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Synthesis of 4-aryl-substituted β-lactam enantiomers by enzyme-catalyzed kinetic resolution

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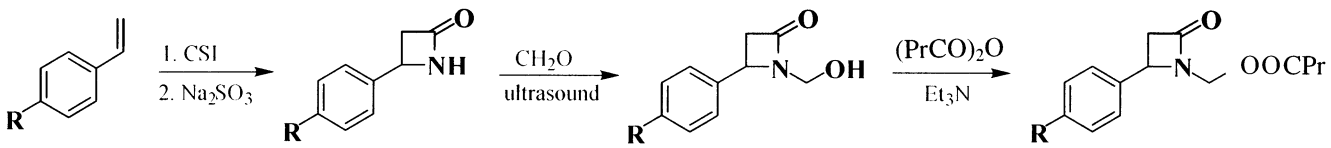
Abstract—Enantiopure 4-phenyl- and 4-(*p*-tolyl)-2-azetidinones **3a**, **3b**, **4a** and **4b** (with e.e.s of ≥96%) were prepared through lipase-catalyzed asymmetric butyrylation of the primary OH group of *N*-hydroxymethylated β-lactams (±)-**5** and (±)-**6** at the (*R*)-stereogenic centre or by lipase-catalyzed asymmetric debutyrylation of *O*-butyryloxymethyl-2-azetidinones (±)-7 and (±)-**8** at the (*R*)-stereogenic centre. The ring-opening of lactams **5a**, **5b**, **6b** and **8a** with HCl/EtOH afforded the corresponding β-amino ester enantiomers **9a**, **9b**, **10a** and **10b** with e.e.s of ≥92%.

1. Introduction

N-Peptidyl-substituted 2-azetidinones, obtained from either racemic or enantiopure 4-phenyl-2-azetidinone, were recently evaluated as inhibitors of the serine protease elastase and the cysteine protease papain.[1] A facile transformation of 3,4-disubstituted 2-azetidinones to chiral 5,6-dihydro-2-pyridones, which can serve as valuable chiral intermediates for different piperidine and indolizidine alkaloids and azasugars, was reported by Lee et al.[2] β-Lactams can be transformed into valuable β-amino acids, which are of immense interest from both pharmacological and chemical viewpoints.[3–6] The increasing importance of acyclic β-amino acid derivatives is reflected by the large number of syntheses published for their preparation in both racemic[7,8] and enantiopure[9–11] form. A convenient method for the preparation of optically active amino acids from α-methylene β-lactams by lipase-catalyzed kinetic resolution was recently described by Adam et al.[12] Because of the importance of β-lactams, a large number of syntheses for racemic and enantiopure 2-azetidinones have been reported. As an example, Bandini et al. synthesized α-halo-β-lactams, which are versatile synthons for a wide variety of functionalized lactams with potential applications as β-lactamases or inhibitors of 3-hydroxy-3-methyl glutarate coenzyme.[13] Optically active 3,4-substituted 2-azetidinones were successfully synthesized by the enzymatic resolution of *N*-acetyloxymethyl or *N*-hydroxymethyl β-lactams.[14] Achilles et al. presented a new synthetic route to enantiopure (*S*)-4-phenyl-2-azetidinone (e.e. = 83%), which was obtained by enantioselective synthesis from (*S*)-β-phenyl-β-alanine, while the (*R*)-enantiomer (e.e. = 84%) was obtained by enzymatic resolution with α-chymotrypsin.[1]

Our aim was to prepare the enantiomerically pure β-lactams **3a**, **3b**, **4a** and **4b** (Scheme 4). The previous results on the enzymatic resolution of alicyclic β-lactams[15–18] suggested the possibility of enantioselective *O*-acylation of the primary hydroxyl group of (±)-**5** and



1 (R = H)
2 (R = Me)

(±)-**3** (R = H)
(±)-**4** (R = Me)

(±)-**5** (R = H)
(±)-**6** (R = Me)

(±)-**7** (R = H)
(±)-**8** (R = Me)

Scheme 1.

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(±)-**6** (Scheme 2). Over and above the primary focus of this work, we wished to search for the most efficient conditions for lipase-catalyzed resolution of (±)-**5** and (±)-**6**, the widespread investigations on β-amino acid derivatives prompted us to study the possible transformations of β-lactam enantiomers into β-amino esters (Scheme 4).

2. Results and discussion

2.1. Syntheses of (±)-5–(±)-8

The racemic β-lactams **3** (R = H) and **4** (R = Me) were prepared from styrene **1** or 4-methylstyrene **2**, respectively, by chlorosulfonyl isocyanate (CSI) addition.[19] The products were transformed with paraformaldehyde under sonication into the *N*-hydroxymethylated β-lactams (±)-**5** (R = H) and (±)-**6** (R = Me), starting substances for lipase-catalyzed asymmetric *O*-acylations (Scheme 1). The *O*-acyl derivatives (±)-**7** (R = H) and (±)-**8** (R = Me), starting compounds for lipase-catalyzed hydrolyses, were synthesized from (±)-**5** and (±)-**6** with butyric anhydride, in the presence of triethylamine.

2.2. Lipase-catalyzed asymmetric acylations of (±)-5 and (±)-6

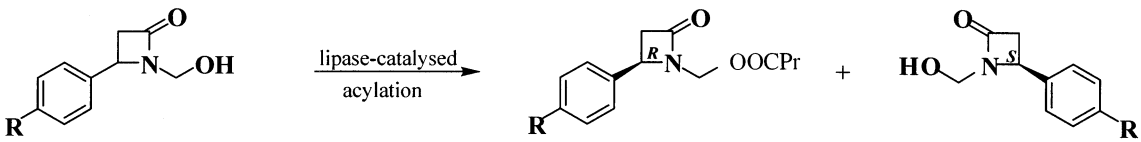
In earlier studies, lipase PS (*Pseudomonas cepacia*) and lipase AK (*Pseudomonas fluorescens*) proved to be applicable for the enantioselective acylation of *N*-hydroxymethylated β-lactams.[14–18] High enantioselectivities (*E* usually >200) were observed, in spite of the relatively large distance between the reaction site and the asymmetric centre. The previous results on the lipase-catalyzed kinetic resolutions of β-lactams suggested the possibility of selective acylation of (±)-**5** (R = H) and (±)-**6** (R = Me) (Scheme 2).

The lipase PS- and lipase AK-catalyzed butyrylations of (±)-**5** with vinyl butyrate (VB) in di-*iso*-propyl ether at 25°C displayed relatively similar high *E* values and reaction times (the times needed to reach 50% conversion) (Table 1, rows 3 and 6). Besides lipase PS and lipase AK, PPL (porcine pancreatic lipase) also proved to be a promising catalyst for the asymmetric butyrylation of (±)-**1** (Table 1, row 8), while CAL-A (lipase from *Candida antarctica* A) was insufficiently selective (Table 1, row 7).

On the basis of our previous experience with lipase PS catalysis,[18,20,21] vinyl butyrate was chosen as the acyl donor for further studies (for practical reasons, vinyl acetate was not used, because the acetate and alcohol peaks partially overlap in the chromatograms in the case of **5**).

Since the nature of the solvent usually influences the enantioselectivity of enzymatic reactions,[18,21] several solvents (mixture of solvents) were tested in the lipase PS-catalyzed butyrylation of (±)-**5**. The reaction proceeded somewhat more slowly and less enantioselectively in tetrahydrofuran (Table 1, row 1) than those completed in acetone, di-*iso*-propyl ether and toluene (Table 1, rows 2, 3 and 5), which all afforded very high enantioselectivities ($E \geq 193$). When a mixture of di-*iso*-propyl ether:$CHCl_3$ (1:1) was used (Table 1, row 4), a longer reaction time and a lower enantioselectivity were observed than in di-*iso*-propyl ether alone (Table 1, row 3). With regard to the reaction rates, toluene was chosen as the solvent for the gram-scale resolution.

It was observed that the butyrylation of (±)-**5** in toluene at 25°C did not stop at 50% conversion: the e.e. value for the product ester started to decrease with time (Fig. 1).



(±)-**5** (R = H)
(±)-**6** (R = Me)

5a (R = H)
6a (R = Me)

5b (R = H)
6b (R = Me)

Scheme 2.

Table 1. Lipase-catalyzed (30 mg mL^{-1}) acylation of (±)-**5** (0.1 M) with VB (0.2 M) at 25°C

Enzyme	Solvent	Time (h)	% Conv.	E.e.$_s$[a] (%)	E.e.$_p$[a] (%)	*E*	Row
Lipase PS[b]	Tetrahydrofuran	24	50	90	91	65	1
Lipase PS[b]	Acetone	7.5	49	94	98	>200	2
Lipase PS[b]	Di-*iso*-propyl ether	2	50	96	96	193	3
Lipase PS[b]	Di-*iso*-propyl ether:$CHCl_3$ (1:1)	17	52	97	91	89	4
Lipase PS[b]	Toluene	1.5	49	94	97	>200	5
Lipase AK[b]	Di-*iso*-propyl ether	2	50	95	95	145	6
CAL-A[b]	Di-*iso*-propyl ether	2	51	42	41	4	7
PPL	Di-*iso*-propyl ether	18	50	91	92	76	8

[a] According to chiral GC.
[b] Contains 20% (w/w) of lipase adsorbed on Celite in the presence of sucrose.

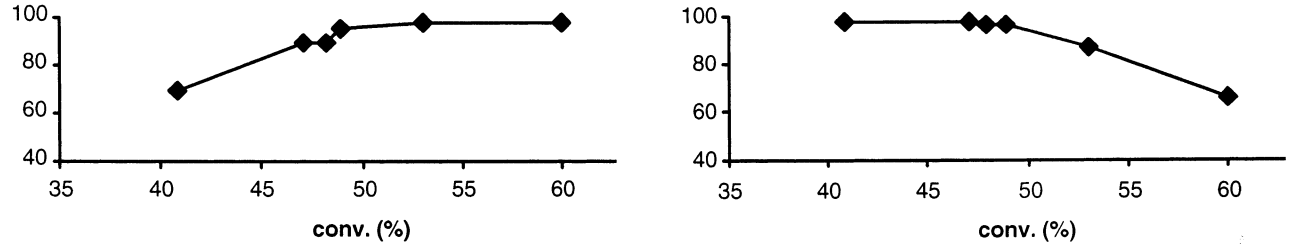


Figure 1. Experimental e.e. values versus conversion for the lipase PS-catalyzed butyrylation of (±)-**5** in toluene at 25°C.

The gram-scale resolutions of (±)-**5** and (±)-**6** were performed in toluene with lipase PS as catalyst and vinyl butyrate as acyl donor at 25°C. The results are presented in Table 2 and in Section 3.

The esters **5a** and **6a** produced by (*R*)-selective butyrylation of the *N*-hydroxymethylated β-lactams (±)-**5** and (±)-**6** were hydrolyzed to the corresponding alcohols **7a** and **8a** in K_2CO_3/MeOH at room temperature, without loss of enantiopurity (Scheme 3).

2.3. Lipase-catalyzed asymmetric debutyrylations of (±)-7 and (±)-8

Since the gram-scale resolution of (±)-**6** did not result in **6a** with the expected enantiopurity (e.e. = 88%), the debutyrylations of (±)-**7** and (±)-**8** were also investigated (Scheme 3).

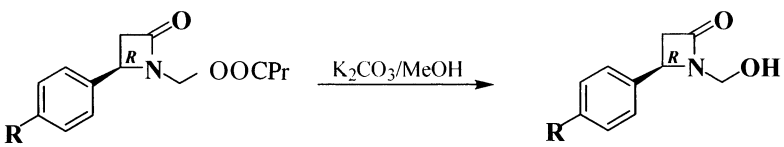
Our recent experience[22] of the enzyme-catalyzed asymmetric *O*-deacylation of *N*,*O*-diacetyl derivatives of cyclic 1,3-amino alcohols, led us to investigate the Novozym-catalyzed hydrolysis of (±)-**7**. Surprisingly, Novozym 435 (lipase from *Candida antarctica* B), which catalyzed the *O*-deacylation reactions of the above-mentioned compounds with high enantioselectivity (*E* usually >200), did not show any selectivity in the debutyrylation of (±)-**7** with ethanol in di-*iso*-propyl ether (1:10) at 60°C (Table 3, row 1).

Nagai et al.[14] described the enantioselective hydrolysis of *N*-acetyloxymethyl β-lactams with lipase B and

Table 2. Lipase PS[a] (30 mg mL^{-1})-catalyzed resolution of (±)-**5** and (±)-**6** with VB (0.2 M) in toluene at 25°C

	Time (h)	Conv. (%)	*E*	Alcohol recovered (**5b** and **6b**)				Ester produced (**5a** and **6a**)			
				Yield[b] (%)	Isomer	E.e.[c] (%)	$[\alpha]_D^{25}$	Yield[b] (%)	Isomer	E.e.[c] (%)	$[\alpha]_D^{25}$
5	1.5	50	>200	78	*S*	98	−166.7[d]	80	*R*	97	+61.4[d]
6	1.5	52	57	56	*S*	95	−168[e]	89	*R*	88	+43.5[d]

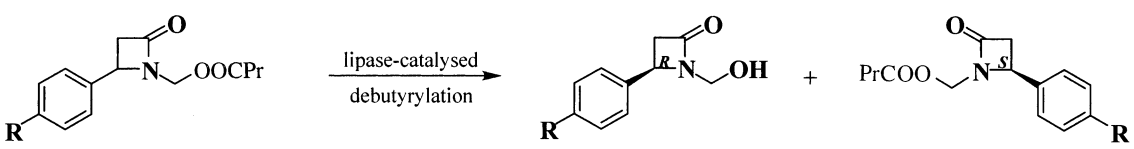
[a] Contains 20% (w/w) of lipase adsorbed on Celite in the presence of sucrose.
[b] Yield 100% at 50% conversion.
[c] According to chiral GC.
[d] *c* = 1, EtOH.
[e] *c* = 0.5, EtOH.



5a (R = H)
6a (R = Me)

7a (R = H)
8a (R = Me)

Scheme 3.



(±)-**7** (R = H)
(±)-**8** (R = Me)

7a (R = H)
8a (R = Me)

7b (R = H)
8b (R = Me)

Scheme 4.

Table 3. Lipase-catalyzed (30 mg mL^{-1}) debutyrylation of (±)-**7** (0.1 M) with EtOH (91 μl mL^{-1}) in di-*iso*-propyl ether

Enzyme	Temp. (°C)	Time (h)	Conv. (%)	E.e.$_s$[a] (%)	E.e.$_p$[a] (%)	*E*	Row
Novozym 435	60	1	95	69	4	1.7	1
Lipase PS[b]	50	4.5	50	96	96	194	2
Lipase PS[b]	40	6	49	94	98	>200	3
Lipase PS[b]	25	22	49	88	91	62	4
Lipase AK[b]	40	6	49	89	93	83	5

[a] According to chiral GC.
[b] Contains 20% (w/w) of lipase adsorbed on Celite in the presence of sucrose.

Table 4. Lipase PS[a] (30 mg mL^{-1})-catalyzed resolutions of (±)-**7** and (±)-**8** with EtOH in di-*iso*-propyl ether (1:10), at 40°C

	Time (h)	Conv. (%)	*E*	Ester recovered (**7b** and **8b**)				Alcohol produced (**7a** and **8a**)			
				Yield[b] (%)	Isomer	E.e.[c] (%)	$[\alpha]_D^{25}$	Yield[b] (%)	Isomer	E.e.[d] (%)	$[\alpha]_D^{25}$
7	7	50	>200	95	*S*	97	−62.5[d]	93	*R*	96	+161[e]
8	6	52	89	80	*S*	97	−62[f]	90	*R*	91	+155.8[g]

[a] Contains 20% (w/w) of lipase adsorbed on Celite in the presence of sucrose.
[b] Yield 100% at 50% conversion.
[c] According to chiral GC.
[d] *c* = 0.65, EtOH.
[e] *c* = 0.35, EtOH.
[f] *c* = 1, EtOH.
[g] *c* = 0.3, EtOH.

lipase PS as suitable catalysts in di-*iso*-propyl ether saturated with water. In order to enhance the enantioselectivity, Novozym was replaced by lipase PS or lipase AK. Both lipases catalyzed the debutyrylation of (±)-**7** with high enantioselectivities (Table 3, rows 2 and 5).

On decreasing the reaction temperature from 50 to 40°C, the reaction rate for the lipase PS-catalyzed debutyrylation of (±)-**7** decreased but the *E* value was slightly enhanced (Table 3, rows 2 and 3). When the reaction was performed at 25°C, the reaction time increased markedly and the enantioselectivity of the reaction decreased to *E* = 62 (Table 3, row 4).

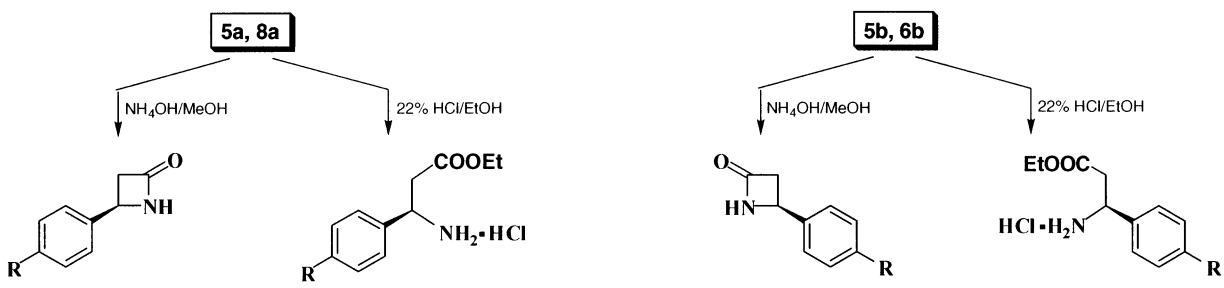
The gram-scale resolutions of (±)-**7** and (±)-**8** were carried out with ethanol in di-*iso*-propyl ether (1:10) at 40°C. The results are presented in Table 4 and in Section 3.

2.4. Transformations of the enantiomers

Treatment of **5a**, **5b**, **6b** and **8a** with NH_4OH/MeOH afforded β-lactams **3a**, **3b** (R = H) and **4a**, **4b** (R = Me), while transformations by ring opening with HCl/EtOH resulted in enantiomers of β-amino esters **9a**, **9b** (R = H) and **10a**, **10b** (R = Me) (Scheme 5). The physical data on the enantiomers prepared are reported in Table 5.

2.5. Absolute configurations

The analyzed chromatograms indicated that the corresponding enantiomers of **5** and **6**, and **7** and **8** react preferentially on lipase PS-catalyzed *O*-acylation and *O*-deacylation, respectively. The absolute configurations were proved by comparing the [α] values with the literature data. The value of $[\alpha]_D^{25} = -136.3$ (*c* = 0.5, EtOH) for **3b** and the literature value[1] for (*S*)-4-phenyl-



3a (R = H) **4a** (R = Me) **9a** (R = H) **10a** (R = Me) **3b** (R = H) **4b** (R = Me) **9b** (R = H) **10b** (R = Me)

Scheme 5.

Table 5. Physical data on enantiomers prepared

Compound	Abs. config.	E.e. (%)	$[\alpha]_D^{25}$
3a	(*R*)	97	+132.4 (*c*=0.5, EtOH)
3b	(*S*)	99	−136.3 (*c*=0.5, EtOH)
4a	(*R*)	96	+122 (*c*=0.5, EtOH)
4b	(*S*)	99	−125.5 (*c*=0.5, EtOH)
9a	(*R*)	95	−11.4 (*c*=0.35, EtOH)
9b	(*S*)	96	+11.8 (*c*=0.5, EtOH)
10a	(*R*)	92	−11.8 (*c*=0.5, EtOH)
10b	(*S*)	97	+12.9 (*c*=1.9, EtOH)

2-azetidinone, $[\alpha]_D^{25}=-130.2$ ($c=1.12$, EtOH), indicate the (*R*)-selectivity of acylation and deacylation. The value of $[\alpha]_D^{25}=+5.9$ ($c=0.7$, MeOH) for **9b** and the literature value[23] for ethyl (*S*)-3-amino-3-phenylpropionate hydrochloride, $[\alpha]_D^{25}=+5.8$ ($c=1$, MeOH), again indicate the *R*-selectivity of hydrolysis and acylation.

In conclusion, an efficient method was developed for the synthesis of 4-aryl-2-azetidinones and the corresponding β-amino ester enantiomers via lipase-catalyzed (*R*)-selective butyrylation or debutyrylation. It is interesting that both butyrylation and debutyrylation had high selectivity rates in the case of phenyl-substituted compounds, while the 4-(*p*-tolyl) derivatives reacted with much lower selectivities.

3. Experimental

3.1. Materials and methods

Vinyl acetate was purchased from Fluka, vinyl butyrate from Aldrich Co., lipase PS and lipase AK from Amano Pharmaceuticals, PPL (type II) from Sigma, and CAL-A and Novozym 435 (as an immobilized preparation) from Novo Nordisk. Before use, lipase PS, lipase AK and CAL-A (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). The lipase preparations thus obtained contained 20% (w/w) of lipase.

In a typical small-scale experiment, racemic 2-azetidinone (0.1 M solution) in an organic solvent (2 mL) was added to the lipase tested (30 mg mL^{-1}). In the case of acylation, VB (0.2 M in the reaction mixture), and in the case of hydrolysis, EtOH (91 μl mL^{-1}) was added. The mixture was shaken at 25°C for acylation and at 40°C for hydrolysis. The progress of the reaction was followed by taking samples from the reaction mixture at intervals and analyzing them by gas chromatography. The e.e. values for the produced enantiomers were determined by gas chromatography on a Chrompack CP-Chirasil-DEX CB column (25 m). Amino esters **9a**, **9b**, **10a** and **10b** were derivatized with hexanoic anhydride in the presence of 4-dimethylaminopyridine and pyridine before gas chromatographic analysis on a Chirasil-*L*-Val column (25 m).

Optical rotations were measured with a Perkin-Elmer 341 polarimeter. ^{1}H NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer. Melting points were determined on a Kofler apparatus.

3.2. Preparation of racemic 4-phenyl-2-azetidinone (±)-3

A solution of styrene **1** (2 g, 19.2 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a stirred solution of chlorosulfonyl isocyanate (1.66 mL, 19.2 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at room temperature for 8 h and left to stand overnight. The resulting liquid was added dropwise to a vigorously stirred solution of Na_2SO_3 (0.24 g) and K_2CO_3 (5.56 g) in H_2O (50 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4) and, after filtration, concentrated. The resulting white solid, racemic **3** (2.34 g, 83%), was recrystallized from di-*iso*-propyl ether (mp 104–105°C, lit.[14] mp 108–109°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.85–2.89 (1H, dd, $J=2$, 14.8, CH_AH) 3.41–3.46 (1H, ddd, $J=2.4$; 5.2; 7.6, CH_BH), 4.71–4.73 (1H, dd, $J=2.5$; 5.3, CH), 6.34 (1H, bs, NH) 7.26–7.40 (5H, m, Ph). Anal. calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52; found: C, 73.12; H, 6.31; N, 9.50%.

3.3. Preparation of racemic 4-(*p*-tolyl)-2-azetidinone (±)-4

With the procedure described above, 4-methylstyrene **2** (2 g, 16.93 mmol) afforded racemic **4** (1.1 g, 40%; mp 85–86°C) as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.35 (3H, s, CH_3) 2.83–2.87 (1H, dd, $J=1.7$; 14.8, CH_AH) 3.39–3.44 (1H, ddd, $J=2.4$; 5.2; 7.6, CH_BH), 4.67–4.69 (1H, dd, $J=2.3$; 5.2, CH), 6.13 (1H, bs, NH) 7.17–7.27 (4H, m, Ph). Anal. calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69; found: C, 74.71; H, 6.91; N, 8.70%.

3.4. Preparation of racemic 1-hydroxymethyl-4-phenyl-2-azetidinone (±)-5

4-Phenyl-2-azetidinone (±)-**3** (2 g, 13.59 mmol) was dissolved in THF (20 mL). Paraformaldehyde (0.41 g, 13.75 mol equiv.), K_2CO_3 (0.11 g) and H_2O (0.78 mL) were added. The solution was sonicated for 5 h. The solvent was evaporated off and the residue was dissolved in ethyl acetate (50 mL). The solution was dried (Na_2SO_4) and then concentrated. The residue was recrystallized from di-*iso*-propyl ether to afford a white crystalline product, (±)-**5** (1.6 g, 66%; mp 83–85°C, lit. mp[14] 84–85°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.88–2.93 (1H, dd, $J=2.4$; 15.2, CH_AH) 3.17 (1H, bs, OH), 3.37–3.42 (1H, dd, $J=5.6$; 15.2, CH_BH), 4.22–4.25 (1H, d, $J=11.6$, NCH_AHOH) 4.82–4.84 (1H, dd $J=2.4$; 5.4. CH), 5.03–5.06 (1H, d, $J=11.6$, NCH_BHOH) 7.32–7.39 (5H, m, Ph). Anal. calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90; found: C, 67.63; H, 6.41; N, 7.90%.

3.5. Preparation of racemic 1-hydroxymethyl-4-(*p*-tolyl)-2-azetidinone (±)-6

With the procedure described above, 4-(*p*-tolyl)-2-azetidinone **4** (1 g, 6.2 mmol) afforded (±)-**6** (1.01 g, 85%; mp 67–71°C) as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.35 (3H, s, CH_3) 2.80–2.84 (1H, bs, OH) 2.87–2.91 (1H, dd, $J=2.4$; 14.8, CH_AH) 3.35–3.40 (1H, dd, $J=5.2$; 14.8, CH_BH), 4.20–4.26 (1H, dd, $J=9.6$; 11.6 NCH_AHOH) 4.78–4.80 (1H, dd $J=2.8$; 5.2, CH), 5.00–5.04 (1H, dd $J=5.2$; 11.6, NCH_BHOH), 7.18–7.25(4H, m, Ph). Anal. calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32; found: C, 68.89; H, 6.81; N, 7.27%.

3.6. Preparation of racemic 1-butyryloxymethyl-4-phenyl-2-azetidinone (±)-7

Racemic 1-hydroxymethyl-4-phenyl-2-azetidinone **5** (0.3 g, 1.69 mmol) was dissolved in CH_2Cl_2 (45 mL). Butyric anhydride (0.53 mL, 3.38 mmol) was added. The solution was stirred at room temperature for one night. After evaporation, the residue was chromatographed on silica. Elution with ethyl acetate:hexane (3:1) afforded an oil of (±)-**3** (0.4 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.89–0.92 (3H, t, $J=7.4$, CH_2CH_3) 1.55–1.61 (2H, m, CH_2CH_3) 2.20–2.24 (2H, m, $CH_2CH_2CH_3$) 2.92–2.96 (1H, dd, $J=2.8$; 15.2, CH_AH) 3.41–3.46 (1H, dd, $J=5.2$; 15.2, CH_BH 4.71–4.73 (1H, dd, $J=2.8$; 5.6 CH), 4.94–4.87 (1H, d, $J=11.6$, NCH_AHOOCOPr) 5.29–5.32 (1H, d $J=11.6$, NCH_BHOCOPr) 7.34–7.39 (5H, m, Ph). Anal. calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66; found: C, 68.13; H, 6.90; N, 5.66%.

3.7. Preparation of racemic 1-butyryloxymethyl-4-(*p*-tolyl)-2-azetidinone (±)-8

With the procedure described above, 1-hydroxymethyl-4-(*p*-tolyl)-2-azetidinone **6** (0.4 g, 2.09 mmol) afforded (±)-**8** (0.41 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.89–0.92 (3H, t, $J=7.4$, CH_2CH_3) 1.55–1.61 (2H, m, CH_2CH_3) 2.20–2.24 (2H, m, $CH_2CH_2CH_3$) 2.35 (3H, s, CH_3) 2.90–2.94 (1H, dd, $J=2.4$; 15.2, CH_AH) 3.38–3.43 (1H, dd, $J=5.6$; 15.2, CH_BH) 4.67–4.09 (1H, dd, $J=2.8$; 5.2 CH) 4.81–4.84 (1H, d, $J=11.2$, NCH_AHOOCOPr) 5.27–5.30 (1H, d $J=11.2$, NCH_BHOCOPr) 7.18–7.26 (4H, m, Ph). Anal. calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36; found: C, 69.11; H, 7.25; N, 5.29%.

3.8. Gram-scale resolution of (±)-5

Racemic **5** (1 g, 5.65 mmol) and vinyl butyrate (0.91 mL, 11.3 mmol) in toluene (60 mL) were added to lipase PS (1.8 g, 30 mg mL^{-1}) and the mixture was shaken at 25°C for 1.5 h. The reaction was stopped by filtering the enzyme off at 50% conversion (e.e. **5a**= 97%, e.e. **5b**=98%). After the solvent had been evaporated off, the residue was chromatographed on silica, with elution with ethyl acetate:hexane (3:1); this afforded the unreacted (*S*)-**5b** [0.39 g, 39%; $[\alpha]_D^{25}=-166.7$ ($c=1$, EtOH); mp 90–91°C (recrystallized from di-*iso*-propyl ether); e.e.=97%] and the ester (*R*)-**5a** [0.56 g, 40%; $[\alpha]_D^{25}=+61.4$ ($c=1$, EtOH); e.e.=97%] as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **5a**: similar to that for (±)-**7**. Anal. calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66; found: C, 68.09; H, 6.66; N, 5.68%.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **5b**: similar to that for (±)-**5**. Anal. calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90; found: C, 67.61; H, 6.34; N, 7.79%.

A mixture of **5a** (0.1 g, 0.4 mmol) and K_2CO_3 (0.14 g, 0.96 mmol) in MeOH (15 mL) was stirred for 6 h at room temperature. After evaporation, the residue was dissolved in H_2O (20 mL) and extracted with diethyl ether. The organic phase was dried (Na_2SO_4), filtered and evaporated. The product (*R*)-**7a** [0.06 g, 84%; $[\alpha]_D^{25}=+159.8$ ($c=1$, EtOH); e.e.=95%] was recrystallized from di-*iso*-propyl ether (mp 86–88°C).

3.9. Gram-scale resolution of (±)-6

With the procedure described above, the reaction of racemic **6** (0.5 g, 2.61 mmol) and vinyl butyrate (0.42 mL, 5.22 mmol) in toluene (30 mL) in the presence of lipase PS (0.9 g, 30 mg mL^{-1}) at 25°C for 1.5 h afforded the unreacted (*S*)-**6b** [0.14 g, 28%; $[\alpha]_D^{25}=-168$ ($c=0.5$, EtOH); mp 98–100°C (recrystallized from di-*iso*-propyl ether); e.e.=95%] and the ester (*R*)-**6a** [0.3 g, 44%; $[\alpha]_D^{25}=+43.5$ ($c=1$, EtOH); e.e.=88%] as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **6a**: similar to that for (±)-**8**. Anal. calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36; found: C, 69.02; H, 7.30; N, 5.22%.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **6b**: similar to that for (±)-**6**. Anal. calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32; found: C, 69.14; H, 6.83; N, 7.34%.

3.10. Methanolysis of 5a and 6a to the corresponding alcohols 7a and 8a

A mixture of **5a** (0.1 g, 0.4 mmol) and K_2CO_3 (0.14 g, 0.96 mmol) in MeOH (15 mL) was stirred for 6 h at room temperature. After evaporation, the residue was dissolved in H_2O (20 mL) and extracted with diethyl ether. The organic phase was dried (Na_2SO_4), filtered and evaporated. The product (*R*)-**7a** [0.06 g, 84%; $[\alpha]_D^{25}=+159.8$ ($c=1$, EtOH); e.e.=95%] was recrystallized from di-*iso*-propyl ether (mp 86–88°C).

Similarly, **6a** (0.1 g, 0.38 mmol) afforded (*R*)-**8a** [0.05 g, 68%; $[\alpha]_D^{25}=+118.4$ ($c=1.9$, EtOH); e.e.=76%].

3.11. Gram-scale resolution of (±)-7

Racemic **7** (0.4 g, 1.62 mmol) was dissolved in di-*iso*-propyl ether (20 mL). Lipase PS (0.6 g, 30 mg mL^{-1}) and ethanol (1 mL) were added and the mixture was shaken at 40°C for 7 h. The enzyme was filtered off at 50% conversion, and the solvent was evaporated off.

The residue was chromatographed on silica, elution with ethyl acetate:hexane (3:1) affording the unreacted ester (*S*)-**7b** [0.19 g, 47%; $[\alpha]_D^{25}=-62.5$ ($c=0.65$, EtOH); e.e.=97%] as a pale-yellow oil and the alcohol (*R*)-**7a** [0.13 g, 46%; $[\alpha]_D^{25}=+161$ ($c=0.35$, EtOH); e.e.=96%) as a white crystalline product (mp 82–84°C, lit. mp[14] 84–85°C).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **7a:** similar to that for (±)-**5**. Anal. calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90; found: C, 67.69; H, 6.42; N, 7.98%.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **7b:** similar to that for (±)-**7**. Anal. calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66; found: C, 67.79; H, 6.92; N, 5.65%.

3.12. Gram-scale resolution of (±)-8

With the procedure described above, the reaction of racemic **8** (0.4 g, 1.53 mmol) and ethanol (1 mL) in di-*iso*-propyl ether (20 mL) in the presence of lipase PS (0.6 g, 30 mg mL^{-1}) at 40°C for 6 h afforded the unreacted (*S*)-**8b** [0.16 g, 40%; $[\alpha]_D^{25}=-62$ ($c=1$, EtOH); e.e.=97%] and the alcohol (*R*)-**8a** (0.12 g, 45%; $[\alpha]_D^{25}=+155.8$ ($c=0.3$, EtOH); mp 100–102°C (recrystallized from di-*iso*-propyl ether); e.e.=91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **8a**: similar to that for (±)-**6**. Anal. calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32; found: C, 68.99; H, 6.80; N, 7.19%.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **8b**: similar to that for (±)-**8**. Anal. calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36; found: C, 69.01; H, 7.34; N, 5.42%.

3.13. Preparation of enantiomerically pure β-lactams 3a, 3b, 4a and 4b

The ester (*R*)-**5a** (0.2 g, 0.81 mmol) was dissolved in MeOH (10 mL), NH_4OH (1 mL) was added and the mixture was stirred at room temperature for 24 h. The solvent was evaporated off, the residue was chromatographed on silica, and elution with ethyl acetate:hexane (3:1) afforded white crystals of (*R*)-**3a** [0.08 g, 67%; $[\alpha]_D^{25}=+132.4$ ($c=0.5$, EtOH); mp 107–110°C (recrystallized from di-*iso*-propyl ether); e.e.=97%].

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **3a**: similar to that for (±)-**7**. Anal. calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52; found: C, 73.12; H, 6.22; N, 9.51%.

Similarly, (*S*)-**5b** (0.2 g, 1.13 mmol) afforded white crystals of (*S*)-**3b** [0.13 g, 78%; $[\alpha]_D^{25}=-136.3$ ($c=0.5$, EtOH); mp 116–117°C (recrystallized from di-*iso*-propyl ether), lit. mp[24] 115.5–116°C; e.e.=99%].
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **3b**: similar to that for (±)-**3**. Anal. calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52; found: C, 73.81; H, 6.13; N, 9.47%.

Similarly, (*S*)-**8a** (0.15 g, 1.78 mmol) afforded white crystals of (*R*)-**4a** [0.09 g, 71%; $[\alpha]_D^{25}=+122$ ($c=0.5$, EtOH); mp 50–54°C (recrystallized from di-*iso*-propyl ether); e.e.=96%].

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **4a**: similar to that for (±)-**4**. Anal. calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69; found: C, 74.38; H, 6.69; N, 8.75%.

Similarly, (*S*)-**6b** (0.2 g, 1.05 mmol) afforded white crystals of (*S*)-**4b** [0.11 g, 65%; $[\alpha]_D^{25}=-125.5$ ($c=0.5$, EtOH); mp 57–60°C (recrystallized from di-*iso*-propyl ether); e.e.=99%].

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **4b**: similar to that for (±)-**4**. Anal. calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69; found: C, 74.66; H, 6.70; N, 8.69%.

3.14. Preparation of enantiomerically pure β-amino ester hydrochlorides 9a, 9a, 10a and 10b

The ester (*R*)-**5a** (0.1 g, 0.4 mmol) was dissolved in 22% HCl/EtOH (10 mL) and refluxed for 5 h. The solvent was evaporated off and the product, (*R*)-**9a** [0.03 g, 32%; $[\alpha]_D^{25}=-11.4$ ($c=0.35$, EtOH); e.e.=95%] was recrystallized from EtOH/di-*iso*-propyl ether (mp 117–119°C).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **9a**: 1.13–1.16 (3H, t, $J=4$, CH_3) 3.00–3.03 (1H, d, $J=15$, CH_AH) 3.23–3.27 (1H, d, $J=15$, CH_BH) 4.03–4.05 (2H, m, CH_2CH_3) 4.70 (1H, m, CH) 7.26–7.50 (5H, m, Ph) 8.74 (2H, bs, NH_2). Anal. calcd for $C_{11}H_{16}NO_2$: C, 57.52; H, 7.02; N, 6.10; found: C, 57.71; H, 6.05; N, 6.10%.

Similarly, the alcohol (*S*)-**5b** (0.1 g, 0.56 mmol) afforded (*S*)-**9b** [0.07 g, 54%; $[\alpha]_D^{25}=+11.8$ ($c=0.5$, EtOH), $[\alpha]_D^{25}=+5.9$ ($c=0.7$, MeOH); lit.[24] $[\alpha]_D^{25}=+5.8$ ($c=1$, MeOH); e.e.=96%; as a slowly crystallizing oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **9b**: similar to that for **9a**. Anal. calcd for $C_{11}H_{16}NO_2$: C, 57.41; H, 7.11; N, 6.18; found: C, 57.71; H, 6.05; N, 6.10%.

Similarly, the alcohol (*R*)-**8a** (0.1 g, 0.52 mmol) afforded (*R*)-**10a** [0.08 g, 63%; $[\alpha]_D^{25}=-11.8$ ($c=0.5$, EtOH); e.e.=92%] as a slowly crystallizing oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **10a**: 1.15 (3H, s, CH_2CH_3) 2.31 (3H, s, CH_3) 3.03 (1H, bs, CH_AH) 3.24 (1H, bs, CH_BH) 4.04 (2H, bs, CH_2CH_3) 4.67 (1H, m, CH) 7.14–7.41 (4H, m, Ph) 8.64 (2H, bs, NH_2). Anal. calcd for $C_{12}H_{18}NO_2$: C, 59.13; H, 7.44; N, 5.75; found: C, 59.01; H, 7.33; N, 5.69%.

Similarly, the alcohol (*S*)-**6b** (0.1 g, 0.52 mmol) afforded (*S*)-**10b** [0.07 g, 54%; $[\alpha]_D^{25}=+12.9$ ($c=1.9$, EtOH); e.e.=97%] as a slowly crystallizing oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **10b**: similar to that for **10a**. Anal. calcd for $C_{12}H_{18}NO_2$: C, 59.13; H, 7.44; N, 5.75; found: C, 59.09; H, 7.21; N, 5.51%.

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