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Stereoselective synthesis of optically active cyclic α- and β-amino esters through lipase-catalyzed transesterification or interesterification processes

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ABSTRACT

A series of cyclic α- and β-amino esters belonging to a family of indolines and quinolines have been efficiently synthesized to study their behavior in lipase-mediated kinetic resolution reactions. The influence of the fused ring structure to the benzene ring and the position of the ester functionality relative to the amino group have been demonstrated, finding excellent values of enantiodiscrimination in the transesterification reaction of methyl indoline-3-carboxylate with *n*-butanol catalyzed by *Candida antarctica* lipase B being observed. On the other hand, low to moderate selectivities have been found when using a wide panel of lipases toward methyl indoline-2-carboxylate or 1,2,3,4-tetrahydroquinoline derivatives in alkoxycarbonylation, transesterification or interesterification reactions.

1. Introduction

Amino acid derivatives are central to chemistry because of their presence in biologically active compounds and pharmaceuticals,[1] in addition to their possibilities as organic chiral building blocks for the generation of ligands or catalysts with applications in asymmetric synthesis.[2] For these reasons, the development of practical synthetic routes to render this type of compounds in a stereoselective fashion has received very much attention in recent years.[3] In particular, the preparation of enantiopure cyclic amino esters has been the focus of a number of investigations,[4] mainly on those compounds with structures similar to proline and pipecolic acid, and amino acids that play a crucial role both in the structural and in the biological properties of peptides.[5]

Nowadays, enzyme-mediated processes are considered elegant and useful methodologies for enantioselective transformations.[6] From the wide set of enzymatic classes, lipases have gained much attention over the last two decades due to their ease of manipulation, low cost, and wide substrate tolerance.[7] Traditionally, most of the lipase-catalyzed enantioselective reactions have efficiently mediated the acylation of alcohols or hydrolysis of esters, whereas the preparation of chiral amides or carbamates has been much less investigated, in spite of the fact that mild reaction conditions are required for the formation of these nitrogenated compounds.[8] There are few examples of enzymatic kinetic or dynamic kinetic resolutions of cyclic secondary amines described in the literature,[9] even though they are present in a large number of biologically relevant systems and are useful building blocks for the preparation of many valuable products. On the other hand, amino esters are very attractive compounds due to their intrinsic bifunctionality. Thus, concerning lipase catalysis, while the nucleophilic amino group is susceptible to acylation or alkoxycarbonylation, the electrophilic ester functionality allows the preparation of amides, carboxylic acids, and related compounds by means of a typical addition–elimination mechanism.[10]

Herein we report the chemical synthesis of methyl indoline and 1,2,3,4-tetrahydroquinoline carboxylates bearing the ester group at the 2- or 3-position, and studied their behavior in different lipase-mediated reactions directed toward the production of optically active compounds. Thus, alkoxycarbonylation, transesterifcation, and interesterification processes have been undertaken.

2. Results and discussion

Recently we have described the enzymatic kinetic resolution of methyl indoline-2-carboxylate using an alkoxycarbonylation reaction, where *Candida antarctica* lipase A (CAL-A) showed excellent levels of activity and stereodiscrmination.[9o] This research continued a previous study from our research group on the enzymatic resolution of a family of 2- and 3-alkyl and 2-phenyl indoline derivatives.[9l] In this case, CAL-A gave the best activity toward the 2-substituted derivatives, while *Candida antarctica* lipase B (CAL-B) was found to be the best catalyst for the kinetic resolution of the 3-methyl indoline. These results encouraged us to test the enzymatic resolution of racemic methyl indoline-3-carboxylate **3**.

Initially, the synthesis of (±)-**3** was performed from indole-3-carboxylic acid **1** in a two-step sequence (Scheme 1). Chemical reduction of the internal C–C double bond of the five-membered

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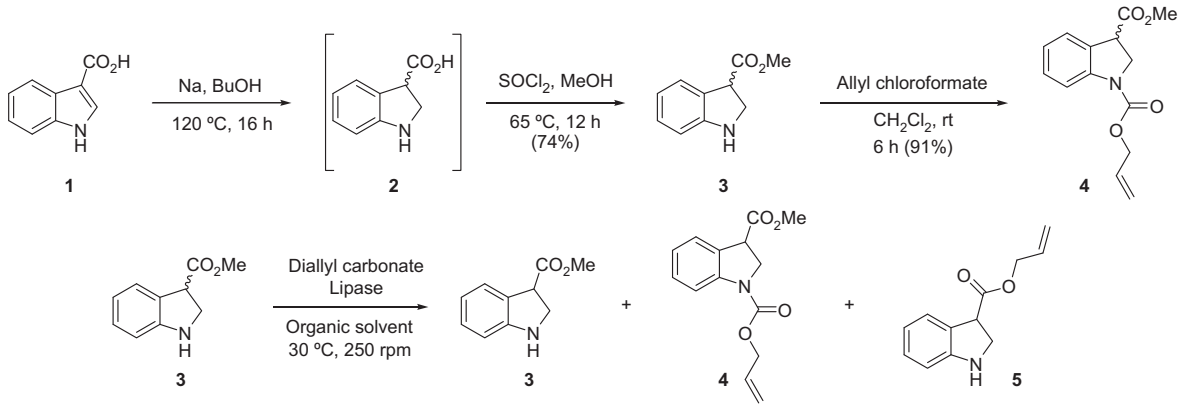
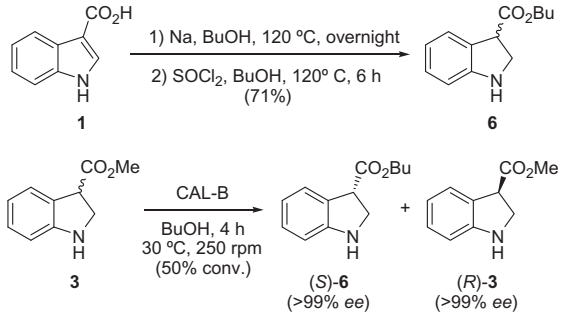


Scheme 1. Chemical synthesis of racemic methyl indoline-3-carboxylate **3** and our attempts at enzymatic kinetic resolution by a lipase-mediated alkoxycarbonylation procedure.

ring using sodium and *n*-butanol (BuOH) as solvent at 120 °C,[11] followed by esterification with MeOH of the obtained racemic amino acid **2** in the presence of thionyl chloride ($SOCl_2$) gave the desired methyl ester in an overall 74% isolated yield. For the study of the enzymatic alkoxycarbonylation reaction, the corresponding allyl carbamate **4** was first prepared chemically, in order to develop adequate chiral HPLC methods for the determination of the enantiomeric excesses of both substrate and product of the enzymatic reaction (see Section 4).

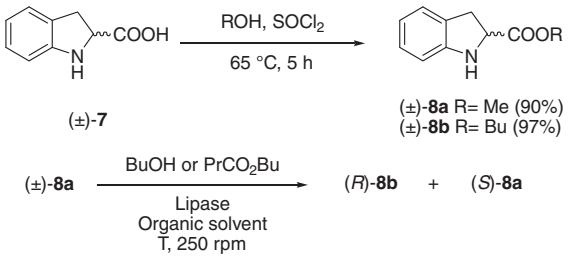
We tested the enzymatic resolution with both types of *C. antarctica* lipases (Scheme 1). As expected, CAL-A has a limited selectivity toward this substrate (56% conversion, 71% ee_S, 56% ee_P after 10 days), while CAL-B presented a high stereoselectivity toward the formation of carbamate **4**. Unfortunately, a lipase-mediated transesterification process also occurred, giving considerable amounts of the allylic ester **5** in the reaction media. The appearance of both amino esters **3** and **5** led to serious problems in the purification step, hence we decided at this point to study other known enzymatic approaches, such as transesterification[12] or interesterification lipase-catalyzed processes.[13] Thereby the transesterification with *n*-butanol was tested with two lipases, CAL-B and *Pseudomonas cepacia* lipase (PSL-C I, also known as *Burkholderia cepacia* lipase). Despite the poor selectivity of the latter enzyme, CAL-B displayed both a great activity and enantiopreference toward the enantiomers of this particular substrate, giving substrate **3** and product **6** at 50% conversion in enantiopure form after a short timespan (Scheme 2).



Scheme 2. Chemical synthesis of amino ester **6** and CAL-B mediated kinetic resolution by an esterification reaction.

The absolute configuration of the remaining methyl aminoester (*R*)-**3** was confirmed by comparison of its specific rotation value, $[\alpha]_D^{20} = -94.7$ (*c* 0.88, CH_2Cl_2), with the one obtained in the enzymatic kinetic resolution of (±)-**3** by a CAL-B-mediated hydrolysis reaction.[14] These successful results in the study of the transesterification reaction of methyl ester **3** encouraged us to study the behavior of lipases toward methyl indoline-2-carboxylate **8a** using the same experimental conditions, both to compare the reactivity of compounds with the same substitutions in different positions of the five-membered ring, but also using the alkoxycarbonylation reaction.[9o]

In this manner racemic methyl ester **8a** and butyl ester **8b** were prepared in excellent yields by simple chemical transesterification of indoline-2-carboxylic acid using MeOH and BuOH, respectively (Scheme 3). The lipase-mediated transesterification reaction of racemic methyl ester **8a** using *n*-butanol as a nucleophile and PSL-C I and CAL-B as biocatalysts was then examined exhaustively (Table 1, entries 1–4).



Scheme 3. Chemical synthesis of amino esters **8a**–**b** and lipase-mediated esterification and transesterification reactions of **8a**.

Initially the use of BuOH as a donor and solvent was tested, observing that while the PSL-C I showed a low selectivity (entry 1), CAL-B reacted with great selectivity for the substrate although the reaction rate was quite high (entry 2). In order to find better selectivities, we decided to test THF as solvent with just two equivalents of BuOH (entries 3 and 4). Even though the data from PSL-C I got better, the enantioselectivity was still low (entry 3). On the other hand, CAL-B was almost equal in terms of enantioslectivity ($E = 7$), reaching 50% conversion values with a moderate enantiomeric excess for both the substrate and product after 7 h (entry 4). Finding that the transesterification process was not as synthetically useful as it was with the 3-substituted derivative (±)-**3**, we decided to explore another enzymatic approach such as the interesterification reaction, employing butyl butanoate and screening different lipases: *Rhizomucor miehei* (RM), *C. antarctica* type-A (CAL-A), *Candida rugosa* (CRL) and from porcine pancreatic (PPL). No reactivity toward the substrate was found except for the RM (entries 5–8), which showed no great improvement from the others. While PSL-C I double the previous *E* value (entries 3 and 9), it

Table 1
Lipase-catalyzed transesterification or interesterification of methyl 2-indoline-carboxylate **8a**

Entry	Solvent	Enzyme	Resolving agent[a]	T (°C)	t (h)	ee_S[b] (%)	ee_P[b] (%)	c[c] (%)	E[d]
1	BuOH	PSL-C I	BuOH (110)	30	23	10	8	57	1
2	BuOH	CAL-B	BuOH (110)	30	8	>99	13	88	6
3	THF	PSL-C I	BuOH (2)	30	20	9	81	10	10
4	THF	CAL-B	BuOH (2)	30	7	61	60	50	7
5	THF	RM	$PrCO_2Bu$ (2)	30	21	11	21	34	2
6	THF	CAL-A	$PrCO_2Bu$ (2)	30	21	0	—	0	—
7	THF	CRL	$PrCO_2Bu$ (2)	30	21	0	—	0	—
8	THF	PPL	$PrCO_2Bu$ (2)	30	21	0	—	0	—
9	THF	PSL-C I	$PrCO_2Bu$ (2)	30	92	78	50	50	20
10	THF	CAL-B	$PrCO_2Bu$ (2)	30	2	76	78	49	18
11	THF	CAL-B	$PrCO_2Bu$ (2)	20	2	77	86	48	30

[a] Number of equivalents in brackets.
[b] Determined by HPLC.
[c] $c = ee_S/(ee_S+ee_P)$.
[d] $E = \ln[(1-c)\times(1-ee_P)]/\ln[(1-c)\times(1+ee_P)]$.[15]

should be noted that the reaction time was higher and the selectivity value was still low (entry 9). Again CAL-B was the biocatalyst that gave a higher stereodiscrimination with a faster reaction rate (entry 10). Finally, we tested the process by decreasing the temperature to 20 °C in order to determine a better stereodiscrimination (entry 11), and although the enantioselectivity increased, this was poor in comparison with previous results achieved using the alkoxycarbonylation approach.[9o]

Next, we decided to study the enzymatic synthesis of related cyclic aminoesteres with similar structures, such as methyl quinoline carboxylates substituted at the 2-position (**11**) or at the 3-position (**15**). For the chemical synthesis of racemic methyl-1,2,3,4-tetrahydroquinoline-2-carboxylate **11**, 2-quinoline carboxylic acid **9** was selected as the ideal starting material, which was chemically esterified to obtain methyl 2-quinoline carboxylate. Selective reduction of the pyridine ring using sodium cyanoborohydride ($NaBH_3CN$) in acidic media, allowed the isolation of **11** in good overall yield (Scheme 4).[16]

Similar to the enzymatic alkoxycarbonylation reaction of indoline **3**, a mixture of products were found in the CAL-B-mediated process; we attempted to overcome this issue by focusing on the study of the transesterification reaction of (±)-**11** using the same pool of enzymes that were used for the indoline ester **8a** (Table 2). As was seen before, CAL-A, CRL, and PPL showed no activity toward the substrate (entries 1–3), while RM, CAL-B, and PSL-C I displayed moderate to high activities (entries 4–6), with only PSL-C I showing good selectivity for the transesterification of the (*R*)-enantiomer. In this process, the butyl ester **12** was isolated in 91% ee and 40% conversion after 30 h at 30 °C (entry 6).[17]

Finally we studied the chemical preparation and lipase-mediated kinetic resolution of the racemic quinoline analogue bearing an ester group at the 3-position. Methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate **15** was prepared in very high yield from 3-quinoline carboxylic acid **13** following an analogous sequence than with the 2-substituted derivative, esterification with MeOH followed by reduction with $NaBH_3CN$ (Scheme 5). As occured with the 2-methyl-1,2,3,4-tetrahydroquinoline analogue, when the transesterification reactions were carried out in THF as solvent and 2 equivalents of BuOH, no reaction was observed with some enzymes (CAL-A or PSL-C I, Table 3, entries 1 and 2); *R. Miehei* lipase showed slightly better stereodiscrimination than CAL-B although with a very modest value (entries 3 and 4). In order to improve the results we attempted the interesterification process with

Table 2
Enzymatic transesterification of methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate **11** in THF at 30 °C

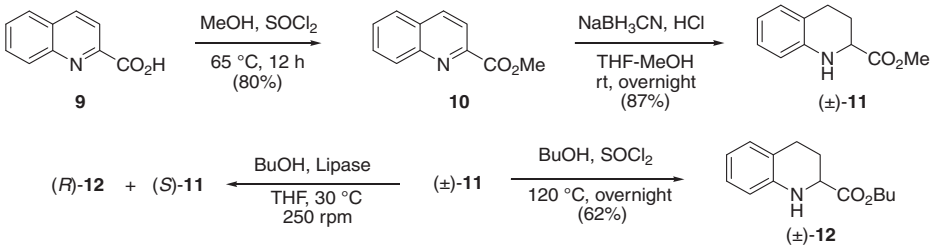
Entry	Enzyme	t (h)	ee_S[a] (%)	ee_P[a] (%)	c[b] (%)	E[c]
1	CAL-A	30	0	—	0	—
2	CRL	72	0	—	0	—
3	PPL	30	0	—	0	—
4	RM	30	40	16	72	2
5	CAL-B	30	70	31	70	4
6	PSL-C I	30	63	91	40	39

[a] Determined by HPLC.
[b] $c = ee_S/(ee_S+ee_P)$.
[c] $E = \ln[(1-c)\times(1-ee_P)]/\ln[(1-c)\times(1+ee_P)]$.[15]

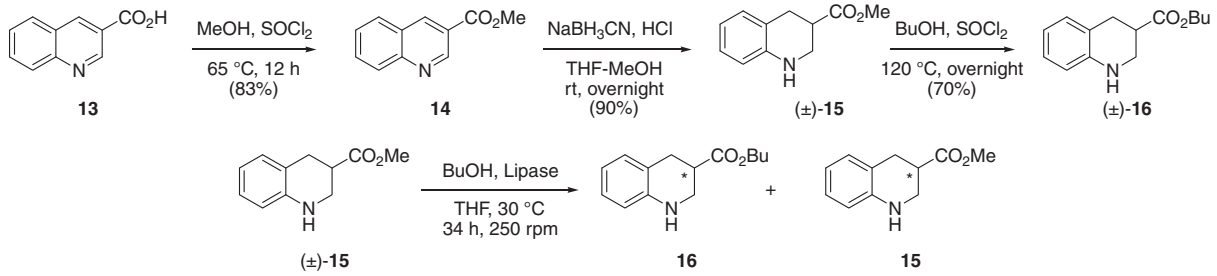
Table 3
Enzymatic transesterification of 1,2,3,4-tetrahydroquinoline-3-carboxylate **15** using BuOH in THF at 30 °C at 250 rpm after 34 h

Entry	Enzyme	ee_S[a] (%)	ee_P[a] (%)	c[b] (%)	E[c]
1	CAL-A	0	—	0	—
2	PSL-C I	0	—	0	—
3	RM	56	69	45	9
4	CAL-B	63	11	70	2

[a] Determined by HPLC.
[b] $c = ee_S/(ee_S+ee_P)$.
[c] $E = \ln[(1-c)\times(1-ee_P)]/\ln[(1-c)\times(1+ee_P)]$.[15]



Scheme 4. Chemical synthesis of racemic methyl and butyl 1,2,3,4-tetrahydroquinoline esters **11** and **12**, and study of the enzymatic kinetic resolution of the methyl ester.



Scheme 5. Chemical synthesis of quinoline derivative **15** and attempts of lipase-mediated kinetic resolutions by using a transesterification reaction.

butyl butanoate and RM lipase and slightly improved upon the stereodiscrimination shown by the enzyme (46% conversion, 50% ee_S, 67% ee_P after 34 h). Finally, much better results were attained when the transesterification reaction was carried out with the same lipase, but in neat butanol as solvent and resolving agent, reaching 54% conversion after 24 h and recovering the substrate in 91% ee and the product in 76% ee.

3. Conclusions

In conclusion, we have developed the chemical synthesis of a series of racemic cyclic α- and β-amino esters to study their behavior in lipase-catalyzed alkoxycarbonylation, transesterification, or interesterification processes. The production of enantiomerically pure alkyl indoline-3-carboxylates has been successfully achieved via the kinetic resolution of methyl indoline-3-carboxylate using *C. antarctica* lipase B as a biocatalyst and butanol for the transesterification reaction. Lipases have shown lower enantiopreferences toward the homologous 2-substituted ester and also 1,2,3,4-tetrahydroquinoline derivatives bearing the ester group at the 2- or 3-position, leading to optically active amino esters with low to high enantiomeric excesses depending on the substrate structure and the choice of transesterification or interesterification process.

4. Experimental

4.1. General

C. antarctica lipase type B (CAL-B, Novozyme 435, 7300 PLU/g) and *R. miehei* lipase (Lipozyme RM IM, <15% in weight) were a gift from Novozymes (Denmark). *C. antarctica* lipase type A was acquired from Codexis (2.6 U/mg using tributyrin). *P. cepacia* lipase type I (PSL-C I, Amano, 1061 U/g), porcine pancreas lipase (PPL) type II (30–90 U/mg of protein using triacetin), and *C. rugosa* lipase (965 U/mg of solid using olive oil) were purchased from Sigma–Aldrich. All other reagents were purchased from Acros Organics or Sigma–Aldrich and used without further purification. Solvents were distilled over an adequate desiccant under nitrogen. Flash chromatography was performed using Silica Gel 60 (230–240 mesh). High performance liquid chromatography (HPLC) analyses were carried out at 30 °C in a Hewlett Packard 1100 chromatograph under the conditions specified for each substrate and with UV monitoring at 210 and 215 nm. IR spectra were recorded using NaCl plates or KBr pellets in a Perkin–Elmer 1720-X FT. ^{1}H, ^{13}C NMR and DEPT experiments were carried out using AC-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) or DPX-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) Bruker spectrometers. The chemical shifts are given in delta (δ) values and the coupling constants (J) in Hertz (Hz). HP1100 chromatograph mass detector was used to record mass spectra experiments (MS) through ESI^+ or $APCI^+$ mass experiments. The measurement of the specific rotation was carried out in a Perkin–Elmer 241 polarimeter.

4.2. Synthesis of indoline-3-carboxylic acid 2[11]

To a heated suspension of indole-3-carboxylic acid (1.0 g, 6.2 mmol) in butanol (30 mL), metallic Na (1.9 g, 82.2 mmol) was carefully added in batches of 200–250 mg every 10 min. After all the sodium was added, the mixture was refluxed at 120 °C overnight. After this time, the mixture was left cool to room temperature and 15 mL of distilled water were added to assure no more sodium was left in the reaction medium. The mixture was then concentrated on a rotary evaporator and in a high-vacuum pump until none of the butanol was present. The solid was redissolved in water (10 mL), neutralized with concentrated HCl, and later acidified to pH 4–5 with an aqueous AcOH solution. The suspension was put on an ice-bath, and after a solid started to precipitate, the formed suspension was filtrated and the mother liquor was saturated with solid NH_4Cl. The solid formed was filtrated and both resulting solids were combined and used without further purification for the synthesis of compounds **3** and **6**.

4.3. Typical procedure for the esterification of indoline-3-carboxylic acid (synthesis of esters 3 and 6)

Carboxylic acid **2** (100 mg, 0.61 mmol) was dissolved in the corresponding alcohol (MeOH or *n*-BuOH, 12 mL) and placed in an ice-bath. Then $SOCl_2$ (61 μL, 0.80 mmol) was added dropwise and the corresponding mixture refluxed overnight (67 °C, for methanol; 120 °C, for *n*-butanol) until no starting material was detected on TLC (10% MeOH/CH_2Cl_2). After that, the mixture was concentrated under reduced pressure, resuspended in water (10 mL), slightly alkalinized until pH 8.0 with an aqueous solution of NaOH 1 M, and extracted with CH_2Cl_2 (3 × 10 mL). The resulting esters were purified by column chromatography (10–30% EtOAc/hexane), obtaining a yellowish oil both for **3** (74%) and **6** (71%).

4.3.1. Methyl indoline-3-carboxylate 3

R_f (30% EtOAc/hexane): 0.26; IR (NaCl): ν 3378, 2952, 2282, 1732, 1606, 1532, 1488, 1465, 1436, 1317, 1254, 1200, 1173, 1051, 751 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz): 3.46 (br s, 1H, NH), 3.74–3.83 (m, 4H, H_2, $3H_{11}$), 3.96 (t, 2H, J = 8.44, H_2), 4.22 (dd, 1H, J = 7.90, 9.20 Hz, H_3), 6.70 (d, 1H, J = 7.68 Hz, H_4), 6.74 (t, 1H, J = 7.45, H_5), 7.11 (t, 1H, J = 6.19, H_6), 7.33 (d, 1H, J = 7.45 Hz, $H_{4,7}$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 47.1 (C_3), 49.1 (C_2), 52.2 (C_{12}), 110.0 (C_7), 118.8 (C_5), 125.0 (C_6), 125.9 (C_9), 128.6 (C_4), 150.9 (C_8), 172.6 (C_{10}). MS ($APCI^+$, m/z): 178.1 [$(M+H)^+$, 100]. HPLC: Chiralcel OJ-H column, hexane/propan-2-ol (90:10), 30 °C, and 0.8 mL/min flow.

4.3.2. Butyl indoline-3-carboxylate 6

R_f (30% EtOAc/hexane): 0.60; IR (NaCl): ν 3378, 2960, 2934, 2874, 1732, 1607, 1533, 1488, 1465, 1256, 1180, 748 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz): 0.98 (t, 3H, J = 7.35 Hz, H_{15}), 1.38–1.50 (m, 2H, H_{14}), 1.65–1.74 (qt, 2H, H_{13}), 3.59 (s, 1H, NH), 3.74 (t, 1H,

J = 9.65 Hz, H_2), 3.96 (dd, 1H, J = 7.67, 7.68 Hz, H_2), 4.18–4.23 (m, 3H, $2H_{12}$+H_3), 6.67 (d, 1H, J = 7.89 Hz, H_4), 6.77 (t, 1H, J = 7.46 Hz, H_5), 7.11 (t, 1H, J = 7.57 Hz, H_6), 7.33 (d, 1H, J = 7.46 Hz, H_7); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 13.5 (C_{15}), 19.0 (C_{14}), 30.5 (C_{13}), 47.1 (C_3), 49.0 (C_2), 64.9 (C_{12}), 109.9 (C_7), 118.7 (C_5), 124.9 (C_6), 126.0 (C_9), 128.5 (C_4), 150.9 (C_8), 172.1 (C_{10}). MS (APCI$^+$, m/z): 220.1 [$(M+H)^+$, 100]. HPLC: Chiralcel OJ-H column, hexane/propan-2-ol (90:10), 30 °C, and 0.8 mL/min flow.

4.4. Synthesis of compound 4 by chemical alkoxycarbonylation reaction

In a similar approach to the one previously described,[9o] to a solution of racemic aminoester **2** (30 mg, 0.17 mmol) and pyridine (14.5 μL, 0.18 mmol) in dry CH_2Cl_2 (1.13 mL) placed into an ice bath under a nitrogen atmosphere, allyl chloroformate (15.3 μL, 0.18 mmol) was added dropwise. The solution was allowed to warm to room temperature and the reaction mixture stirred for 6 h until no starting material was detected by TLC analysis (40% EtOAc/hexane). Then, the solvent was evaporated under reduced pressure, and the resulting residue was purified by flash chromatography (10–20% EtOAc/hexane), yielding carbamate **4** (91% isolated yield) as a yellow oil.

4.4.1. 3-Methyl 1-prop-2-en-1-yl 2,3-dihydro-1*H*-indole-1,3-dicarboxylate 4

R_f (40% EtOAc/hexane): 0.65; IR (NaCl): ν 3378, 2952, 2282, 1732, 1606, 1532, 1488, 1465, 1436, 1317, 1254, 1200, 1173, 1051, 751 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz): 3.79 (s, 3H, H_{11}), 4.14–4.24 (m, 2H, H_2), 4.50 (dd, 1H, J = 4.84, 4.84 Hz, H_3), 4.74 (br s, 2H, H_{14}), 5.34 (dd, 2H, J = 17.07, 10.25, H_{16}), 5.94–6.11 (m, 1H, H_{15}), 7.01 (t, 1H, J = 7.54, H_5), 7.27 (t, 1H, J = 7.54, H_6), 7.39 (d, 1H, J = 7.69 Hz, H_4), 7.91 (br s, 1H, H_7); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 44.8 (C_2), 49.4 (C_3), 52.6 (C_{11}), 65.9 (C_{14}), 114.9 (C_7), 122.7 (C_5), 125.0 (C_6), 127.4 (C_9), 129.0 (C_4), 132.3 (C_{15}), 142.2 (C_8), 152.2 (C_{12}), 171.6 (C_{10}). MS (APCI$^+$, m/z): 262.1 [$(M+H)^+$, 10]. HPLC: Chiralcel OD column, hexane/propan-2-ol (90:10), 20 °C, and 0.8 mL/min flow.

4.5. Synthesis of allyl indoline-3-carboxylate 5

Indoline-3-carboxylic acid **2** (50 mg, 0.6 mmol) was dissolved in allylic alcohol (12 mL) by gentle heating and magnetic stirring. After a solution was formed, it was placed in an ice-bath. Then $SOCl_2$ (61 μL, 0.8 mmol) was added dropwise and the corresponding mixture heated overnight (75 °C), until no starting material was detected on TLC (60% EtOAc/hexane). After that, the mixture was concentrated under reduced pressure, resuspended in water (10 mL), slightly alkalinized until pH 8.0 with an aqueous solution of NaOH 1 M, and extracted with CH_2Cl_2 (3 × 10 mL). The resulting esters were purified by column chromatography (20% EtOAc/hexane), to give **5** (42%) as a yellowish oil.

4.5.1. Allyl indoline-3-carboxylate 5

R_f (40% hexane/EtOAc): 0.55; IR (NaCl): ν 3378, 2952, 2282, 1732, 1606, 1532, 1488, 1465, 1436, 1317, 1254, 1200, 1173, 1051, 751 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz): 3.77 (t, 1H, J = 9.99, H_2), 3.98 (t, 1H, J = 8.43, H_3), 4.24 (t, 1H, J = 8.58 Hz, H_2), 4.69 (dd, 2H, J = 1.23, 1.26, H_{11}), 5.26–5.39 (m, 2H, H_{13}), 5.91–6.04 (m, 1H, H_{12}), 6.69 (d, 1H, J = 7.80, H_4), 6.77 (t, 1H, J = 7.49, H_6), 7.11 (t, 1H, J = 7.64 Hz, H_5), 7.34 (d, 1H, J = 7.48 Hz, H_7); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 47.1 (C_2), 49.1 (C_3), 65.7 (C_{11}), 110.0 (C_7), 118.4 (C_{13}), 118.8 (C_5), 125.1 (C_6), 125.8 (C_9), 128.7 (C_4), 131.9 (C_{12}), 151.0 (C_8), 171.8 (C_{10}). MS (APCI$^+$, m/z): 204.1 [$(M+H)^+$, 100]. HPLC: Chiralcel OD column, hexane/propan-2-ol (90:10 or 95:5), 20 °C, and 0.8 mL/min flow.

4.6. Typical procedure for the lipase-mediated transesterification or interesterification reactions of amino esters 3, 8a, 11 and 15

To a mixture of the corresponding substrate (0.10 mmol) and the lipase (1:1 in weight) was added the corresponding solvent (1 mL) under a nitrogen atmosphere. At this point, *n*-BuOH or $PrCO_2Bu$ (0.20 mmol) was added. The resulting suspension was shaken at the given temperature and 250 rpm in an orbital shaker, following the time course of the reactions by HPLC analysis (Chiralcel OJ-H column, hexane/propan-2-ol 90:10, 30 °C, and 0.8 mL/min flow for **3** and **8a**; Chiralcel OD column, hexane/propan-2-ol 90:10, 30 °C, and 0.8 mL/min flow for **11** and **15**). After the indicated time the reaction was stopped, and the enzyme filtered off and washed with 5 mL of CH_2Cl_2. The solvent was evaporated under reduced pressure and the reaction crude purified by *flash* chromatography on silica gel using different gradients of EtOAc/hexane as eluent (10% EtOAc/hexane for the indoline derivative and 30% EtOAc/hexane for the quinoline derivatives) to afford the desired amino esters, which were injected in the HPLC for measurement of their enantiomeric excesses. $[\alpha]_D^{20} = -94.7$ (c 0.88, CH_2Cl_2) for (*R*)-**3** in >99% ee, $[\alpha]_D^{20} = +78.3$ (c 0.60, CH_2Cl_2) for (*S*)-**6** in >99% ee; and $[\alpha]_D^{20} = -47.3$ (c 0.28, CH_2Cl_2) for (*R*)-**8a** in >99% ee (Scheme 5).

4.7. Enzymatic kinetic resolution of racemic compounds 3 and 11 by alkoxycabonylation reactions

To a suspension of the amino ester **3** or **11** (50 mg, 0.28 mmol) and the corresponding lipase (100 mg, 2:1 in weight relative to the starting material) in TBME or THF (1.9 mL) under a nitrogen atmosphere, the corresponding carbonate (allyl carbonate or 3-methoxyphenyl allyl carbonate, 0.70 mmol) was added. The mixture was shaken at 30 °C and 250 rpm and the reaction course followed by HPLC. At the desired time, the reaction mixture was filtered off and the filtrate was concentrated under reduced pressure. The reaction crude was purified by *flash* chromatography (eluent gradient 10–30% EtOAc/hexane).

4.8. Synthesis of methyl indoline-2-carboxylate 8a and butyl indoline-2-carboxylate 8b

To a solution of commercially available 2-indoline carboxylic acid **7** (100 mg, 0.61 mmol) in MeOH or *n*-BuOH (12.2 mL), was carefully added $SOCl_2$ (67.1 μL, 0.91 mmol) at 0 °C. The mixture was then heated at reflux (65 °C or 120 °C, respectively) for 5 h, after which none of the starting material could be detected by TLC (30% EtOAc/hexane). The reaction was concentrated on a rotary evaporator, resuspended in water, slightly alkalinized until pH 8.0 with an aqueous solution of NaOH 1 M, and extracted with CH_2Cl_2 (4 × 10 mL). The resulting esters were purified by column chromatography (10% EtOAc/hexane), to give **8a** (90%) and **8b** (97%) as colorless oils.

Spectroscopic data for **8a** are already described.[9o] HPLC: Chiralcel OJ-H column, hexane/propan-2-ol (90:10), 30 °C, and 0.8 mL/min flow.

4.8.1. Butyl indoline-2-carboxylate 8b

R_f (30% EtOAc/hexane): 0.57; IR (NaCl): ν 3373, 3055, 2961, 2934, 2874, 1733, 1610, 1531, 1486, 1467, 1396, 1308, 1244, 1198, 1076, 1019, 738 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz): 0.98 (t, 3H, J = 7.35 Hz, H_{14}), 1.36–1.48 (m, 2H, H_{13}), 1.63–1.72 (qt, 2H, H_{12}), 3.31–3.48 (m, 2H, H_3), 4.19 (t, 2H, J = 6.69 Hz, H_{11}) 4.34–4.43 overlap (m, 1H, H_2; br s, 1H, NH), 6.73–6.81 (m, 2H, H_5+H_7), 7.06–7.13 (m, 2H, H_4+H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 13.4 (C_{14}), 18.9 (C_{13}), 30.4 (C_{12}), 33.5 (C_3), 59.7 (C_2), 65.0 (C_{11}), 109.9 (C_7), 119.2 (C_5), 124.2 (C_6), 126.5 (C_9), 127.4 (C_4), 150.0 (C_8), 174.0 (C_{10}). MS

(ESI$^+$, m/z): 242.1 [(M+Na)$^+$, 100]. HPLC: Chiralcel OJ-H column, hexane/propan-2-ol (90:10), 30 °C, and 0.8 mL/min flow.

4.9. Typical procedure for the methyl esterification of the 2- and 3-quinaldic acid derivatives (synthesis of 10 and 14)

The corresponding quinoline derivative **9** or **13** (500 mg, 2.90 mmol) was dissolved in MeOH (57.8 mL) and the solution was cooled on an ice-bath. Then $SOCl_2$ (291.4 μL, 3.90 mmol) was carefully added and the mixture refluxed overnight until no more starting material was detected by TLC (30% EtOAc/hexane). At this point the reaction was left to cool to room temperature and the solvent evaporated under reduced pressure. The crude was resuspended in water and slightly alkalinized until pH 8.0 with an aqueous solution of NaOH 1 M and extracted with CH_2Cl_2 (3 × 15 mL). The crude was finally purified by column chromatography (30% EtOAc/hexane), to give amino esters **10** (432 mg, 80%), and **14** (446 mg, 83%) as white solids.

4.9.1. Methyl quinoline-2-carboxylate 10

R_f (30% EtOAc/hexane): 0.24; mp 87–89 °C; IR (KBr): ν 3054, 2954, 1725, 1463, 1320, 1266, 1212, 1138, 1108, 846, 779, 736 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz): 4.09 (s, 3H, CH_3), 7.65 (t, J = 7.1 Hz, 1H, H_{arom}), 7.79 (t, J = 8.5 Hz, 1H, H_7), 7.88 (d, J = 8.1 Hz, 1H, H_5), 8.20 (d, J = 8.56 Hz, 1H, H_2), 8.31 (d, J = 8.56 Hz, 2H, H_4+H_8); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 53.1 (C_{13}), 120.9 (C_3), 127.4 (C_5), 128.6 (C_6), 129.3 (C_{10}), 130.3 (C_8), 130.6 (C_7), 137.3 (C_4), 147.4 (C_9), 147.8 (C_2), 165.9 (C_{12}); MS (ESI$^+$, m/z): 187 (M$^+$, 90), 156 [(M−CH_4O)$^+$, 100%].

4.9.2. Methyl quinoline-3-carboxylate 14

R_f (30% EtOAc/hexane): 0.32; mp 87–89 °C; IR (KBr): ν 3054, 2954, 1725, 1463, 1320, 1266, 1212, 1138, 1108, 846, 779, 736 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz): 4.02 (s, 3H, H_{12}), 7.59–7.65 (m, 1H, H_7), 7.80–7.84 (m, 1H, H_6), 7.93 (t, J = 8.33, 1H, H_5), 8.16 (d, J = 8.33, 1H, H_8), 8.84 (d, J = 1.53, 1H, H_4), 9.45 (d, J = 1.97, 1H, H_2); ^{13}C ($CDCl_3$, 75.5 MHz): 53.4 (C_{12}), 122.9 (C_3), 126.7 (C_5), 127.4 (C_6), 129.0 (C_{10}), 129.4 (C_7), 131.8 (C_8), 138.7 (C_4), 149.1 (C_9), 149.9 (C_2), 165.7 (C_{11}); MS (ESI$^+$, m/z): 187 (M$^+$, 90), 156 [(M−CH_4O)$^+$, 100%].

4.10. Typical procedure for the hydrogenation of methyl quinoline carboxylates 10 and 14 (synthesis of 11 and 15)

To a solution of the corresponding quinoline ester **10** or **14** (250 mg, 1.30 mmol) in THF (4.7 mL) and MeOH (2.3 mL) under a nitrogen atmosphere, $NaBH_3CN$ (355 mg, 5.50 mmol) was added. Once the entire solid had dissolved, a small amount of bromocresol green (pH indicator) was added, and the solution acquired a bluish color (alkaline). Then, a 4 M HCl solution in dioxane was added dropwise onto the reaction mixture from time to time, till the mixture maintained a yellowish color (acid). After that, the beaker was put on an ice-bath and the proper volume of a saturated aqueous solution of $NaHCO_3$ was added to neutralize the medium. The mixture was extracted with EtOAc (3 × 10 mL) and the organic phases combined and concentrated under reduced pressure. The crude was purified by column chromatography (10–20% EtOAc/hexane), to give **11** (87%) and **15** (90%) both as yellowish oils.

4.10.1. Methyl-1,2,3,4-tetrahydroquinoline-2-carboxylate 11

R_f (30% EtOAc/hexane): 0.40; IR (NaCl): ν 3400, 3017, 2951, 2844, 1739, 1608, 1497, 1437, 1343, 1301, 1247, 1171, 1019, 749 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz): 1.98–2.10 (m, 1H, H_3), 2.27–2.36 (m, 1H, H_3), 2.73–2.92 (m, 2H, H_4), 3.81 (s, 3H, OCH_3), 4.07 (dd, J = 3.95, 3.73 Hz, 1H, H_2), 6.61–6.71 (m, 2H, H_6+H_8), 6.98–7.07 (m, 2H, H_5+H_7); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 24.5 (C_4), 25.6 (C_3), 52.2 (C_2), 53.8 (C_{12}), 114.4 (C_8), 117.5 (C_6), 120.4 (C_{10}), 126.9 (C_7), 129.0 (C_5), 142.8 (C_9), 173.6 (C_{11}). MS (APCI$^+$, m/z): 192.1 [(M+H)$^+$, 100]. HPLC: Chiralcel OD column, hexane/propan-2-ol (90:10), 30 °C, and 0.8 mL/min flow.

4.10.2. Methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate 15

R_f (30% EtOAc/hexane): 0.32; IR (NaCl): ν 3409, 3055, 2855, 1734, 1608, 1500, 1439, 1379, 1311, 1267, 1197, 1169, 1121, 1071, 738 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz): 2.94–3.00 (m, 1H, H_4), 3.03–3.06 (m, 2H, H_3+H_4), 3.39 (dd, 1H, J = 8.99, 8.99 Hz, H_2), 3.56–3.61 (m, 1H, H_2), 3.76 (br s, 4H, NH+H_{12}), 6.55 (d, 1H, J = 8.11 Hz, H_5), 6.68 (t, 1H, J = 6.0 Hz, H_6), 7.02 (t, 2H, H_7+H_8); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 24.5 (C_4), 25.6 (C_3), 52.2 (C_2), 53.8 (C_{12}), 114.4 (C_8), 117.5 (C_6), 120.4 (C_{10}), 126.9 (C_7), 129.0 (C_5), 142.8 (C_9), 173.6 (C_{11}). MS (APCI$^+$, m/z): 192.1 [(M+H)$^+$, 100]. HPLC: Chiralcel OD column, hexane/propan-2-ol (90:10), 30 °C, and 0.8 mL/min flow.

4.11. Typical procedure for the transesterification with *n*-butanol of 11 and 15 (synthesis of 12 and 16)

The corresponding quinoline methyl ester derivative **11** or **15** (30 mg, 0.16 mmol) was dissolved in BuOH (3.1 mL) and the solution was cooled on an ice-bath. Then $SOCl_2$ (15.7 μL, 0.22 mmol) was carefully added and the mixture refluxed overnight until no more starting material was found on TLC (30% EtOAc/hexane). At this point the reaction was left to cool to room temperature and the solvent evaporated under reduced pressure. The crude product was resuspended in water and slightly alkalinized until pH 8.0 with an aqueous solution of NaOH 1 M and extracted with CH_2Cl_2 (3 × 5 mL). The crude was finally purified by column chromatography (10–20% EtOAc/hexane), to give aminobutyl esters **12** (23 mg, 62%), and **16** (26 mg, 70%) as white semi-solids.

4.11.1. Butyl-1,2,3,4-tetrahydroquinoline-2-carboxylate 12

R_f (30% EtOAc/hexane): 0.56; IR (NaCl): ν 3414, 3054, 2963, 2874, 1735, 1608, 1587, 1491, 1390, 1343, 1299, 1211, 1139, 738 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz): 0.97 (t, 3H, J = 7.34 Hz, H_{15}), 1.35–1.48 (m, 2H, H_{14}), 1.63–1.72 (m, 2H, H_{13}), 2.27–2.37 (m, 1H, H_4), 2.73–2.92 (m, 1H, H_4), 4.03–4.06 (dd, 1H, J = 3.73, 3.73 Hz, H_2), 4.14–4.27 (m, 2H, H_{12}), 6.61–6.70 (m, 1H, H_6+H_8), 6.97–7.06 (m, 2H, H_5+H_7); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 13.6 (C_{15}), 19.0 (C_{14}), 24.7 (C_4), 25.8 (C_3), 30.5 (C_{13}), 53.9 (C_2), 65.0 (C_{12}), 114.5 (C_8), 117.5 (C_6), 120.5 (C_{10}), 126.9 (C_7), 129.0 (C_5), 142.9 (C_9), 173.2 (C_{11}). MS (APCI$^+$, m/z): 234.1 [(M+H)$^+$, 100]. HPLC: Chiralcel OD column, hexane/propan-2-ol (90:10), 30 °C, and 0.8 mL/min flow.

4.11.2. Butyl-1,2,3,4-tetrahydroquinoline-3-carboxylate 16

R_f (30% EtOAc/hexane): 0.54; IR (NaCl): ν 3407, 3055, 2961, 2873, 1728, 1608, 1587, 1500, 1467, 1375, 1310, 1267, 1186, 1120, 738 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz): 0.96 (t, 3H, J = 7.26 Hz, H_{15}), 1.34–1.46 (m, 2H, H_{14}), 1.60–1.69 (m, 2H, H_3), 2.93–2.99 (m, 1H, H_4), 3.04 (d, 2H, J = 7.26 Hz, H_3+H_4), 3.39 (t, 1H, J = 10.26 Hz, H_2), 3.59 (dd, 1H, J = 2.67, 3.63 Hz, H_2), 4.15 (t, 2H, J = 6.63 Hz, H_{12}), 6.58 (d, 1H, J = 8.37 Hz, H_8), 6.70 (t, 1H, J = 7.41 Hz, H_6), 7.02 (t, 2H, J = 7.11 Hz, H_7+H_5); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 13.6 (C_{15}), 19.0 (C_{14}), 29.5 (C_4), 30.6 (C_{13}), 38.3 (C_3), 43.5 (C_2), 64.5 (C_{12}), 114.6 (C_8), 117.9 (C_6), 120.0 (C_{10}), 127.0 (C_7), 129.5 (C_5), 143.1 (C_9), 173.6 (C_{11}). MS (ESI$^+$, m/z): 234.1 [(M+H)$^+$, 100]. HPLC: Chiralcel OD column, hexane:IPA (90:10), 30 °C, and 0.8 mL/min flow.

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