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Burkholderia cepacia lipase is an excellent enzyme for the enantioselective hydrolysis of β-heteroaryl-β-amino esters

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ABSTRACT

The enantioselective (E >200) lipase PS-catalysed hydrolysis of β-heteroaryl-β-amino esters is described. The reactions were performed with H_2O (0.5 equiv) in either diisopropyl ether or *tert*-butyl methyl ether at 25 °C. The resulting β-heteroaryl-substituted β-amino acid enantiomers were formed in high enantiomeric excess (ee ⩾ 97%) and in good yield (⩾40%).

1. Introduction

In view of their successful applications in peptidomimetics and as valuable building blocks, β-amino acids are currently a focus of pharmaceutical research.[1] β-Heteroaryl-substituted β-amino acids have wide-ranging potential applications as indicated by the following examples. A substituted (*R*)-3-amino-3-(2-pyridyl)propionic acid **6f** moiety has been identified as the β-amino acid component of kedarcidin, a potent antitumour antibiotic.[2] Additionally, the synthetic L-azatyrosine analogue methyl (*R*)-3-amino-3-(5-hydroxy-2-pyridyl)propanoate is an important compound in anticancer research.[3] Several promising antithrombotic fibrinogen receptor antagonists contain a β-heteroaryl-β-amino acid unit. A valuable member of this family is elarofiban (RWJ-53308), which contains (*S*)-3-amino-3-(3-pyridyl)propionic acid **7a**.[4] Elarofiban has progressed successfully through human phase II clinical trials involving oral or intravenous administration.[4d] Compound **7a** has also been used in the synthesis of a peptidomimetic $\alpha_v\beta_3$-receptor antagonist which could be a valuable agent in the treatment of osteoporosis.[5] (*R*)-3-Amino-3-(3-pyridyl)propionic acid **6a** has been tested as a component of an inhibitor of hepatitis C virus (HCV) NS5B polymerase, a valid target for antiviral therapy against HCV.[6] Acylated (*R*)-3-amino-3-(4-methoxy-3-pyridyl)propionic acid has been described as a potent, specific and orally bioavailable antagonist of VLA-4.[7] Therapeutic targets for this receptor include asthma, rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease. Moreover, several heteroaromatic taxanes have been prepared and display good to excellent activity in a microtubule assembly assay in comparison with paclitaxel.[8]

The development of new enantioselective approaches for the preparation of heteroaryl-substituted β-amino acid enantiomers is of high priority, even if numerous asymmetric strategies have been described, for example, (i) asymmetric Mannich reactions;[9] (ii) stereoselective reductions of an enamine;[10] (iii) preparation of a diastereomeric salt with (1*R*,2*S*)-ephedrine or quinine;[11] (iv) enolate additions to a chiral imine;[12] (v) addition of a Reformatsky reagent to a chiral imine;[13] (vi) Michael addition to an α,β-unsaturated ester;[14] or (vii) ozonolysis of a chiral N-acylated allylamine.[15]

In addition to the asymmetric methods,[9–15] a number of enzymatic studies have been reported for the preparation of β-aryl- and β-heteroaryl-β-amino acid enantiomers. As an example, we initially performed the indirect enantioselective resolution of acyclic β-lactams through the acylation of *N*-hydroxymethyl-β-lactams and hydrolysis of the corresponding *N*-hydroxymethyl esters,[16] followed by ring opening of the enantiomeric lactams with aqueous HCl. Next, we devised a direct enzymatic method for the enantioselective ring cleavage of β-lactams.[17a] Later, we extended the method to 4-aryl- and 4-arylalkyl-substituted β-lactams.[17b,c] Recently, on the basis of a newly patented direct enzymatic method,[18] we reported the synthesis of carbocyclic *cis*- and *trans*-β-amino acid enantiomers through enantioselective hydrolysis of β-amino esters in organic media, enantioselective hydrolysis of β-aryl-substituted β-amino esters resulting in biologically valuable enantiomers has also been achieved.[19] Some other methods relate to (i) hydrolysis of N-acylated β-amino esters,[4a,20] (ii) N-acylation of β-amino esters,[21] (iii) hydrolysis of β-amino esters in an aqueous medium[22] or (iv) β-aminotransferase-catalysed amination of β-keto esters.[23]

Herein, we turned our attention to β-heteroaryl-substituted β-amino esters and planned to carry out the lipase-catalysed hydrolysis of the pharmaceutically important substrates **3a**–**g**.

2. Results and discussion

2.1. Syntheses of ethyl 3-amino-3-heteroaryl-propanoates 3a–g

Racemic compounds **2a**–**e** were synthesized by a modified Rodionov synthesis[19] through the reactions of **1a**–**e** with malonic

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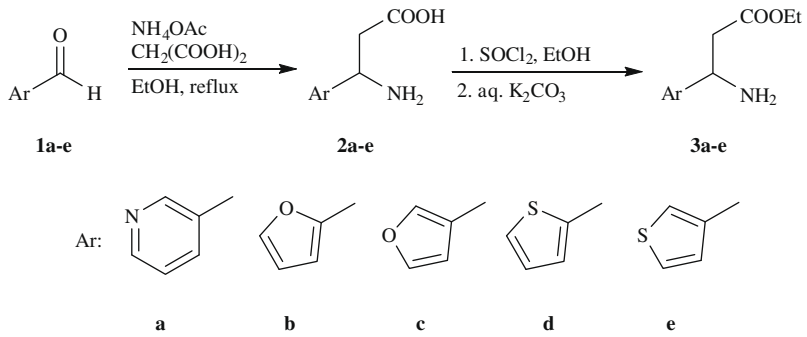


Scheme 1. Synthesis of **3a–e**.

acid in the presence of NH_4OAc in EtOH at reflux (Scheme 1). Compounds **3a–e**·HCl were prepared by the esterification of **2a–e** in the presence of $SOCl_2$ in EtOH. The free bases **3a–e** were liberated by treatment of **3a–e**·HCl with aqueous K_2CO_3 (Scheme 1).

Racemic **3f** and **3g** were prepared by the decarboxylative Blaise reaction[24] of **1f** and **1g** following $Pd(OH)_2$-catalysed reduction of enamines **2f** and **2g** (Scheme 2).

2.2. Lipase-catalysed enantioselective hydrolysis of 3a–g

The preliminary experiments were started with enzyme screening, using **3a** as the model compound (Scheme 3). Among the lipases tested (Table 1), Chyrazyme L-5 (lipase A from *Candida antarctica*) and Lipolase (lipase B from *C. antarctica*) did not exhibit any selectivity towards **3a** at 45 °C in *i*-Pr_2O with 0.5 equiv of H_2O, while PPL (porcine pancreas lipase) and lipase AK (*Pseudomonas fluorescens*) catalysed the reaction with moderate enantioselectivity ($E \leqslant 6$) (entries 1 and 2). As lipase PS (*Burkholderia cepacia*) afforded high enantioselectivity ($E = 99$) (entry 3), we chose this lipase for further investigation.

When we decreased the temperature, the enantioselectivity increased to an excellent value ($E > 200$) (Table 1, entries 4 and 5). Moreover, as the reaction did not slow down at 25 °C (entry 4) when compared with 45 °C (entry 3), we continued further experiments at 25 °C.

Next, we analysed the effects of solvents (Table 2). The reaction rates were highest in *i*-Pr_2O, *t*-BuOMe and *n*-hexane (entries 1, 2 and 3) and lowest in Me_2CO (entry 9). The enantioselectivities were high ($E > 100$) in all cases except in *tert*-amyl alcohol (entry 5). On the basis of our previous results,[25] we developed a fully green method for the resolution of **3a** in a solvent-free system: we achieved high enantioselectivity ($E = 116$), but a low reaction rate (entry 10), when the reaction was performed with 0.5 equiv of H_2O using 30 mg mL^{-1} of lipase PS at 25 °C. Further experiments were carried out in *i*-Pr_2O.

Table 1
Conversion and enantioselectivity of the hydrolysis of **3a**[a]

Entry	Enzyme[c]	*T* (°C)	*t* (h)	Conv. (%)	ee_s[b] (%)	ee_p[b] (%)	*E*
1	PPL	45	17	37	43	74	10
2	Lipase AK	45	17	90	70	8	2
3	Lipase PS	45	17	52	>99	90	99
4	Lipase PS	25	17	50	>99	98	>200
5	Lipase PS	3	72	50	>99	98	>200

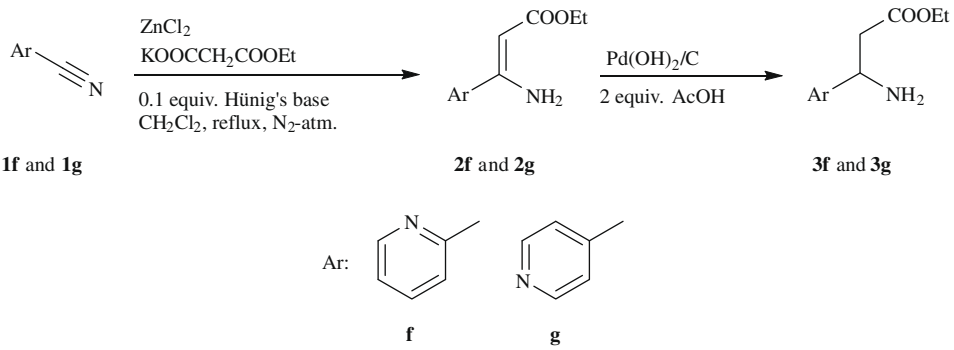
[a] 0.05 M substrate, 1 mL *i*-Pr_2O, 30 mg mL^{-1} enzyme, 0.5 equiv of H_2O.
[b] According to HPLC (Section 4).
[c] Contains 20% (w/w) lipase adsorbed on Celite in the presence of sucrose.

When we increased the amount of added water (1–5 equiv), the enantioselectivities decreased, while the reaction rates slightly increased (Table 3). We observed that the enantioselectivities were low ($E \leqslant 3$) in a 1/1 (v/v) mixture of H_2O and *i*-Pr_2O, and also in neat H_2O. In a small-scale experiment, we could perform the

Table 2
Effects of solvents on the hydrolysis of **3a**[a]

Entry	Solvent (1 mL)	Conv. (%)	ee_s[b] (%)	ee_p[b] (%)	*E*
1	*i*-Pr_2O	48	>99	98	>200
2	*t*-BuOMe	50	>99	98	>200
3	*n*-hexane	52	>99	92	126
4	Toluene	40	66	98	197
5	*t*-amyl alcohol	31	38	83	16
6	THF	17	20	98	120
7	1,4-dioxane	13	14	98	114
8	$CHCl_3$	6	6	98	105
9	Me_2CO	2	2	98	101
10	—[c]	14	16	98	116

[a] 0.05 M substrate, 30 mg mL^{-1} lipase PS, 0.5 equiv of H_2O at 25 °C after 18 h.
[b] According to HPLC (Section 4).
[c] Without solvent.



Scheme 2. Syntheses of **3f** and **3g**.

Table 3
Effect of added water on the hydrolysis of **3a**[a]

Entry	H_2O (equiv)	Conv. (%)	ee_s[b] (%)	ee_p[b] (%)	*E*
1	0	46	80	98	>200
2	0.5	48	90	98	>200
3	1	53	94	83	38
4	5	55	>99	81	49

[a] 0.05 M substrate, 1 mL *i*-Pr_2O, 30 mg mL^{-1} lipase PS at 25 °C after 7 h.
[b] According to HPLC (Section 4).

hydrolysis without the addition of any added H_2O with excellent enantioselectivity (entry 1). As a conclusion, H_2O in the reaction medium (<0.1%) or at the surface of the enzyme preparation (<5% w/w H_2O) was responsible for the hydrolysis of **3a**.

When more enzyme was added to the reaction mixture, higher reaction rates were observed (Table 4). 75 mg mL^{-1} of lipase PS resulted in the highest rates with excellent enantioselectivity (entry 6). For economic reasons, preparative-scale resolutions were performed with 30 mg mL^{-1} of enzyme.

Table 4
Effect of the quantity of lipase PS on the hydrolysis of **3a**[a]

Entry	Lipase PS[c] (mg mL^{-1})	Conv. (%)	ee_s[b] (%)	ee_p[b] (%)	*E*
1	10	16 (49% after 22 h)	18	98	118
2	20	24	31	98	134
3	30	32	47	98	158
4	40	37	58	98	179
5	50	42	72	98	>200
6	75	49	93	98	>200

[a] 0.05 M substrate, 1 mL *i*-Pr_2O, 0.5 equiv of H_2O at 25 °C after 3 h.
[b] According to HPLC (Section 4).
[c] Contains 20% (w/w) lipase adsorbed on Celite in the presence of sucrose.

Racemic compounds **3b–g** were also hydrolysed with excellent enantioselectivities (*E* >200) under the optimum conditions, that is, with 0.5 equiv of H_2O in the presence of 30 mg mL^{-1} lipase PS in *i*-Pr_2O at 25 °C. The preparative-scale resolutions of **3a–g** were performed. The products were characterized by good enantiomeric excess (ee ⩾ 97%) at close to 50% conversion. The results are reported in Table 5 and in Section 4.

2.3. Transformations of the enantiomers

The transformations involving the hydrolysis of **4a–g** with aqueous HCl afforded **6a–g** (ee ⩾ 97%) (Scheme 4). Treatment of **5a–g** with 22% HCl/EtOH resulted in the corresponding enantiopure **7a–g** (ee ⩾ 98%).

2.4. Absolute configurations

The absolute configurations and selectivities were proven by comparing the specific rotation values with the literature data (Section 4). The absolute configurations of **3f** and **3g** were given on the basis of comparative specific rotations (**5a–g** negative, **6a–g** positive), assuming the same selectivity of lipase PS towards **3a–g**. Thus, the absolute configurations indicated the (*S*)-selective hydrolysis of **3a–g**.

3. Conclusions

An efficient, direct enzymatic hydrolysis of the desired pharmacologically valuable β-heteroaryl-substituted β-amino acid enantiomers has been devised. The lipase PS-catalysed (*S*)-selective hydrolysis of **3a–g** with H_2O (0.5 equiv) as a nucleophile in *i*-Pr_2O or in *t*-BuOMe at 25 °C (*E* >200) resulted in the enantiomers of **4a–g** (ee ⩾ 97%) and **5a–g** (ee ⩾ 98%) in good yields (⩾40%). The products could be easily separated. Ester enantiomers **4a–g** were readily hydrolysed with 18% aqueous HCl, resulting in acids **6a–g** (ee ⩾ 97%).

4. Experimental

4.1. Materials and methods

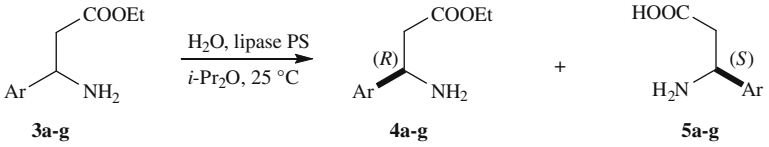
Lipase PS and lipase AK were from Amano Pharmaceuticals, Lipolase (lipase B from *C. antarctica*, produced by submerged fermentation of a genetically modified *Aspergillus oryzae* microorganism and adsorbed on a macroporous resin) and PPL (type II) were from Sigma, and Chyrazyme L-5 was from Novo Nordisk. Before use, lipase PS, lipase AK, CAL-A and PPL (5 g) were dissolved in Tris–HCl buffer (0.02 M; pH 7.8) in the presence of sucrose (3 g), followed by adsorption on Celite (17 g) (Sigma). Heteroaromatic aldehydes were from Aldrich. 2-Cyanopyridine and 4-cyanopyridine were from Fluka. Diethylamine (DEA), triethylamine (TEA) and glacial acetic acid (AcOH) were from Aldrich. Triethylammonium acetate buffer (TEAA) was prepared by adding AcOH to a 0.1% aqueous solution of TEA to give pH 4.1. The solvents were of the highest analytical grade.

Optical rotations were measured with a Perkin–Elmer 341 polarimeter. ^1H NMR and ^{13}C NMR spectra were recorded on a

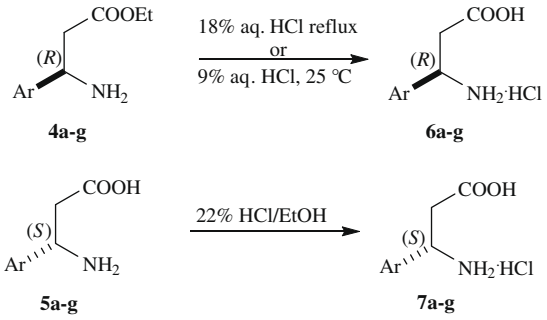
Table 5
Lipase PS-catalysed hydrolysis of **3a-g**[a]

	Time (h)	Conv. (%)	*E*	β-Amino acid·HCl (**6a–g**)				β-Amino acid (**5a–g**)			
				Yield (%)	Isomer	ee (%)	$[\alpha]_D^{25}$ (H_2O)	Yield (%)	Isomer	ee (%)	$[\alpha]_D^{25}$ (H_2O)
3a	40	50	>200	40	(*R*)	>99[b]	+4.1[d]	46	(*S*)	>99[b]	−5.1[e]
3b	60	49	>200	44	(*R*)	97[b]	+5.4[f]	46	(*S*)	>99[b]	−5.8[g]
3c	47	50	>200	49	(*R*)	>99[c]	+5.3[h]	44	(*S*)	>99[c]	−6.7[i]
3d	60	50	>200	46	(*R*)	>99[b]	+4.1[d]	44	(*S*)	>99[b]	−3.1[d]
3e	42	50	>200	46	(*R*)	>99[c]	+4.0[i]	43	(*S*)	>99[c]	−3.2[f]
3f	67	50	>200	45	(*R*)	98[b]	+9.7[f]	42	(*S*)	>99[b]	−18.2[f]
3g	24	50	>200	43	(*R*)	97[b]	+3.2[j]	45	(*S*)	98[b]	−11.7[j]

[a] 30 mg mL^{-1} lipase PS in *i*-Pr_2O, 0.5 equiv of H_2O at 25 °C.
[b] According to HPLC.
[c] According to GC.
[d] *c* 0.33.
[e] *c* 0.41.
[f] *c* 0.32.
[g] *c* 0.52.
[h] *c* 0.42.
[i] *c* 0.34.
[j] *c* 0.36.



Scheme 3. Lipase PS-catalysed enantioselective hydrolysis of **3a–g** (for the meanings of letters **a–g**, see Schemes 1 and 2).



Scheme 4. Transformation of **4a–g** to **6a–g** and **5a–g** to **7a–g** (for the meanings of letters **a–g**, see Schemes 1 and 2).

Bruker Avance DRX 400 spectrometer. Melting points were determined on a Kofler apparatus. Elemental analyses (CHNS) corresponded closely (within ±3%) with the calculated ones in all cases.

In a typical small-scale enzyme test, racemic **3a** (0.05 M solution) in an organic solvent or in a 1/1 (v/v) mixture of *i*-Pr_2O and H_2O or in neat H_2O (1 mL) was added to the enzyme tested (10, 20, 30, 40, 50 or 75 mg mL^{-1}), followed by H_2O (0, 0.5, 1 or 5 equiv). The mixture was shaken at 3, 25 or 45 °C.

The ee values for the unreacted β-amino ester and the β-amino acid enantiomers produced were determined by HPLC or GC as follows:

Compounds **4a**, **4b**, **4d** and **5a**, **5b**, **5d**: HPLC [**4a**, **4b**, **4d** were pre-column hydrolysed with aq HCl to **6a**, **6b**, **6d**]; Chirobiotic TAG column (4.6 mm × 250 mm); eluent: MeOH/AcOH/TEA (100/0.1/0.1); flow rate: 0.8 mL min^{-1} for **5a**, **5b**, 0.3 mL min^{-1} for **5d**; detection at 205 nm; retention times (min) for **5a**: 33.70, **6a**: 26.95; **5b**: 12.98, **6b**: 14.25; **5d**: 39.62, **6d**: 36.86.

Compounds **4c**, **4e** and **5c**, **5e**: GC [**5c**, **5e** were pre-column derivatized[26] with (i) CH_2N_2 (**Caution!** derivatization with CH_2N_2 should be performed under a well-working hood) and (ii) **5c** with $(PrCO)_2O$, **5e** with $(EtCO)_2O$ in the presence of 4-dimethylaminopyridine; **4c** with $(PrCO)_2O$; and **4e** with $(EtCO)_2O$]; Chirasil-L-Val column (20 m), 130 °C for **4c** and **5c**, 140 °C for **4e** and **5e**; column flow: 0.7 mL min^{-1}; retention times (min) for **4c**: 43.78 (antipode: 44.58); **5c**: 33.98 (antipode: 32.09); **4e**: 43.13 (antipode: 44.55); **5e**: 34.44 (antipode: 33.20).

Compounds **4f** and **5f**: HPLC, [**5f** was pre-column derivatized[26] with CH_2N_2, and **4f** was pre-column hydrolysed with aq HCl to **6f**, then derivatized with CH_2N_2]; Chiralpak IA column (4.6 mm × 250 mm); eluent: *n*-hexane (0.1% DEA)/EtOH (80/20); flow rate: 0.5 mL min^{-1}; detection at 250 nm; retention times (min) for **5f**: 30.11, **6f**: 25.88.

Compounds **4g** and **5g**: HPLC [**4g** was pre-column hydrolysed with aq HCl to **6g**]; Chirobiotic TAG column (4.6 mm × 250 mm); eluent: TEAA/MeOH (20/80); flow rate: 0.15 mL min^{-1}; detection at 250 nm; retention times (min) for **5g**: 67.80, **6g**: 70.85.

4.2. General procedure for the synthesis of racemic β-amino acids 2a–e

The synthesis was based on a modified Rodionov synthesis.[19] To a solution of the corresponding **1a–e** (5 mmol) in EtOH (40 mL) were added malonic acid (1 equiv) and NH_4OAc (2 equiv). The mixture was refluxed for 6 h. The resulting precipitated crystals were filtered off, washed with Me_2CO and recrystallized.

4.2.1. (±)-3-Amino-3-(3-pyridyl)propanoic acid 2a

Yield: 0.39 g (44%), white crystals; mp 225–228 °C (recrystallized from H_2O/Me_2CO) lit.[27] mp 224–228 °C. The ^1H NMR data are in accordance with those reported in the literature.[27] ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 40.5, 51.2, 125.7, 133.5, 137.4, 148.0, 149.9, 177.3.

4.2.2. (±)-3-Amino-3-(2-furyl)propanoic acid 2b

Yield: 0.34 g (44%), brown crystals; mp 222–225 °C (decomp.) (recrystallized from H_2O/Me_2CO) lit.[17] mp 219–221 °C). The ^1H NMR data are in accordance with those reported in the literature.[17] ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 38.1, 46.6, 109.7, 111.3, 144.6, 149.3, 177.4.

4.2.3. (±)-3-Amino-3-(3-furyl)propanoic acid 2c

Yield: 0.18 g (23%), dark-brown crystals; mp 232–235 °C (decomp.) (recrystallized from H_2O/Me_2CO) lit.[21] mp >250 °C. The ^1H NMR data are in accordance with those reported in the literature.[21] ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 39.5, 45.0, 108.2, 121.4, 141.2, 144.7, 177.5.

4.2.4. (±)-3-Amino-3-(2-thienyl)propanoic acid 2d

Yield: 0.36 g (42%), white crystals; mp 225–228 °C (recrystallized from H_2O/Me_2CO) lit.[21] mp 225–228 °C. The ^1H NMR data are in accordance with those reported in the literature.[21] ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 41.6, 48.9, 108.2, 127.9, 128.3, 128.4, 177.6.

4.2.5. (±)-3-Amino-3-(3-thienyl)propanoic acid 2e

Yield: 0.35 g (41%), pale-brown crystals; mp 237–239 °C (recrystallized from H_2O/Me_2CO) lit.[21] mp 239–242 °C. The ^1H NMR data are in accordance with those reported in the literature.[21] ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 40.6, 48.8, 124.7, 126.3, 128.2, 136.9, 177.3.

4.3. General procedure for the syntheses of racemic β-amino esters 3a–e

To 40 mL of EtOH were added dropwise 0.47 mL (1.3 equiv) of $SOCl_2$, with the temperature being kept under −10 °C with saline ice. To this solution, **2a–e** (5 mmol) was added. The mixture was stirred at 0 °C for 30 min, and then at room temperature for 3 h, and then finally heated at reflux for 1 h. The solvent was evaporated off and the resulting **3a–f**·HCl were recrystallized from EtOH and Et_2O. Treatment of **3a–e**·HCl with aqueous K_2CO_3 resulted in the **3a–e** as oils.

4.3.1. Ethyl (±)-3-amino-3-(3-pyridyl)propanoate hydrochloride 3a·HCl

Yield: 0.83 g (82%), white crystals; mp 168–171 °C (recrystallized from EtOH). The ^1H NMR and ^{13}C NMR data are in accordance with those reported in the literature.[28]

4.3.2. Ethyl (±)-3-amino-3-(2-furyl)propanoate hydrochloride 3b·HCl

Yield: 1.01 g (92%), brown crystals; mp 95–97 °C. The ^{1}H NMR data are in accordance with those reported in the literature.[21] ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 13.7, 36.2, 45.5, 63.1, 110.4, 111.4, 145.0, 148.2, 171.9.

4.3.3. Ethyl (±)-3-amino-3-(3-furyl)propanoate hydrochloride 3c·HCl

Yield: 0.93 g (85%), brown crystals; mp 118–120 °C. The ^{1}H NMR data are in accordance with those reported in the literature.[21] ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 13.7, 38.0, 44.2, 63.0, 108.8, 120.4, 141.4, 144.8, 171.8.

4.3.4. Ethyl (±)-3-amino-3-(2-thienyl)propanoate hydrochloride 3d·HCl

Yield: 1.07 g (91%), off-white crystals; mp 109–111 °C. The ^{1}H NMR data are in accordance with those reported in the literature.[21] ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 14.0, 39.5, 47.7, 63.4, 128.4, 128.5, 128.8, 137.8, 172.1.

4.3.5. Ethyl (±)-3-amino-3-(3-thienyl)propanoate hydrochloride 3e·HCl

Yield: 1.04 g (88%), brown crystals; mp 88–90 °C. The ^{1}H NMR data are in accordance with those reported in the literature.[21] ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 13.7, 38.5, 47.5, 63.0, 125.4, 126.2, 128.6, 136.2, 172.2.

4.4. Synthesis of β-enamino esters 2f and 2g

Compounds **2f** and **2g** were synthesized by a decarboxylative Blaise reaction according to a literature method.[24] To the solution of the corresponding **1f** and **1g** (5 mmol) in CH_2Cl_2 (5 mL) were added $KOOCCH_2COOEt$ (1.5 equiv), dry $ZnCl_2$ (0.5 equiv) and Hünig's base (0.1 equiv). After refluxing for 7 h under a nitrogen atmosphere, the mixture was cooled to room temperature and saturated NH_4Cl solution (5 mL) was added. The organic layer was separated, dried over Na_2SO_4 and concentrated in vacuo, resulting in the crude solid.

4.4.1. Ethyl 3-amino-3-(2-pyridyl)propenoate 2f

Yield: 0.82 g (85%), pale-yellow crystals; mp 58–59 °C (recrystallized from *n*-hexane). The ^{1}H NMR and ^{13}C NMR data are in accordance with those reported in the literature.[24]

4.4.2. Ethyl 3-amino-3-(4-pyridyl)propenoate 2g

Yield: 0.80 g (83%), yellow crystals; mp 109–111 °C (recrystallized from *n*-hexane/EtOAc 2/1). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.19–1.22 (3H, t, J = 7.10 Hz, CH_2CH_3), 4.05–4.10 (2H, m, CH_2CH_3), 4.90 (1H, s, CH), 7.57–7.59 (2H, m, Ar), 8.65–8.66 (2H, m, Ar). ^{13}C NMR (100.62 MHz, DMSO-d_6) δ (ppm): 14.9, 59.2, 83.4, 121.7, 143.4, 151.0, 158.5, 169.7 (the signals of C2,C6 and C3,C5 are overlapping).

4.5. Synthesis of racemic β-amino esters 3f and 3g

To a solution of **2f** or **2g** (5 mmol) in EtOH (30 mL) were added 0.96 g (10 wt %) of $Pd(OH)_2$ (20% on carbon) and AcOH (2 equiv). The mixture was hydrogenated at atmospheric pressure at room temperature for 24 h. The reaction was stopped by filtering the catalyst off. The solvent was evaporated off, resulting in the acetate salt of **3f** or **3g** as a brown oil. Treatment of **3f**·AcOH and **3g**·AcOH with aqueous K_2CO_3 resulted in the formation of free **3f** and **3g** as yellow oils.

4.5.1. Ethyl (±)-3-amino-3-(2-pyridyl)propanoate 3f

Yield: 0.80 g (82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.23–1.27 (3H, t, J = 7.14 Hz, CH_2CH_3), 2.69–2.91 (2H, m, CH_2CO), 4.13–4.18 (2H, m, CH_2CH_3), 4.44–4.48 (1H, m, CH), 7.18–7.19 (1H, m, Ar), 7.36–7.38 (1H, m, Ar), 7.67–7.68 (1H, m Ar), 8.57–8.58 (1H, m, Ar). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ (ppm): 14.6, 43.4, 54.2, 60.9, 121.4, 122.6, 137.1, 149.7, 172.3.

4.5.2. Ethyl (±)-3-amino-3-(4-pyridyl)propanoate 3g

Yield: 0.72 g (74%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.19–1.22 (3H, t, J = 7.15 Hz, CH_2CH_3), 2.63–2.71 (2H, m, CH_2CO), 4.13–4.19 (2H, m, CH_2CH_3), 4.41–4.44 (1H, m, CH), 7.30–7.33 (2H, m, Ar), 8.57–8.59 (2H, m, Ar). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ (ppm): 14.6, 44.0, 52.1, 61.2, 121.8, 150.5, 153.7, 171.7.

4.6. General procedure for the preparative-scale resolutions of 3a–g

Racemic compounds **3a**–**g** (3 mmol) were dissolved in *i*-Pr_2O (25 mL). Lipase PS (0.75 g, 30 mg mL^{-1}) and H_2O (27 μL, 1.5 mmol) were added and the mixture was shaken in an incubator shaker at 25 °C for 24–67 h (Table 4). The reaction was stopped by filtering off the enzyme at 50% conversion. The solvent was evaporated off and the residues (*R*)-**4a**–**g** were immediately hydrolysed either by refluxing with 6 mL of 18% aqueous HCl solution for 5 h (**4a**, **4f** and **4g**) or by shaking with 6 mL of 9% aqueous HCl at 25 °C (**4b**–**e**) for 12 h to give (*R*)-**6a**–**g**·HCl. The filtered-off enzyme was washed with distilled H_2O (3 × 15 mL), and the H_2O was evaporated off, yielding the crystalline (*S*)-**5a**–**g**. When (*S*)-**5a**–**g** (50 mg) were treated with 22% HCl/EtOH (5 mL), (*S*)-**7a**–**g** were obtained.

4.6.1. Hydrochloride salt of (*R*)-3-amino-3-(3-pyridyl)propanoic acid 6a

Yield: 243 mg (40%), white crystals; recrystallized from MeOH and Et_2O; $[\alpha]_D^{25} = +4.1$ (*c* 0.33, H_2O); mp 220–223 °C (with decomp.); ee >99%. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.26–3.41 (2H, m, CH_2), 5.18–5.22 (1H, t, J = 6.98 Hz, CH), 8.24–8.28 (1H, m, Ar), 8.83–8.85 (1H, m, Ar), 8.95–8.97 (1H, m, Ar), 9.07 (1H, m, Ar). ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 37.6, 49.1, 128.6, 136.2, 141.8, 143.2, 146.0, 172.6. When **4a** was treated with 5% TFA/EtOH (5 mL), **4a**·TFA was obtained {yellow oil, $[\alpha]_D^{25} = -2.3$ (*c* 4, DMF) lit.[14a] $[\alpha]_D^{25} = +3.3$ (*c* 10, DMF) for the (*S*) enantiomer}.

4.6.2. (*S*)-3-Amino-3-(3-pyridyl)propanoic acid 5a

Yield: 230 mg (46%), white crystals; recrystallized from H_2O and Me_2CO; $[\alpha]_D^{25} = -5.1$ (*c* 0.41, H_2O); mp 212–215 °C (with decomp.); ee >99%. The ^{1}H NMR (400 MHz, D_2O) and ^{13}C NMR (100.62 MHz, D_2O) δ (ppm) data for **5a** are similar to those for **2a**.

4.6.3. Hydrochloride salt of (*S*)-3-amino-3-(3-pyridyl)propanoic acid 7a

Quantitative yield, white crystals; $[\alpha]_D^{25} = -3.9$ (*c* 0.33; H_2O); mp 218–220 °C (with decomp.); ee >99%. The ^{1}H NMR (400 MHz, D_2O) and ^{13}C NMR (100.62 MHz, D_2O) δ (ppm) data for **7a** are similar to those for **6a**.

4.6.4. Hydrochloride salt of (*R*)-3-amino-3-(2-furyl)propanoic acid 6b

Yield: 253 mg (44%), off-white crystals; recrystallized from EtOH and Et_2O; $[\alpha]_D^{25} = +5.4$ (*c* 0.32; H_2O); mp 170–173 °C; ee = 97%. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.17–3.20 (2H, m, CH_2), 4.94–4.98 (1H, m, CH), 6.56–6.58 (1H, m, Ar), 6.64–6.65 (1H, m, Ar), 7.65–7.66 (1H, m, Ar). ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 35.9, 45.5, 110.2, 111.4, 144.9, 148.3, 173.9. When **4b** (20 mg) was treated with 22% HCl/EtOH (5 mL), **4b**·HCl was

obtained {brown oil, $[\alpha]_D^{25} = +9.3$ (*c* 0.97, MeOH) lit.[21] $[\alpha]_D^{25} = +9.5$ (*c* 1.00, MeOH)}.

4.6.5. (*S*)-3-Amino-3-(2-furyl)propanoic acid 5b

Yield: 213 mg (46%), white crystals; recrystallized from H_2O and Me_2CO; $[\alpha]_D^{25} = -5.8$ (*c* 0.52, H_2O) lit.[11b] $[\alpha]_D^{25} = +12.9$ (*c* 1.00, H_2O) for (+)-3-amino-3-(2-furyl)propanoic acid, which could be assigned to the L series,[11b] but the absolute configuration was not given; mp 208–211 °C (with decomp.) lit.[11b] mp 205–207 °C (with decomp.); ee >99%. The ^{1}H NMR (400 MHz, D_2O) and ^{13}C NMR (100.62 MHz, D_2O) δ (ppm) data for **5b** are similar to those for **2b**.

4.6.6. Hydrochloride salt of (*S*)-3-amino-3-(2-furyl)propanoic acid 7b

Quantitative yield, off-white crystals; $[\alpha]_D^{25} = -4.9$ (*c* 0.32, H_2O); mp 197–200 °C; ee >99%. The ^{1}H NMR (400 MHz, D_2O) and ^{13}C NMR (100.62 MHz, D_2O) δ (ppm) data for **7b** are similar to those for **6b**.

4.6.7. Hydrochloride salt of (*R*)-3-amino-3-(3-furyl)propanoic acid 6c

Yield: 282 mg (49%), off-white crystals; recrystallized from EtOH and Et_2O; $[\alpha]_D^{25} = +5.3$ (*c* 0.42, H_2O); mp >145 °C (with decomp.); ee >99%. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.11–3.24 (2H, m, CH_2), 4.87–4.91 (1H, m, CH), 6.68 (1H, m, Ar), 7.66 (1H, m, Ar), 7.78 (1H, m, Ar). ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 37.6, 44.3, 108.8, 121.0, 142.0, 145.3, 174.0. When **4c** (20 mg) was treated with 22% HCl/EtOH (5 mL), **4c**·HCl was obtained {brown oil, $[\alpha]_D^{25} = +6.4$ (*c* 1.30, MeOH) lit.[21] $[\alpha]_D^{25} = +7.25$ (*c* 1.00, MeOH)}.

4.6.8. (*S*)-3-Amino-3-(3-furyl)propanoic acid 5c

Yield: 203 mg (44%), white crystals; recrystallized from H_2O and Me_2CO; $[\alpha]_D^{25} = -6.7$ (*c* 0.34, H_2O); mp >219 °C (with decomp.); ee >99%. The ^{1}H NMR (400 MHz, D_2O) and ^{13}C NMR (100.62 MHz, D_2O) δ (ppm) data for **5c** are similar to those for **2c**.

4.6.9. Hydrochloride salt of (*S*)-3-amino-3-(3-furyl)propanoic acid 7c

Quantitative yield, off-white crystals; $[\alpha]_D^{25} = -4.6$ (*c* 0.42, H_2O); mp >142 °C (with decomp.); ee >99%. The ^{1}H NMR (400 MHz, D_2O) and ^{13}C NMR (100.62 MHz, D_2O) δ (ppm) data for **7c** are similar to those for **6c**.

4.6.10. Hydrochloride salt of (*R*)-3-amino-3-(2-thienyl)propanoic acid 6d

Yield: 287 mg (46%), off-white crystals; recrystallized from EtOH and Et_2O; $[\alpha]_D^{25} = +4.1$ (*c* 0.33, H_2O); mp 183–186 °C; ee >99%. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.20–3.25 (2H, m, CH_2), 5.15–5.18 (1H, t, *J* = 7.00 Hz, CH), 7.18–7.21 (1H, m, Ar), 7.35–7.36 (1H, m, Ar), 7.61–7.62 (1H, m, Ar). ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 38.9, 47.4, 128.1, 128.2, 128.4, 137.6, 173.2. When **4d** (20 mg) was treated with 22% HCl/EtOH (5 mL), **4d**·HCl was obtained {yellow oil, $[\alpha]_D^{25} = +6.8$ (*c* 1.07, MeOH) lit.[21] $[\alpha]_D^{25} = +4.6$ (*c* 1.00, MeOH)}.

4.6.11. (*S*)-3-Amino-3-(2-thienyl)propanoic acid 5d

Yield: 228 mg (44%), white crystals; recrystallized from H_2O and Me_2CO; $[\alpha]_D^{25} = -9.9$ (*c* 0.41, H_2O) lit.[11b] $[\alpha]_D^{25} = +15.3$ (*c* 1.00, H_2O) for (+)-3-amino-3-(2-thienyl)propanoic acid, which could be assigned to the L series,[11b] but the absolute configuration was not given; mp 212–215 °C (with decomp.) lit.[11b] mp 206–208 °C (with decomp.); ee >99%. The ^{1}H NMR (400 MHz, D_2O) and ^{13}C NMR (100.62 MHz, D_2O) δ (ppm) data for **5d** are similar to those for **2d**.

4.6.12. Hydrochloride salt of (*S*)-3-amino-3-(2-thienyl)propanoic acid 7d

Quantitative yield, off-white crystals; $[\alpha]_D^{25} = -3.1$ (*c* 0.33, H_2O); mp 184–187 °C; ee >99%. The ^{1}H NMR (400 MHz, D_2O) and ^{13}C NMR (100.62 MHz, D_2O) δ (ppm) data for **7d** are similar to those for **6d**.

4.6.13. Hydrochloride salt of (*R*)-3-amino-3-(3-thienyl)propanoic acid 6e

Yield: 274 mg (44%), brown crystals; recrystallized from EtOH and Et_2O; $[\alpha]_D^{25} = +4.0$ (*c* 0.34, H_2O); mp >150 °C (with decomp.); ee >99%. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.20–3.25 (2H, m, CH_2), 5.15–5.18 (1H, t, J = 7.00 Hz, CH), 7.18–7.21 (1H, m, Ar), 7.35–7.36 (1H, m, Ar), 7.61–7.62 (1H, m, Ar). ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 38.9, 47.4, 128.1, 128.2, 128.4, 145.3, 174.0. When **4e** (20 mg) was treated with 22% HCl/EtOH (5 mL), **4e**·HCl was obtained {brown oil, $[\alpha]_D^{25} = +2.3$ (*c* 1.00, MeOH) lit.[21] $[\alpha]_D^{25} = +1.00$ (*c* 1.00, MeOH)}.

4.6.14. (S)-3-Amino-3-(3-thienyl)propanoic acid 5e

Yield: 221 mg (43%), white crystals; recrystallized from H_2O and Me_2CO; $[\alpha]_D^{25} = -3.2$ (*c* 0.32, H_2O); mp 220–222 °C (with decomp.); ee >99%. The ^{1}H NMR (400 MHz, D_2O) and ^{13}C NMR (100.62 MHz, D_2O) δ (ppm) data for **5e** are similar to those for **2e**.

4.6.15. Hydrochloride salt of (*S*)-3-amino-3-(3-thienyl)propanoic acid 7e

Quantitative yield, pale-brown crystals; $[\alpha]_D^{25} = -3.6$ (*c* 0.34, H_2O); mp >140 °C (with decomp.); ee >99%. The ^{1}H NMR (400 MHz, D_2O) and ^{13}C NMR (100.62 MHz, D_2O) δ (ppm) data for **7e** are similar to those for **6e**.

4.6.16. Hydrochloride salt of (*R*)-3-amino-3-(2-pyridyl)propanoic acid 6f

Yield: 262 mg (45%), white crystals; recrystallized from MeOH and Et_2O; $[\alpha]_D^{25} = +9.7$ (*c* 0.32, H_2O); mp 155–158 °C; ee = 98%. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.24–3.30 (2H, m, CH_2), 5.00–5.05 (1H, m, CH), 7.61–7.67 (2H, m, Ar), 8.07–8.12 (1H, m, Ar), 8.69–8.72 (1H, m, Ar). ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 37.1, 51.1, 125.2, 127.4, 145.5, 145.7, 172.8.

4.6.17. (*S*)-3-Amino-3-(2-pyridyl)propanoic acid 5f

Yield: 209 mg (42%), white crystals; recrystallized from H_2O and Me_2CO; $[\alpha]_D^{25} = -18.2$ (*c* 0.32; H_2O); mp 208–210 °C; ee >99%. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.25–3.28 (2H, m, CH_2), 5.02–5.05 (1H, t, *J* = 6.82 Hz, CH), 7.65–7.77 (2H, m, Ar), 8.13–8.19 (1H, m, Ar), 8.70–8.71 (1H, m, Ar). ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 40.2, 53.3, 122.7, 124.7, 138.9, 148.2, 153.7, 176.8.

4.6.18. Hydrochloride salt of (*S*)-3-amino-3-(2-pyridyl)propanoic acid 7f

Quantitative yield, white crystals; $[\alpha]_D^{25} = -8.6$ (*c* 0.31; H_2O); mp 159–162 °C; ee >99%. The ^{1}H NMR (400 MHz, D_2O) and ^{13}C NMR (100.62 MHz, D_2O) δ (ppm) data for **7f** are similar to those for **6f**.

4.6.19. Hydrochloride salt of (*R*)-3-amino-3-(4-pyridyl)propanoic acid 6g

Yield: 251 mg (43%), white crystals; recrystallized from MeOH and Et_2O; $[\alpha]_D^{25} = +3.2$ (*c* 0.36, H_2O); mp >195 °C (with decomp.); ee = 97%. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.29–3.39 (2H, m, CH_2), 5.20–5.24 (1H, m, CH), 8.25–8.28 (2H, m, Ar), 8.95–8.98 (2H, m, Ar). ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 37.5, 50.8, 126.5, 142.8, 155.9, 173.1.

4.6.20. (*S*)-3-Amino-3-(4-pyridyl)propanoic acid 5g

Yield: 224 mg (45%), white crystals; recrystallized from H_2O and Me_2CO; $[\alpha]_D^{25} = -11.7$ (*c* 0.36, H_2O); mp 220–223 °C (with decomp.); ee = 98%. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 2.92–2.95 (2H, m, CH_2), 4.77–4.78 (1H, t, *J* = 7.09 Hz, CH), 7.56–7.58 (2H, m, Ar), 8.66–8.67 (2H, m, Ar). ^{13}C NMR (100.62 MHz, D_2O) δ (ppm): 40.5, 55.0, 122.8, 146.1, 150.0, 176.4.

4.6.21. Hydrochloride salt of (*S*)-3-amino-3-(4-pyridyl)propanoic acid 7g

Quantitative yield, white crystals; $[\alpha]_D^{25} = -3.6$ (*c* 0.35, H_2O); mp >191 °C (with decomp.); ee = 98%. The ^{1}H NMR (400 MHz, D_2O) and ^{13}C NMR (100.62 MHz, D_2O) δ (ppm) data for **7g** are similar to those for **6g**.

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