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Lipase-catalyzed kinetic resolution of 1,2,3,4-tetrahydroisoquinoline-1-acetic acid esters

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ABSTRACT

The enantiomers of 1,2,3,4-tetrahydroisoquinoline- and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetic acids were prepared via *Burkholderia cepacia* lipase (lipase PS-D)-catalyzed kinetic resolution of the corresponding ethyl and 2-methoxyethyl esters using enantioselective ($E > 200$) hydrolysis in DIPE. The (*S*)-acids were produced enzymatically, whereas the (*R*)-acids were obtained via the chemical hydrolysis of the unreacted (*R*)-esters. The solvent and its water content had major effects on both reactivity and enantioselectivity. The methoxyethyl moiety of the ester had a key role concerning the reactivity of the substrates.

1. Introduction

Interesting results obtained in the study of β-peptides during the last decade have given chemical and therapeutic importance to β-amino acids. Resembling α-peptides, β-peptides are self-organizing, capable of self-association, and some of them exert similar biological effects as antimicrobial α-peptides and cyclic α-peptide hormones.[1–3] In some cases, it is useful to replace an α-amino acid with a β-analogue in biologically active α-peptides in order to modulate their therapeutic effects by stabilizing secondary structures, such as γ-turn sequences.[4,5] 1,2,3,4-Tetrahydroisoquinoline-1-acetic acid is a sterically constrained analogue of β^3-phenylalanine. As β^3-phenylalanine itself, the title compounds are valuable building blocks, which can be used in the synthesis of melanocortin receptor agonists,[6] integrin inhibitors[7], or bradykinin-1 antagonists.[8] Driven by increasing needs for enantiopure β-amino acids, a large number of resolutions of racemic mixtures and enantioselective syntheses have been developed.[9,10] Methods for the preparation of enantiopure 1,2,3,4-tetrahydroisoquinoline-1-acetic acid derivatives are mostly based on metal complex catalysis, employing chiral ligands. These methods comprise the enantioselective hydrogenation of the corresponding 3,4-dihydroisoquinolines (with a chiral Ru complex)[11] and the addition of ketene silyl acetals[12] or vinyl ethers[13] to 3,4-dihydroisoquinoline N-oxide (catalyzed by Ti or Al complexes with chiral BINOL ligands, respectively). As previously reviewed, lipase catalysis offers effective, large-scale applicable and sustainable methods for the kinetic resolution of β-amino acid derivatives and precursors.[10,14] An enzymatic method for the resolution of cyclic β-amino acids has recently been developed, using CAL-B-catalyzed hydrolysis of the corresponding esters.[15]

In addition to being the sterically constrained analogue of β^3-phenylalanine, 1,2,3,4-tetrahydroisoquinoline-1-acetic acid is a benzene-fused (piperidin-2-yl)acetic acid (Fig. 1). In our previous work, we had demonstrated the lipase-catalyzed kinetic and dynamic kinetic resolution of various 2-piperidyl-based amino acid derivatives.[16–20] Herein, we report the lipase-catalyzed kinetic resolution of 1,2,3,4-tetrahydroisoquinoline-1-acetic acid esters (±)-**1**–(±)-**4** (Scheme 1). It should be mentioned that the N-acylation of (piperidin-2-yl)acetic acid derivatives is unsuccessful although the N-acylation of pipecolic acid methyl ester proceeds nicely with *Candida antarctica* lipase A (CAL-A).[16–18] On the other hand, the kinetic resolution of *N*-protected (piperidin-2-yl)acetic acid methyl ester with *Burkholderia cepacia* lipase (lipase PS) was reported to be successful through interesterification[18] and hydrolysis,[21] that is, through reactions directed to the ester function. Enantioselective hydrolysis of β^3-phenylalanine ethyl ester was also previously accomplished with lipase PS.[22] The kinetic resolution of the pres-

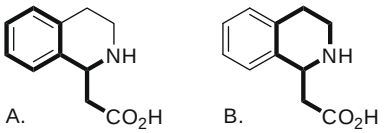

Figure 1. β^3-Phenylalanine (A) and piperidylacetic acid (B) skeletons of 1,2,3,4-tetrahydroisoquinoline-1-acetic acid.

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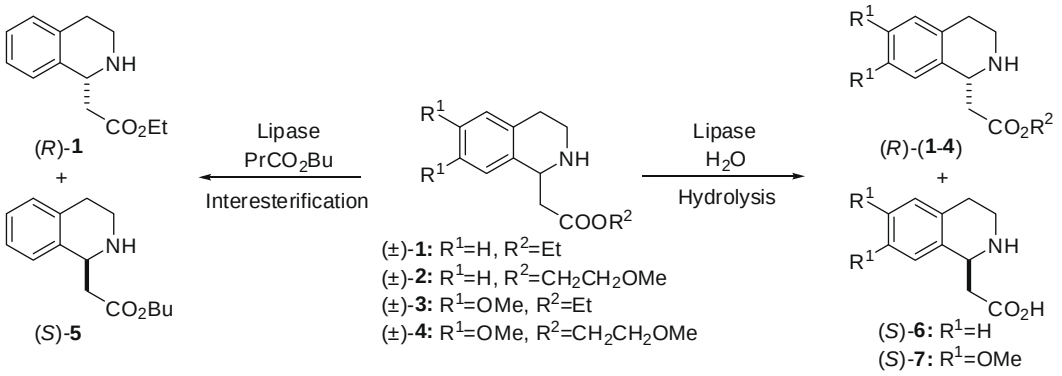

Scheme 1.

ent substrates (±)-**1**–(±)-**4** has been studied using lipase-catalyzed interesterification and hydrolysis reactions (Scheme 1).

2. Results and discussion

2.1. Preparation of racemic substrates

3,4-Dihydroisoquinolines were prepared using the Bischler–Napieralski cyclization of the corresponding *N*-phenethylformamides (formed in situ from 2-arylethylamine and formic acid).[23] The addition of ethyl hemimalonate to the 3,4-dihydroisoquinolines followed by decarboxylation furnished compounds (±)-**1** and (±)-**3**.[24] Alkyl-activated (±)-**2** and (±)-**4** were prepared from the corresponding ethyl esters (±)-**1** and (±)-**3** using acid-catalyzed transesterification with 2-methoxyethanol.

2.2. Lipase-catalyzed kinetic resolution

Lipase screening with CAL-A on Celite,[25] *Candida antarctica* lipase B (CAL-B as Novozym 435), lipase PS as lipase PS-C II (Amano preparation on Toyonite 200M) and lipase PS-D (Amano lipase PS on Celite) preparations were started using (±)-**1** as a model substrate for interesterification with butyl butanoate in *tert*-butylmethyl ether (TBME) and diisopropyl ether (DIPE) (Scheme 1). CAL-A did not catalyze the reaction, while CAL-B provided no enantioselectivity in the terms of enantiomer ratio ($E = 2$). With lipase PS preparations, relatively good initial enantioselectivities started to drop during the reaction, indicating that interesterification was not the only reaction taking place (Table 1). Competing alcoholyses (interesterification is basically an alcoholysis reaction with BuOH which competes with EtOH) can spoil an initially effective kinetic resolution, while also enzymatic hydrolysis of the butyl ester (*S*)-**5** may also have an effect on *E* values even if the proportion of hydrolysis is minimal. When *N*-Boc- and *N*-formyl-protected (±)-**1** were subjected under interesterification conditions in the mixture of DIPE/PrCOOBu [1:1 (v/v)], all the lipases used were inactive with no measurable conversion in 24 h.

Hydrolysis of (±)-**1** in aqueous buffer (at pH 8, in 0.1 M Tris–HCl, room temperature) was studied next. Unfortunately, very low enantioselectivity was detected in the presence of various lipases, lipase PS-D showing the highest enantioselectivity ($E = 7$). The previously reported enantioselective hydrolysis[22] of β^3-phenylalanine ethyl ester with lipase PS in DIPE encouraged us to turn our attention to the hydrolysis of (±)-**1** with 0.5–4 equiv of added H_2O in DIPE with lipase PS-D and lipase PS-C II preparations (Table 2). Reactivities with both preparations were generally low. However, there was a remarkable increase in reactivity (time needed to reach 50% conversion) with increasing water contents, the increase being more pronounced with lipase PS-D compared to lipase PS-C II. More importantly, enantioselectivity also increased, becoming excellent ($E > 200$) for lipase PS-D when 2 equiv or more H_2O was added. The highly enantioselective and economical lipase PS-D was selected for further studies.

Table 1
Lipase PS-D-catalyzed interesterification of (±)-**1** (0.05 M) in the mixture of solvent/$PrCO_2Bu$ [1:1 (v/v)] in the presence of lipase PS-D (75 mg mL^{-1}) at room temperature

Solvent	Time (h)	ee$^{(R)\text{-}1a}$ (%)	ee$^{(S)\text{-}5a}$ (%)	Conv.[a] (%)	'E'
TBME	12	32	96	25	67
	36	59	92	39	44
	60	81	87	48	36
DIPE	12	29	97	23	87
	36	69	92	43	50
	60	88	87	50	42

[a] Determined by GC.

Table 2
The effect of the added H_2O on the hydrolysis of (±)-**1** (0.05 M) with lipase PS preparations (50 mg mL^{-1}) in DIPE, at room temperature

Entry	Lipase	Added H_2O (equiv)	Time (h)	ee$^{(R)\text{-}1a}$ (%)	ee$^{(S)\text{-}6a}$ (%)	Conv. (%)	*E*
1	PS-CII	0.5	192	91	94	49	103
2		2	68	95	94	50	121
3		4	48	95	95	50	146
4	PS-D	0.5	504	96	95	50	154
5		2	96	95	97	49	>200
6		4	78	94	97	49	>200

[a] Determined by GC.

Compound (±)-**1** (0.05 M) was subjected to hydrolysis with 2–4 equiv of added H_2O in Et_2O, TBME, DIPE, toluene, and 2-methyl-THF (Table 3). DIPE with 4 equiv of added H_2O (corresponds to 0.2 M H_2O in DIPE, where DIPE is saturated with H_2O at 23 °C) proved to be the best solvent concerning both the reactivity and the enantioselectivity (Table 3, entry 6). The reactivity still stayed low. When the reaction was performed at elevated temperature (47 °C), the reactivity was enhanced while enantioselectivity was notably decreased (Table 3, entry 7). Another way to increase reactivity is to increase the electrophilic character of the carbonyl carbon in the ester substrate. Accordingly, 2-methoxyethyl ester (±)-**2** was prepared and subjected to hydrolysis under the reaction conditions described above (Table 4). Substantial reactivity enhancement was evident (Table 4, entry 2 vs entry 1) without a change in the excellent enantioselectivity. The same trend was observed when the enzymatic hydrolyses of (±)-**3** and (±)-**4** were per-

Table 3
Solvent and temperature effects on the hydrolysis of (±)-**1** (0.05 M) with lipase PS-D (50 mg mL^{-1})

Entry	Solvent	Added H_2O (equiv)	Time (days)	ee$^{(R)\text{-}\mathbf{1}c}$ (%)	ee$^{(S)\text{-}\mathbf{6}c}$ (%)	Conv. (%)	*E*
1	2-Methyl-THF[a]	4	21	82	94	47	83
2	Et_2O[a]	4	21	94	94	50	115
3	Et_2O[a]	Saturated	35	73	96	43	108
4	TBME[a]	Saturated	22	93	96	49	168
5	Toluene[a]	0.65	35	75	97	44	149
6	DIPE[a]	4	3	94	97	49	>200
7	DIPE[b]	4	1	92	93	50	91

[a] Reaction at room temperature.
[b] Reaction temperature 47 °C.
[c] Determined by GC.

Table 4
Hydrolysis of (±)-**1**–**4** (0.05 M) with lipase PS-D (50 mg mL^{-1}) in DIPE with 4 equiv of added H_2O at room temperature

Entry	Substrate	Time (h)	ee$^{(S)\text{-}\mathbf{1\text{–}4}}$ (%)	ee$^{(R)\text{-}\mathbf{6/7}}$ (%)	Conv. (%)	*E*
1	(±)-**1**	78	94[b]	97[b]	49	>200
2	(±)-**2**	16	97[b]	98[b]	50	>200
3	(±)-**2**[a]	37	98[b]	97[b]	50	>200
4	(±)-**3**	32	89[c]	98[c]	48	>200
5	(±)-**4**	18	97[c]	96[c]	50	>200

[a] 0.1 M substrate and 2 equiv of added H_2O in DIPE; lipase PS-D 25 mg mL^{-1}.
[b] Determined by GC.
[c] Determined by HPLC.

formed (Table 4, entries 4 and 5). Methoxy substitutions on the benzene ring clearly enhanced the reactivity of (±)-**3** compared to the unsubstituted case, (±)-**1**, whereas alkyl-activated (±)-**2** and (±)-**4** reacted in similar ways.

To this end, the preparative scale resolutions of (±)-**1**–(±)-**3** were performed, as shown in Section 4. In order to use more economical conditions, the resolutions were performed with 0.1 M substrate in DIPE with 2 equiv of added H_2O (corresponds to 0.2 M H_2O in DIPE) and with the lipase PS-D content of 25 mg mL^{-1}. Accordingly, we reduced the enzyme content at the expense of reactivity (Table 4, entry 2 vs entry 3). The gram-scale resolutions resulted in excellent yields (46–49% for the separated enantiomers, the theoretical yields in racemic mixtures being 50%) and high enantiopurities (ee 96–98%, Table 5). The absolute configurations of the enantiomers were assigned comparing the measured specific rotation data with the literature, which justifies that the lipase PS-catalyzed hydrolysis is (*S*)-selective in all cases. There is a discrepancy between the $[\alpha]_D^{25}$ value observed in the present work for (*R*)-**1** (Table 5, entry 1) and the literature value[11] {$[\alpha]_D^{25} = -12.5$ (*c* 0.2, $CHCl_3$; ee 99%)} for the (*S*)-enantiomer. In order to show that the kinetic resolution of (±)-**1** produced the unreacted ethyl ester as an (*R*)-enantiomer and that our compound was correct, the unreacted ethyl ester was transformed into the methyl ester (*R*)-**1a** by refluxing with methanolic HCl solution and by the successive release of (*R*)-**1a** with K_2CO_3 treatment. Indeed, the obtained $[\alpha]_D^{25} = +92$ (*c* 1.0, $CHCl_3$; ee > 99%) is in accordance with the literature value[26] $[\alpha]_D^{25} = +95$ (*c* 1.0, $CHCl_3$; ee 95%) for (*R*)-**1a**.

Table 5
Data for the prepared enantiomers

Sub-strate	(*R*)-**1**–(*R*)-**3**ee (%)/$[\alpha]_D^{25}$ (*c* 0.2, $CHCl_3$)	(*S*)-**6**ee (%)/$[\alpha]_D^{25}$ (*c* 0.25, H_2O)	(*S*)-**7**ee (%)/$[\alpha]_D^{25}$ (*c* 0.25, H_2O)
(±)-**1**	96/+81	>99/−46	–
(±)-**2**	97/+64	>99/−46	–
(±)-**3**	98/+52[a]	–	>99/+51

[a] *c* 1.0, $CHCl_3$.

3. Conclusions

The enantiomers of 1,2,3,4-tetrahydroisoquinoline- and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetic acids were prepared via *Burkholderia cepacia* lipase (lipase PS-D)-catalyzed kinetic resolution of the corresponding ethyl and 2-methoxyethyl esters using enantioselective hydrolysis in DIPE. The enzymatic hydrolysis in aqueous buffer was not enantioselective. Also N-acylation and interesterification were studied. The reactivity was remarkably improved when the alkyl part of the ester was changed from ethyl to 2-methoxyethyl, and when 2–4 equiv of water was added to the reaction mixture. The preparative scale kinetic resolutions provided the enantiomeric products in good yields (46–49% the theoretical yields of each enantiomer being 50%) and with high enantiopurities (96–98%).

4. Experimental

4.1. Materials and methods

Lipase PS (*Burkholderia cepacia* lipase) preparations (lipase PS-D and PS-C II) and CAL-A and CAL-B (lipase A and lipase B from *Candida antarctica*) were purchased from Amano Pharmaceuticals and Novo Nordisk, respectively. CAL-A was used after immobilization on Celite in the presence of sucrose as previously described, and the preparation contained 20% (w/w) of lipase.[25] Solvents were of highest analytical grade.

In a typical small-scale experiment, lipase was added to (±)-**1** (0.05 M) in organic solvent/$PrCO_2Bu$ [1:1 (v/v)] or in an organic solvent containing small amount (0.5–4 equiv) of added H_2O (1–2 mL). The reactions were performed at room temperature (23 °C) if not otherwise stated. The reactions were followed by taking samples from the reaction mixture at intervals and analyzing them. In the case of compounds (±)-**1** and (±)-**2**, GC analyses were performed on a CP Chirasil-DEX CB-coated chiral capillary column, containing permethylated β-cyclodextrin (manufactured by Varian). For the reactions of (±)-**3** and (±)-**4,** analyses were performed by HPLC using a Chiralcel OD-H chiral HPLC column (manufactured by Daicel).

Compounds **1** and the corresponding methyl esters **1a**, **2**, and **5** were analyzed by GC after derivatization with trifluoroacetic anhydride in the presence of *N*,*N*-dimethylaminopyridine (DMAP) in pyridine. Amino acid **6** was analyzed by GC after derivatization with diazomethane, followed by a second derivatization with trifluoroacetic anhydride in the presence of DMAP in pyridine. Compounds **3** and **4** were analyzed by HPLC, eluting with EtOH/*n*-hexane (contained 0.1% Et_2NH) [15:85 (v/v)]; 0.5 mL min^{-1} flow, 25 °C. Amino acid **7** was analyzed in a similar way after derivatization with diazomethane.

Optical rotations were measured with a Perkin–Elmer 341 polarimeter. ^{1}H NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer. The water concentrations of the solvents were determined using a coulometric Karl Fischer instrument. Melting points were determined on a Kofler apparatus.

4.2. Preparation of the racemic substrates

4.2.1. (±)-2-Methoxyethyl 1,2,3,4-tetrahydroisoquinoline-1-acetate (±)-2

Compound (±)-**1** (2.0 g, 9.12 mmol) was dissolved in 2-methoxyethanol (15 mL, 152.19 mmol), and sulfuric acid (1.0 mL) was added. The mixture was refluxed for 4 h before the solvent was evaporated. The residue was neutralized with ice-cold aqueous K_2CO_3, and the free amino ester extracted with Et_2O. The crude product was purified as (±)-**2**·**HCl** by crystallization from

2-methoxyethanol/Et_2O and subsequent treatment with ice-cold aqueous K_2CO_3, followed by extraction with Et_2O to give (±)-**2** as a light yellow oil (1.6 g, 6.48 mmol, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.44–2.27 (br s, 1H, N*H*), 2.72–2.98 (overlapping multiplets, 4H, CH_2–COO and C*H*$_2$–CH_2–NH), 3.00–3.10 (m, 1H, CH_2–C*H*H–NH), 3.17–3.28 (m, 1H, CH_2–C*H*H–NH), 3.41 (s, 3H, OCH_3), 3.55–3.68 (t, 2H, J = 4.7 Hz, CH_2–C*H*$_2$–OCH_3), 4.23–4.39 (m, 2H, C*H*$_2$–CH_2–OCH_3), 4.46–4.56 (dd, 1H, J = 9.8, 2.9 Hz, Ar-C*H*–NH), 7.06-7.23 (m, 4H, Ar).

4.2.2. (±)-2-Methoxyethyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetate (±)-4

Compound (±)-**4** was prepared by a method similar to (±)-**2**, and (±)-**4** (710 mg, 2.29 mmol, 32% yield) was isolated as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.67–2.15 (br s, 1H, N*H*), 2.59–2.93 (overlapping multiplets, 4H, CH_2–COO and C*H*$_2$–CH_2–NH), 2.94–3.07 (m, 1H, CH_2–C*H*H–NH), 3.09–3.13 (m, 1H, CH_2–C*H*H–NH), 3.37 (s, 3H, CH_2–CH_2–OC*H*$_3$), 3.53–3.67 (t, 2H, J = 4.7 Hz, CH_2–C*H*$_2$–OCH_3), 3.75 and 3.93 (s, 6H, *H*$_3$CO–Ar-OC*H*$_3$), 4.20-4.34 (m, 2H, C*H*$_2$–CH_2–OCH_3), 4.34-4.46 (dd, J = 9.6, 3.3 Hz, 1H, Ar-C*H*–NH), 6.51 (s, 2H, Ar).

4.3. Gram-scale kinetic resolutions

4.3.1. Kinetic resolution of (±)-1

Compound (±)-**1** (0.50 g, 2.28 mmol) was dissolved in DIPE (freshly distilled, 20 mL), and H_2O (73.8 μL, 4.1 mmol) and lipase PS-D (0.5 g) were added. The mixture was shaken at room temperature. The reaction was stopped by filtering off the enzyme and the DIPE insoluble (*S*)-**6** at 50% conversion after 17 days. The organic phase was dried on Na_2SO_4, and evaporated to yield (*R*)-**1** as a light yellow oil {238 mg, 1.09 mmol, 48% yield, ee 96%, $[\alpha]_D^{25} = +81$ (*c* 0.2 $CHCl_3$), for (*S*)-**1** lit.[11] $[\alpha]_D^{25} = -12.5$ (*c* 0.2 $CHCl_3$, ee 99%)}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.16–1.36 (t, 3H, J = 7.1 Hz, O–CH_2–C*H*$_3$), 1.95–2.17 (br s, 1H, N*H*), 2.67–2.93 (overlapping multiplets, 4H, CH_2–COO and C*H*$_2$–CH_2–NH), 2.96–3.09 (m, 1H, CH_2–C*H*H–NH), 3.13–3.27 (m, 1H, CH_2–C*H*H–NH), 4.09–4.27 (q, 2H, J = 7.1 Hz, O–C*H*$_2$–CH_3), 4.40–4.53 (dd, 1H, J = 9.7, 3.1 Hz, Ar-C*H*–NH), 7.01–7.22 (m, 4H, Ar).

Compound (*S*)-**6** was dissolved in water, filtered, and the water was evaporated under vacuum. After recrystallization from water, (*S*)-**6** was obtained as a white crystalline powder {204 mg, 1.07 mmol, 47% yield, mp 226–228 °C, ee ⩾ 99%, $[\alpha]_D^{25} = -46$ (*c* 0.25 H_2O)}. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 2.82–2.98 (m, 2H, CH_2–COO), 3.02–3.23 (m, 2H, C*H*$_2$–CH_2–NH), 3.35–3.49 (m, 1H, CH_2–C*H*H–NH) 3.53–3.68 (m, 1H, CH_2–C*H*H–NH), 4.77–4.83 (m, 1H, Ar-C*H*–NH), 7.20–7.41 (m, 4H, Ar).

4.3.2. Kinetic resolution of (±)-2

Compound (±)-**2** (1.0 g, 4.01 mmol) was dissolved in DIPE (freshly distilled, 40 mL), followed by the addition of H_2O (147.6 μL, 8.2 mmol) and lipase PS-D (1.0 g) as above. The reaction was stopped by filtering off the enzyme and the DIPE insoluble (*S*)-**6** at 50% conversion after 37 h. The work-up produced (*R*)-**2** as an orange oil {486 mg, 1.95 mmol, 49% yield, ee 97%, $[\alpha]_D^{25} = +64$ (*c* 0.2 $CHCl_3$)}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.78–2.09 (br s, 1H, N*H*), 2.70–2.96 (overlapping multiplets, 4H, CH_2–COO and C*H*$_2$–CH_2–NH), 2.97-3.08 (m, 1H, CH_2–C*H*H–NH), 3.13–3.26 (m, 1H, CH_2–C*H*H–NH), 3.38 (s, 3H, OCH_3), 3.52–3.67 (t, 2H, J = 4.7 Hz, CH_2–C*H*$_2$–OCH_3), 4.20–4.35 (m, 2H, C*H*$_2$–CH_2–OCH_3), 4.42–4.52 (dd, 1H, J = 9.8, 2.9 Hz, Ar-C*H*–NH), 7.01–7.18 (m, 4H, Ar).

Compound (*S*)-**6** was dissolved in water, filtered, and the water was evaporated under vacuum. After recrystallization from water, (*S*)-**6** was obtained as a white crystalline powder {357.6 mg, 1.87 mmol, 47% yield, mp 226–228 °C, ee ⩾ 99%, $[\alpha]_D^{25} = -46$ (*c* 0.25 H_2O}.

4.3.3. Kinetic resolution of (±)-3

(±)-**3** (1.0 g, 3.58 mmol) was dissolved in DIPE (freshly distilled, 35.8 mL), followed by the addition of H_2O (128.9 μL, 7.16 mmol) and lipase PS-D (895 mg) as above. The reaction was stopped by filtering off the enzyme and the DIPE insoluble (*S*)-**7** at 50% conversion after 160 h. The work-up produced (*R*)-**3**, which readily crystallized as a light yellow crystalline mass {483 mg, 1.73 mmol, 48% yield, mp 85–88 °C (described previously as an oil[11,12]), ee 98%, $[\alpha]_D^{25} = +52$ (*c* 1.0 $CHCl_3$) and $[\alpha]_D^{25} = +46.5$ (*c* 1.22 EtOH); for (*S*)-**3** lit.[13] $[\alpha]_D^{25} = -10.2$ (*c* 1.0 $CHCl_3$, ee 58%) lit.[12] $[\alpha]_D^{25} = -30.5$ (*c* 1.22 EtOH, ee 99%)}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.23–1.37 (t, 3H, J = 7.1 Hz, O–CH_2–C*H*$_3$), 1.67–2.03 (br s, 1H, N*H*), 2.66–2.88 (overlapping multiplets, 4H, CH_2–COO and C*H*$_2$–CH_2–NH), 2.98–3.09 (m, 1H, CH_2–C*H*H–NH), 3.16–3.27 (m, 1H, CH_2–C*H*H–NH), 3.79–3.97 (br s, 6H, C*H*$_3$O–Ar-OC*H*$_3$) 4.24–4.38 (q, 2H, J = 7.1 Hz, O–C*H*$_2$–CH_3), 4.37–4.48 (dd, 1H, J = 9.5, 3.5 Hz, Ar-C*H*–NH), 6.61 (s, 2H, Ar).

(*S*)-**7** was washed with water from the solid residue, and the water was evaporated under vacuum. After recrystallization from water, (*S*)-**7** was obtained as a white crystalline powder {413 mg, 1.64 mmol, 46% yield, mp 225–227 °C, ee ⩾ 99%, $[\alpha]_D^{25} = -53.5$ (*c* 0.25 H_2O}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.37–2.47 (dd, 1H, J = 16.3, J = 10.4, C*H*H–COO), 2.53–2.62 (dd, 1H, J = 16.3, J = 4.1, C*H*H–COO), 2.65–2.83 (m, 2H, C*H*$_2$–CH_2–NH), 3.03–3.23 (m, 2H, CH_2–C*H*$_2$–NH), 3.61 and 3.82 (s, 6H, C*H*$_3$O–Ar-OC*H*$_3$), 4.21-4.34 (dd, 1H, J = 10.3, 3.9 Hz, Ar-C*H*–NH), 6.68 (s, 1H, Ar), 6.80 (s, 1H, Ar).

4.3.4. Transformation of (*R*)-1 into the methyl ester (*R*)-1a

Compound (*R*)-**1** (290 mg, 1.16 mmol) was dissolved in methanol (15 mL), after which HCl in methanol (20 g HCl/100 mL methanol, 0.48 mL) was added. The solution was refluxed for 4 h before evaporation. (*R*)-**1a**·**HCl** was recrystallized from methanol/Et_2O, and the colorless crystals were treated with aqueous K_2CO_3 under cooling. Extraction with Et_2O followed by evaporation of the solvent produced (±)-**1a** as an almost colorless oil {138 mg, 0.67 mmol, 58% yield, ee ⩾ 99%, $[\alpha]_D^{25} = +92.0$ (*c* 1.0 $CHCl_3$), lit.[26] $[\alpha]_D^{25} = +95$ (*c* 1.0 $CHCl_3$, ee 95%)]. (*R*)-**1a**·**HCl** ^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.12–3.36 (overlapping multiplets, 4H, CH_2–COO and C*H*$_2$–CH_2–NH), 3.40–3.56 (m, 1H, CH_2–C*H*H–NH), 3.57–3.79 (m, 1H, CH_2–C*H*H–NH), 3.70–3.86 (br s, 3H, O–CH_3), 4.94–5.12 (m, 1H, Ar-C*H*–NH), 7.18–7.47 (m, 4H, Ar).

4.3.5. (*R*)-1,2,3,4-Tetrahydroisoquinoline-1-acetic acid, (*R*)-6

Compound (*R*)-**1** (250 mg, 1.00 mmol) was mixed with H_2O (10 mL), and the mixture was refluxed for 4 h. The water was evaporated off, the crystalline residue was washed with acetone, and recrystallized from water/acetone. (*R*)-**6** {120 mg, 0.63 mmol, 63% yield, mp 226–228 °C, ee ⩾ 99%, $[\alpha]_D^{25} = +46.0$ (*c* 0.25 H_2O)} was obtained as colorless crystals. ^{1}H NMR spectrum similar to (*S*)-**6**.

4.3.6. (*R*)-6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetic acid, (*R*)-7

Compound (*R*)-**3** (200 mg, 0.72 mmol) was mixed with H_2O (10 mL), and the mixture was refluxed for 4 h. The work-up produced (*R*)-**7** as colorless crystals {107 mg, 0.43 mmol, 60% yield, mp 224–226 °C, ee ⩾ 99%, $[\alpha]_D^{25} = +51$ (*c* 0.25 H_2O)}. ^{1}H NMR spectrum similar to (*S*)-**7**.

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