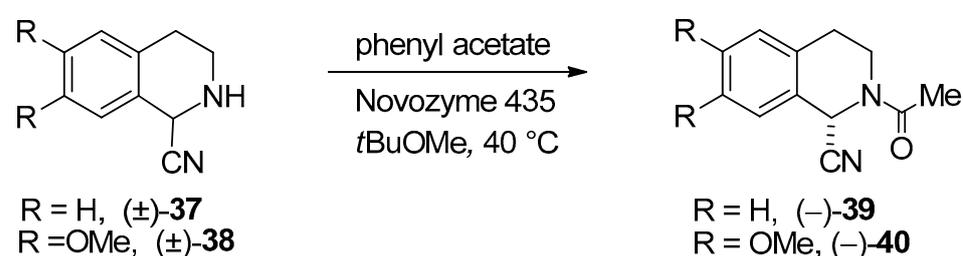
* 0.0125 mmol substrate; 30 mg mL⁻¹ CALB; 4 equiv. phenyl allyl carbonate; 1 mL *i*Pr₂O; 10 μ L Et₃N; 60 °C, daily ultrasound shaking. ^b According to HPLC equipped with a Chiralpak IA column.

Preparative-scale resolutions of (\pm)-28, (\pm)-31, and (\pm)-33 resulted in carbamides (*R*)-30, (*R*)-32, and (*R*)-34 and unreacted amines (*S*)-28, (*S*)-31, and (*S*)-33 with excellent enantiomeric excess values (\geq 97%). The enantiomeric amines and carbamates were separated by column chromatography (silica, elution with CH₂Cl₂:MeOH (25:1) (yields \geq 40%). The product (*R*)-carbamates ((*R*)-32,34) (*ee* = 99%) were hydrolyzed into the corresponding

(*R*)-enantiomers of the free amines (*R*)-**31** and (*R*)-**33** (*ee* = 99%, yields > 87%), with the use of Pd₂(dba)₃.CHCl₃ as the catalyst.

2.1.2. DKR through *N*-Acylation

DKR of 1-cyano-1,2,3,4-THIQ derivatives (\pm)-**37** and (\pm)-**38** through lipase (Novozyme 435, PS-C I, PFL and PS)-catalyzed racemization and asymmetric amidation in the presence of phenyl acetate as acyl donor, in *t*BuOMe at 40 °C has been described [57]. When using Novozyme 435 (lipase from *Candida antarctica*) as catalyst, α -aminonitrile products (–)-**39** and (–)-**40** (Scheme 8) were obtained with excellent enantiomeric excess values (*ee* \geq 95%) and good chemical yields (\geq 92%). These results showed that dual-function lipase promiscuity resulted in simultaneous racemization and asymmetric amidation of α -aminonitriles (\pm)-**37** and (\pm)-**38**, thus providing a useful synthetic method to optically active α -aminonitrile amides (–)-**39** and (–)-**40**.



Scheme 8. Synthesis of enantiomeric 1-cyano-1,2,3,4-THIQ derivatives.

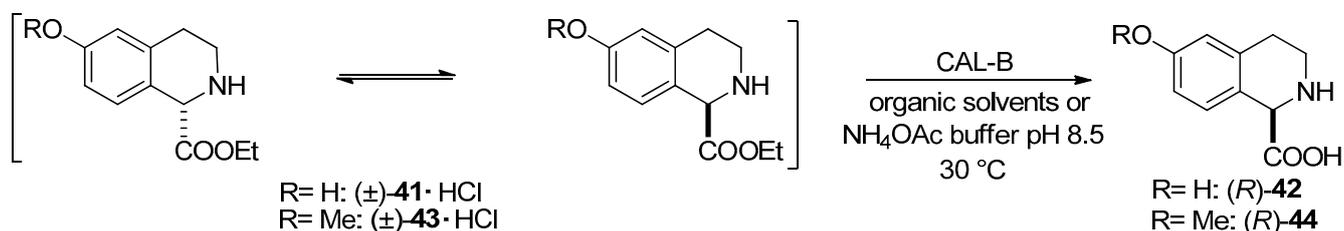
- Preparation of (*R*)-6,7-dihydroxy-1-methyl-1,2,3,4-THIQ (salsolinol) through *Candida antarctica* lipase A-catalyzed *N*-acylation of 1-methyl-6,7-dimethoxy-1,2,3,4-THIQ [(\pm)-**25**] was reported [54].
- The synthesis of both enantiomers of salsolidine (the (*R*)-enantiomer has a monoamine oxidase A (MAO A) inhibiting effect) and its analogue 1-methyl-1,2,3,4-TH β C carried out through *Candida rugosa* lipase- and *Candida antarctica* lipase B-catalyzed *N*-alkoxycarbonylation of racemic 1-methyl-6,7-dimethoxy-1,2,3,4-THIQ ((\pm)-**25**) and 1-methyl-1,2,3,4-TH β C ((\pm)-**28**) was described [55].
- In the frame of substrate specificity, the influence of different alkyl chain substituents (Me, Et, Pr, *i*Pr) on the enantioselectivity and reaction rate of *Candida antarctica* lipase B-catalyzed *N*-alkoxycarbonylation of 1-substituted TH β Cs (Me ((\pm)-**28**), Et ((\pm)-**31**), Pr ((\pm)-**33**), *i*Pr ((\pm)-**35**)) was studied [56].
- The synthesis of 1-cyano-1,2,3,4-THIQ enantiomers through *Candida* lipase-catalyzed DKR (racemization and asymmetric amidation) of racemic 1-cyano-1,2,3,4-THIQ (((\pm)-**39**)) and 1-cyano-6,7-dimethoxy-1,2,3,4-THIQ (((\pm)-**40**)) was described [57].

2.2. DKR through COOEt Hydrolysis

Successful lipase-catalyzed DKR methods were devised for the preparation of enantiomeric 1,2,3,4-THIQ- and 1,2,3,4-TH β C-1-CAs with good yield and high enantiomeric excess value through hydrolysis of the hydrochloride salt of 1,2,3,4-THIQ- and 1,2,3,4-TH β C-1-CE. The reactions were performed in a buffer solution as a batch reaction.

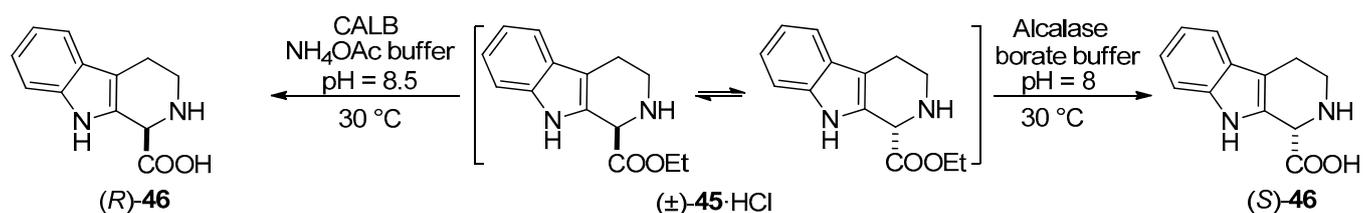
Enantiomeric 6-hydroxy-1,2,3,4-THIQ-1-CA and its 6-methoxy analogue have been synthesized through CALB-catalyzed DKR of the corresponding amino carboxylic ester (CE) hydrochlorides (\pm)-**41**·HCl and (\pm)-**43**·HCl (Scheme 9) [58]. Resolution of (\pm)-**41**·HCl performed in aqueous NH₄OAc buffer (pH = 8.5) at 30 °C and resolution of (\pm)-**43**·HCl in organic solvents (*i*Pr₂O:MeCN (3:2), Pr₂NH) furnished the desired (1*R*)-6-hydroxy- and (1*R*)-6-methoxy-substituted 1,2,3,4-THIQ-1-CAs (*R*)-**42** and (*R*)-**44** with excellent enantiomeric excess values (*ee* > 99%). After filtering the enzyme and evaporating the solvent, (*R*)-**42** and (*R*)-**44** were isolated with good chemical yields (>87%). (*R*)-**44** can be transformed into (*R*)-2-*tert*-butyl-1-methyl-6-hydroxy-3,4-dihydroisoquinoline-1,2(1*H*)-dicarboxylate, which is the key intermediate of a Liver X Receptor agonist [59]. The *N*-Boc-protected form of racemic

1,2,3,4-TH β C-1-CA ((\pm)-**44**) is a building block in the synthesis of diketopiperazine-fused TH β Cs through Ugi four-component reaction [60].



Scheme 9. Synthesis of 6-hydroxy- and 6-methoxy-1,2,3,4-THIQ-1-CA enantiomers.

Directed DKR strategies were developed for the preparation of both enantiomers of 1,2,3,4-TH β C-1-CA ((*R*)-**46** and (*S*)-**46**) through the hydrolysis of the hydrochloride salt of ethyl 1,2,3,4-TH β C-1-carboxylate (\pm)-**45**·HCl [61]. The CALB-catalyzed reactions, performed in NH₄OAc aqueous buffer (pH = 8.5) at 30 °C (Scheme 10), gave amino CA (*R*)-**46** with an excellent *ee* of 98%. The solvent was evaporated, the residue dissolved in H₂O, and the pH 4 set with 5% hydrochloric acid. The solvent was evaporated and (*R*)-**46**·HCl with an *ee* of 98% and a yield of 90% was isolated. The Alcalase (cross-linked immobilized protease aggregation from *Subtilisin Carlsberg*)-catalyzed DKR of (\pm)-**45**·HCl in borate buffer (pH = 8.0) at 30 °C afforded (*S*)-**46** with an *ee* of 60%. (*S*)-**46**·HCl was obtained with an *ee* of 60% and a yield of 66%.



Scheme 10. Synthesis of 1,2,3,4-TH β C-1-CA enantiomers.

The authors noted that in (\pm)-**45**, the ring with the active carboxylate at position 1 is fused to a heteroaromatic pyrrole ring as against a benzene ring, as was the case with tetrahydroisoquinolines (\pm)-**41**·HCl and (\pm)-**43**·HCl investigated earlier, which considerably influences the racemization.

- Preparation of (*R*)-6-hydroxy-1,2,3,4-THIQ-1-CA through *Candida antarctica* lipase B-catalyzed DKR of the hydrochloride salt of ethyl 6-hydroxy- and 6-methoxy-1,2,3,4-THIQ-1-carboxylate ((\pm)-**41**·HCl and (\pm)-**43**·HCl) was reported. Note that the starting material can be transformed into (*R*)-2-*tert*-butyl-1-methyl-6-hydroxy-3,4-dihydroisoquinoline-1,2(1*H*)-dicarboxylate, which is the key intermediate of a Liver X Receptor agonist [58].
- Both enantiomers of 1,2,3,4-TH β C were prepared through *Candida antarctica* lipase B-catalyzed stereocomplementary new DKR processes. The enzymatic hydrolysis of the hydrochloride salts as starting amino CE racemates furnished the desired enantiomeric AAs quantitatively [61].

Presented in Table 3 are the lipase-catalyzed reactions performed in the usable *t*BuOMe and green H₂O as solvents and those carried out in a continuous-flow system, with clear advantages that include atom economy, reproducibility, safer solvents, short reaction time, rapid heating and compression vs. shaker reactions.

Table 3. Green aspects of enzymatic strategies.

Type of the Enzymatic Reaction	Enzymatic Strategies with Green Aspects *	Schemes	Refs
KR through <i>O</i> -acylation	Total synthesis of the antitumor-active alkaloid crispine A enantiomers, KR in <i>t</i> BuOMe	Scheme 2	[47]
	Synthesis of calycotomine enantiomers, preliminary experiments of KR in a continuous-flow system	Scheme 3	[49]
	Synthesis of homocalycotomine enantiomers. A systematic study on the <i>O</i> -acylation of THIQ amino alcohol homologues containing a remote stereogenic center, in a continuous-flow system	Scheme 3	[50]
	KR of new 1-hydroxymethyl TH β C derivatives in batch and continuous-flow systems	Scheme 4	[52]
KR through <i>N</i> -acylation	KR of salsolidine and its analogue 1-methyl-1,2,3,4-TH β C in <i>t</i> BuOMe in a continuous-flow system	Scheme 6	[55]
DKR through <i>N</i> -acylation	DKR of 1-cyano-1,2,3,4-THIQ derivatives in <i>t</i> BuOMe	Scheme 8	[57]
DKR through COOEt hydrolysis	DKR of 6-hydroxy- and 6-methoxy-1,2,3,4-THIQ-1-CE hydrochlorides in aqueous NH ₄ OAc buffer (pH 8.5)	Scheme 9	[58]
	Directed DKR of 1,2,3,4-TH β C-1-CE hydrochloride (in aqueous NH ₄ OAc buffer (pH 8.5), borate buffer (pH 8.0))	Scheme 10	[61]

* Reactions in *t*BuOMe and aqueous NH₄OAc buffer; reactions in continuous-flow system.

3. Conclusions and Outlook

This compilation presents the most important lipase-catalyzed strategies reported over the last decade for the preparation of pharmaceutically and chemically important THIQ and TH β C enantiomers, with simple molecular structure through *O*-acylation of the primary hydroxy group (with remote stereocenter), *N*-acylation of the secondary amino group, and COOEt hydrolysis of the corresponding racemic amino alcohols and amino CEs.

The strategies are classified as KR and DKR and presented in chronological order. The reactions resulted in the formation of the desired products with excellent *ee* values and good chemical yields isolated either by column chromatography or by organic solvent–H₂O extraction. The pharmacological importance of the products together with their synthesis is given in the *main text*.

The lipase-catalyzed reactions performed in the usable *t*BuOMe and green H₂O as solvents and those carried out in a continuous-flow system, with clear advantages including atom economy, reproducibility, safer solvents, short reaction time, rapid heating and compression vs. shaker reactions, are highlighted in the *main text* and summarized in Table 3.

Because of the growing demand for biologically active enantiomeric compounds in pharmaceutical chemistry (e.g., derivatives containing the THIQ or TH β C moiety), it is predicted that a large number of new green chemoenzymatic strategies (e.g., flow biocatalysis) will be devised for the preparation of such enantiomers.

Author Contributions: E.F. planned and designed the project. G.O. and E.F., after fruitful discussions, prepared the manuscript for publication. All authors have read and agreed to the published version of the manuscript.

Funding: The authors' thanks are due to the Hungarian Research Foundation (OTKA No. K-138871) and the Ministry of Human Capacities, Hungary, grant TKP-2021-EGA-32.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Muthukrishnan, I.; Sridharan, V.; Menéndez, J.C. Progress in the chemistry of tetrahydroquinoline. *Chem. Rev.* **2019**, *119*, 5057–5191. [[CrossRef](#)] [[PubMed](#)]
2. Wang, J.; Gong, F.; Liang, T.; Xie, Z.; Yang, Y.; Cao, C.; Gao, J.; Lu, T.; Chen, X. A review of synthetic bioactive tetrahydro- β -carbolines: A medicinal chemistry perspective. *Eur. J. Med. Chem.* **2021**, *225*, 113815. [[CrossRef](#)] [[PubMed](#)]
3. Kaufm, T.S. Synthetic pathways to salsolidine. *Tetrahedron Asymmetry* **2004**, *15*, 1203–1237. [[CrossRef](#)]
4. Boyd, E.M.; Knight, L.M. The expectorant action of cephaeline, emetine and 2-dehydroemetine. *J. Pharm. Pharmacol.* **1964**, *16*, 118–124. [[CrossRef](#)] [[PubMed](#)]
5. Al-Yahya, M.A.; Hassan, M.M.A. Noscapine. *Anal. Profiles Drug Subst.* **1982**, *11*, 407–461. [[CrossRef](#)]
6. Poveda, A.; Ray-Coquard, I.; Romero, I.; Lopez-Guerrero, J.A.; Colombo, N. Emerging treatment strategies in recurrent platinum-sensitive ovarian cancer: Focus on trabectedin. *Cancer Treat. Rev.* **2014**, *40*, 366–375. [[CrossRef](#)]
7. Liu, Z.-Z.; Wang, Y.; Tang, Y.-F.; Chen, S.-Z.; Chen, X.-G.; Li, H.-Y. Synthesis and antitumor activity of simplified ecteinascidin-saframycin analogs. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1282–1285. [[CrossRef](#)]
8. Kashiwada, Y.; Aoshima, A.; Ikeshiro, Y.; Chen, Y.-P.; Furukawa, H.; Itoigawa, M.; Fujioka, T.; Mihashi, K.; Cosentino, L.M.; Morris-Natschke, S.-L.; et al. Anti-HIV benzylisoquinoline alkaloids and flavonoids from the leaves of *Nelumbo nucifera*, and structure-activity correlations with related alkaloids. *Bioorg. Med. Chem.* **2005**, *13*, 443–448. [[CrossRef](#)]
9. Leal, J.F.M.; García-Hernández, V.; Moneo, V.; Domingo, A.; Bueren-Calabuig, J.A.; Negri, E.; Gago, F.; Guillén-Navarro, M.J.; Avilés, P.; Cuevas, C.; et al. Molecular pharmacology and antitumor activity of Zalypsis[®] in several human cancer cell lines. *Biochem. Pharmacol.* **2009**, *78*, 162–170. [[CrossRef](#)]
10. Zhang, Z.-J.; Yang, J.; He, J.; Wu, X.-D.; Shao, L.-D.; Li, Y.; Huang, S.-X.; Li, R.-T.; Zhao, Q.-S. Vincamajorines A and B, monoterpenoid indole alkaloids with new carbon skeletons from *Vinca major*. *Tetrahedron Lett.* **2014**, *55*, 6490–6494. [[CrossRef](#)]
11. Cong, H.-J.; Zhao, Q.; Zhang, S.-W.; Wei, J.-J.; Wang, W.-Q.; Xuan, L.-J. Terpenoid indole alkaloids from *Mappianthus iodoides* Hand.-Mazz. *Phytochemistry* **2014**, *100*, 76–85. [[CrossRef](#)] [[PubMed](#)]
12. Kam, T.-S.; Sim, K.-M. Alkaloids from *Kopsia griffithii*. *Phytochemistry* **1998**, *47*, 145–147. [[CrossRef](#)]
13. Davis, R.A.; Duffy, S.; Avery, V.M.; Camp, D.; Hooper, J.N.A.; Quinn, R.J. (+)-7-Bromotrypargine: An antimalarial β -carboline from the Australian marine sponge *Ancorina* sp. *Tetrahedron Lett.* **2010**, *51*, 583–585. [[CrossRef](#)]
14. Brock, G.B.; McMahon, C.G.; Chen, K.K.; Costigan, T.; Shen, W.; Watkins, V.; Anglin, G.; Whitaker, S. Effect of tadalafil in chronic renal failure rabbits: Relevance to erectile dysfunction. *J. Urol.* **2002**, *168*, 1332–1336. [[CrossRef](#)]
15. He, S.; Dobbelaar, P.H.; Guo, L.; Ye, Z.; Liu, J.; Jian, T.; Truong, Q.; Shah, S.K.; Du, W.; Qi, H.; et al. SAR exploration at the C-3 position of tetrahydro- β -carboline sstr3 antagonists. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1529–1535. [[CrossRef](#)] [[PubMed](#)]
16. Brokamp, R.; Bergmann, B.; Müller, I.B.; Bienz, S. Stereoselective preparation of pyridoxal 1,2,3,4-tetrahydro- β -carboline derivatives and the influence of their absolute and relative configuration on the proliferation of the malaria parasite *Plasmodium falciparum*. *Bioorganic Med. Chem.* **2014**, *22*, 1832–1837. [[CrossRef](#)]
17. Spindler, A.; Stefan, K.; Wiese, M. Synthesis and investigation of tetrahydro- β -carboline derivatives as inhibitors of the Breast Cancer Resistance Protein (ABCG2). *J. Med. Chem.* **2016**, *59*, 6121–6135. [[CrossRef](#)]
18. Shankaraiah, N.; da Silva, W.A.; Andrade, C.K.R.; Santos, L.S. Enantioselective total synthesis of (S)-(-)-quinolactacin B. *Tetrahedron Lett.* **2008**, *49*, 4289–4291. [[CrossRef](#)]
19. Szabó, T.; Volk, B.; Milen, M. Recent Advances in the Synthesis of β -Carboline Alkaloids. *Molecules* **2021**, *26*, 663. [[CrossRef](#)]
20. Chrzanowska, M.; Rozwadowska, M.D. Asymmetric Synthesis of Isoquinoline Alkaloids. *Chem. Rev.* **2004**, *104*, 3341–3370. [[CrossRef](#)]
21. Miyazaki, M.; Ando, N.; Sugai, K.; Seito, Y.; Fukuoka, H.; Kanemitsu, T.; Nagata, K.; Odanaka, Y.; Nakamura, K.T.; Itoh, T. Catalytic asymmetric allylation of 3,4-dihydroisoquinolines and its application to the synthesis of isoquinoline alkaloids. *J. Org. Chem.* **2011**, *76*, 534–542. [[CrossRef](#)]
22. Dai, J.; Dan, W.; Schneider, U.; Wang, J. β -Carboline alkaloid monomers and dimers: Occurrence, structural diversity, and biological activities. *Eur. J. Med. Chem.* **2018**, *157*, 622–656. [[CrossRef](#)]
23. Buaban, K.; Phutdhawong, W.; Taechowisan, T.; Phutdhawong, W.S. Synthesis and investigation of tetrahydro- β -carboline derivatives as inhibitors of plant pathogenic fungi. *Molecules* **2021**, *26*, 207. [[CrossRef](#)]
24. Sánchez-Muñoz, G.K.; Ortega-Rojas, M.A.; Chavelas-Hernández, L.; Razo-Hernández, R.S.; Valdéz-Camacho, J.R.; Escalante, J. Solvent-free lipase-catalyzed transesterification of alcohols with methyl esters under vacuum-assisted conditions. *ChemistrySelect* **2022**, *7*, e202202643. [[CrossRef](#)]
25. Dolzhenko, A.V.; Dolzhenko, A.V. Green solvents for eco-friendly synthesis of bioactive heterocyclic compounds. In *Green Synthetic Approaches for Biologically Relevant Heterocycles*, 1st ed.; Brahmachari, G., Ed.; Elsevier: Amsterdam, The Netherlands, 2015; Chapter 5, pp. 101–139, ISBN 9780128000700.
26. Sousa, R.R.; Silva, A.S.; Fernandez-Lafuente, R.; Ferreira-Leitão, V.S. Solvent-free esterifications mediated by immobilized lipases: A review from thermodynamic and kinetic perspectives. *Catal. Sci. Technol.* **2021**, *11*, 5696–5711. [[CrossRef](#)]
27. Gustini, L.; Finzel, L.; Lavilla, C.; Noordover, B.A.J.; Hendrix, M.M.R.M.; Gehrels, C.; Koning, C.E. Understanding the limitations of the solvent-free enzymatic synthesis of sorbitol-containing polyesters. *ACS Sustain. Chem. Eng.* **2016**, *4*, 2259–2268. [[CrossRef](#)]
28. Serrano-Arnaldos, M.; Máximo-Martín, M.F.; Montiel-Morte, M.C.; Ortega-Requena, S.; Gómez-Gómez, E.; Bastida-Rodríguez, J. Solvent-free enzymatic production of high quality cetyl esters. *Bioprocess Biosyst. Eng.* **2016**, *39*, 641–649. [[CrossRef](#)] [[PubMed](#)]

29. Sheldon, R.A.; Brady, D. Green chemistry, biocatalysis, and the chemical industry of the future. *ChemSusChem* **2022**, *15*, e202102628. [[CrossRef](#)] [[PubMed](#)]
30. Godoy, C.A.; Pardo-Tamayo, J.S.; Barbosa, O. Microbial lipases and their potential in the production of pharmaceutical building blocks. *Int. J. Mol. Sci.* **2022**, *23*, 9933. [[CrossRef](#)]
31. Belafriekh, A.; Secundo, F.; Serra, S.; Djeghaba, Z. Enantioselective enzymatic resolution of racemic alcohols by lipases in green organic solvents. *Tetrahedron Asymmetry* **2017**, *28*, 473–478. [[CrossRef](#)]
32. Farrán, A.; Cai, C.; Sandoval, M.; Xu, Y.; Liu, J.; Hernáiz, M.J.; Linhardt, R.J. Green solvents in carbohydrate chemistry: From raw materials to fine chemicals. *Chem. Rev.* **2015**, *115*, 6811–6853. [[CrossRef](#)] [[PubMed](#)]
33. Moniruzzaman, M.; Nakashima, K.; Kamiya, N.; Goto, M. Recent advances of enzymatic reactions in ionic liquids. *Biochem. Eng. J.* **2010**, *48*, 295–314. [[CrossRef](#)]
34. Hernáiz, M.J.; Alcántara, A.R.; García, J.I.; Sinisterra, J.V. Applied biotransformations in green solvents. *Chem. Eur. J.* **2010**, *16*, 9422–9437. [[CrossRef](#)] [[PubMed](#)]
35. Yang, Z.; Pan, W. Ionic liquids: Green solvents for nonaqueous biocatalysis. *Enzyme Microb. Technol.* **2005**, *37*, 19–28. [[CrossRef](#)]
36. Byrne, F.P.; Jin, S.; Paggiola, G.; Petchey, T.H.M.; Clark, J.H.; Farmer, T.J.; Hunt, A.J.; McElroy, C.R.; Sherwood, J. Tools and techniques for solvent selection: Green solvent selection guides. Tools and techniques for solvent selection: Green solvent selection guides. *Sustain. Chem. Process.* **2016**, *4*, 7. [[CrossRef](#)]
37. De Santis, P.; Meyer, L.-E.; Kara, S. The rise of continuous flow biocatalysis—Fundamentals, very recent developments and future perspectives. *React. Chem. Eng.* **2020**, *5*, 2155–2184. [[CrossRef](#)]
38. Thompson, M.P.; Peñafliel, I.; Cosgrove, S.C.; Turner, N.J. Biocatalysis using immobilized enzymes in continuous flow for the synthesis of fine chemicals. *Org. Process Res. Dev.* **2019**, *23*, 9–18. [[CrossRef](#)]
39. Xiao, Y.; Zheng, M.; Liu, Z.; Shi, J.; Huang, F.; Luo, X. Constructing a continuous flow bioreactor based on a hierarchically porous cellulose monolith for ultrafast and nonstop enzymatic esterification/transesterification. *ACS Sustain. Chem. Eng.* **2019**, *7*, 2056–2063. [[CrossRef](#)]
40. Britton, J.; Majumdar, S.; Weiss, G.A. Continuous flow biocatalysis. *Chem. Soc. Rev.* **2018**, *47*, 5891–5918. [[CrossRef](#)]
41. Gruber, P.; Carvalho, F.; Marques, M.P.C.; O’Sullivan, B.; Subrizi, F.; Dobrijevic, D.; Ward, J.; Hailes, H.C.; Fernandes, P.; Wohlgemuth, R.; et al. Enzymatic synthesis of chiral amino-alcohols by coupling transketolase and transaminase-catalyzed reactions in a cascading continuous-flow microreactor system. *Biotechnol. Bioeng.* **2018**, *115*, 586–596. [[CrossRef](#)]
42. Woodcock, L.L.; Wiles, C.; Greenway, G.M.; Watts, P.; Wells, A.; Eyley, S. Enzymatic synthesis of a series of alkyl esters using Novozyme 435 in a packed-bed, miniaturized, continuous flow reactor. *Biocatal. Biotransform.* **2008**, *26*, 466–472. [[CrossRef](#)]
43. Zdun, B.; Kopyńska, I.; Dranka, M.; Reiter, T.; Kroutil, W.; Borowiecki, P. Chemoenzymatic synthesis of optically active alcohols possessing 1,2,3,4-tetrahydroquinoline moiety employing lipases or variants of the acyltransferase from *Mycobacterium smegmatis*. *Catalysts* **2022**, *12*, 1610. [[CrossRef](#)]
44. Breen, G.F. Enzymatic resolution of a secondary amine using novel acylating reagents. *Tetrahedron Asymmetry* **2004**, *15*, 1427–1430. [[CrossRef](#)]
45. Stirling, M.; Blacker, J.; Page, M.I. Chemoenzymatic dynamic kinetic resolution of secondary amines. *Tetrahedron Lett.* **2007**, *48*, 1247–1250. [[CrossRef](#)]
46. Zhang, Q.; Tu, G.; Zhao, Y.; Cheng, T. Total synthesis of the antitumor active pyrrolo[2,1-*a*]isoquinoline alkaloid (±)-crispine A. *Tetrahedron* **2002**, *58*, 6795–6798. [[CrossRef](#)]
47. Forró, E.; Schönstein, L.; Fülöp, F. Total synthesis of crispine A enantiomers through a *Burkholderia cepacia* lipase-catalysed kinetic resolution. *Tetrahedron Asymmetry* **2011**, *22*, 1255–1260. [[CrossRef](#)]
48. Kanemitsu, T.; Yamashita, Y.; Nagata, K.; Itoh, T. Synthesis of (-)-Trolline, (-)-Crispin A and (-)-Crispine E. *Heterocycles* **2007**, *74*, 199–203. [[CrossRef](#)]
49. Schönstein, L.; Forró, E.; Fülöp, F. Continuous-flow enzymatic resolution strategy for the acylation of amino alcohols with a remote stereogenic centre: Synthesis of calycotomine enantiomers. *Tetrahedron Asymmetry* **2013**, *24*, 202–206. [[CrossRef](#)]
50. Schönstein, L.; Forró, E.; Fülöp, F. Enzymatic reaction for the preparation of homocalycotomine enantiomers. *Tetrahedron Asymmetry* **2013**, *24*, 1059–1062. [[CrossRef](#)]
51. Yamada, M.; Azuma, K.; Takizawa, I.; Ejima, Y.; Yamano, M.; Satoh, K.; Doi, T.; Ueda, H.; Tokuyama, H. Efficient and scalable I asymmetric total synthesis of (–)-Emetine with pharmaceutical grade quality; First multigram scale synthesis. *Org. Process Res. Dev.* **2023**, *27*, 343–357. [[CrossRef](#)]
52. Megyesi, R.; Forró, E.; Fülöp, F. Enzymatic strategy for the resolution of new 1-hydroxymethyl tetrahydro-β-carboline derivatives in batch and continuous-flow systems. *ChemistryOpen* **2016**, *5*, 254–260. [[CrossRef](#)] [[PubMed](#)]
53. Megyesi, R.; Forró, E.; Fülöp, F. Substrate engineering: Effects of different N-protecting groups in the CAL-B catalysed asymmetric O-acylation of 1-hydroxymethyl-tetrahydro-β-carbolines. *Tetrahedron* **2018**, *74*, 2634–2640. [[CrossRef](#)]
54. Ding, W.; Li, M.; Dai, R.; Deng, Y. Lipase-catalyzed synthesis of the chiral tetrahydroisoquinoline (R)-salsolinol. *Tetrahedron Asymmetry* **2012**, *23*, 1376–1379. [[CrossRef](#)]
55. Kovács, B.; Megyesi, R.; Forró, E.; Fülöp, F. Efficient lipase-catalyzed route for the kinetic resolution of salsolidine and its β-carboline analogue. *Tetrahedron Asymmetry* **2017**, *28*, 1829–1833. [[CrossRef](#)]
56. Kovács, B.; Forró, E.; Fülöp, F. *Candida antarctica* lipase B catalyzed kinetic resolution of 1,2,3,4-tetrahydro-β-carbolines: Substrate specificity. *Tetrahedron* **2018**, *74*, 6873–6877. [[CrossRef](#)]

57. Sakulsombat, M.; Vongvilai, P.; Ramström, O. Efficient asymmetric synthesis of 1-cyano-tetrahydroisoquinolines from lipase dual activity and opposite enantioselectivities in α -aminonitrile resolution. *Chem. Eur. J.* **2014**, *20*, 11322–11325. [[CrossRef](#)]
58. Forró, E.; Megyesi, R.; Paál, T.A.; Fülöp, F. Efficient dynamic kinetic resolution method for the synthesis of enantiopure 6-hydroxy- and 6-methoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid. *Tetrahedron Asymmetry* **2016**, *27*, 1213–1216. [[CrossRef](#)]
59. Anderson, W.K.; McPherson, H.L., Jr.; New, J.S.; Rick, A.C. Synthesis and murine antineoplastic activity of bis[carbamoyloxymethyl] derivatives of pyrrolo[2,1-*a*]isoquinoline. *J. Med. Chem.* **1984**, *27*, 1321–1325. [[CrossRef](#)]
60. Grill, I.S.; Kick, E.; Richlin-Zack, K.; Yang, W.; Wang, Y.; Patel, R.N. Enzymatic resolution of methyl (1R)-N-tBoc-6-hydroxy-3,4-dihydro-1H-isoquinoline-1-carboxylate by Seaprose S. *Tetrahedron Asymmetry* **2007**, *18*, 2147–2154. [[CrossRef](#)]
61. Megyesi, R.; Mándi, A.; Kurtán, T.; Forró, E.; Fülöp, F. Dynamic kinetic resolution of ethyl 1,2,3,4-tetrahydro- β -carboline-1-carboxylate. Use of different hydrolases for stereocomplementary processes. *Eur. J. Org. Chem.* **2017**, *32*, 4713–4718. [[CrossRef](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.