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Chemoenzymatic preparation of the enantiomers of β-tryptophan ethyl ester and the β-amino nitrile analogue

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Abstract—Racemic α-tryptophan was chemoselectively transformed into the enantiomers of β-tryptophan ethyl ester. The key step in achieving enantiopurity was the *N*-acylation of the 3-amino-4-(3-indolyl)butanenitrile intermediate with *Candida antarctica* lipase A (CAL-A). The enzymatic *N*-acylation of racemic β-tryptophan ethyl ester was also studied. CAL-A was highly (*R*)-enantioselective in the present kinetic resolutions, leading to a mixture of the butanamide product with an (*R*)-configuration and the unreacted starting material with an (*S*)-configuration at 50% conversion.
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1. Introduction

In recent years, there has been increased interest in β-amino acids, as a result of their unique pharmacological effects, their ability to modify biologically active peptides and their importance in the preparation of peptidomimetics and natural products.[1–3] Synthetic methods leading to both racemic and enantiomeric β^3-amino acids and esters include the classical Rodionov reaction from the corresponding aldehyde through condensation with malonic acid in the presence of ammonium acetate, the Arndt–Eistert homologation from the corresponding *N*-protected α-amino acid through diazoketone intermediates and the stereoselective reduction of the corresponding enamines.[4–7] Moreover, the preparation of *N*-protected β-amino nitriles has been described.[8,9]

Our interest has long been in the preparation of the enantiomers of β-amino esters by using lipase catalysis for enantioselective *N*-acylation. In these studies, it has become clear that *Candida antarctica* lipase A (CAL-A), bearing a GGGX motif in the oxyanion hole, is highly applicable in the case of β^3-amino esters.[10–12] CAL-A has also proven to be an excellent catalyst for the preparation of highly enantiopure cyanohydrin esters (precursors for non-natural α-amino acids) through kinetic and dynamic kinetic resolution, indicating that cyano-substituted substrates are well accepted by the lipase.[13,14] Herein we report chemoenzymatic and safe ways for the preparation of ethyl 3-amino-4-(1*H*-3-indolyl)butanoate [(*R*)- and (*S*)-**5,** Scheme 1]. In order to introduce enantiopurity in the molecule the focus was on the kinetic resolution of nitrile *rac*-**4**. Just as cyanohydrins are important intermediates for various applications, 3-aminoalkylnitriles serve as intermediates for various kinds of synthetic purposes, for example, (*S*)-**4** has been used in the preparation of bridged indole alkaloids of ajmaline–sarpagine family, dregamine and epidregamine.[8] The CAL-A-catalyzed acylation of *rac*-**5** as *N*-heterocyclic β-amino ester was also found to be attractive in order to learn more about the behaviour of CAL-A. Furthermore, the catalytic behaviour of *C. antarctica* lipase B (CAL-B) has also been studied.

2. Results and discussion

As the basis to achieve the present work, we found two interesting transformations of α-amino acid, L-tryptophan: the Arndt–Eistert methodology leading to the *N*-protected β-tryptophan through the tryptophan-derived diazoketone[3] and the formation of the *N*-tosylated nitrile through the tryptophan-derived ditosylated 2-amino-1-propanol (*S*)-**8** (Scheme 1).[8] We concentrated on the latter method in order to avoid using hazardous diazomethane, and also because nitriles are known to

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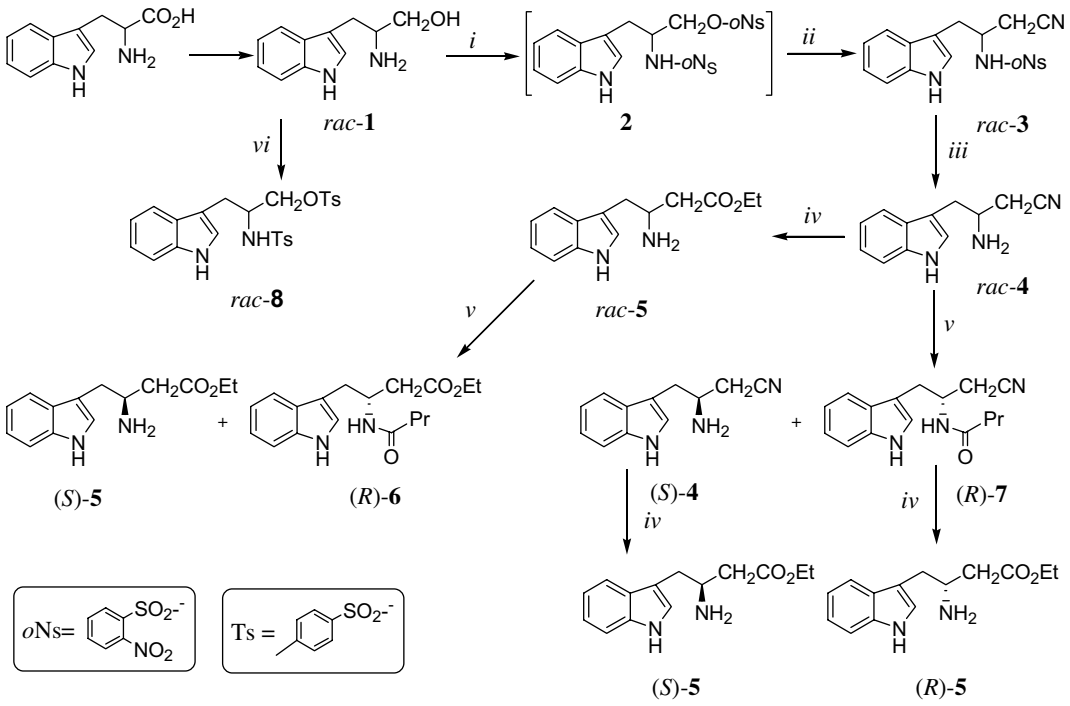

Scheme 1. Reagents and conditions: (i) 2-nitrobenzenesulfonyl chloride (2-NsCl), pyridine, CH_2Cl_2; (ii) KCN, methanol, reflux; (iii) thiophenol, K_2CO_3 and CH_3CN, room temperature; (iv) HCl (0.7 M) in ethanol, then NH_4OH (1%); (v) an achiral ester and CAL-A or CAL-B in a solvent; (vi) 4-toluenesulfonyl chloride (TsCl), pyridine, CH_2Cl_2.

yield carboxylic acids in aqueous acids and esters in acidic alcohols.

For the preparation of β-tryptophan ethyl ester *rac*-**5**, α-tryptophan was first reduced to the corresponding amino alcohol *rac*-**1** in tetrahydrofuran (THF) using lithium aluminium hydride as previously described (Scheme 1).[8] The next step concerned the evaluation of a suitable *N*-protecting group. Tosylation has been used earlier, and accordingly the ditosylate *rac*-**8** was obtained easily.[8] However, the cleavage of the *N*-tosyl group later required harsh conditions, such as the use of sodium in liquid ammonia. As a result, the formation of two unidentified products took place at the expense of the desired compound. For these reasons, tosylation was replaced by nosylation using excess 2-nitrobenzenesulfonyl chloride (2-NsCl) and pyridine. Due to the possible anchimeric assistance of the amino nitrogen, the presence of an *N*-2-nitrobenzene sulfonylated aziridine in the reaction mixture containing the highly unstable product **2** cannot be excluded. As a support, *N*-4-nitrobenzenesulfonyl-2-benzylaziridine was separated when the amino alcohol was protected using 4-nitrobenzenesulfonyl chloride.[9] We used 2-NsCl rather than 4-NsCl because it was reported to cleave more readily than the latter.[15] Without separation, **2** was treated with potassium cyanide yielding *rac*-**3** at 81% isolated yield from *rac*-**1**. The following transformation into *rac*-**4** with thiophenol and potassium carbonate in acetonitrile was accomplished without difficulty as described in the Experimental section. Finally, *rac*-**5** was produced when *rac*-**4** was treated with anhydrous HCl–EtOH under gentle reflux. This transformation was very slow. Thus, after the reaction of 2 days the isolated yields of unreacted *rac*-**4** and produced *rac*-**5** were 30% and 64%, respectively. The above indicates that *rac*-tryptophan can be effectively transformed into *rac*-**5**.

The benefits of successful lipase-catalyzed kinetic resolutions are that chiral induction is introduced by the catalyst under mild reaction conditions and that both enantiomers are simultaneously obtained indicating that the reaction is highly enantioselective. Inspired by our previous success in the kinetic resolution of β^3-amino esters,[10–12] *rac*-**4** was allowed to react with butanoate or acetate esters in mixed solvents, containing *tert*-butylmethyl ether (TBME) or diisopropyl ether (DIPE) in the presence of CAL-A. Due to the low solubility of polar *rac*-**4** in ether, acetonitrile (AN), butyl butanoate or butylacetate was added. In *rac*-**4**, the indole nitrogen did not react under the enzymatic reaction conditions. Thus, the amino group was the only reactive functional group. As shown in Table 1, the reaction proceeded with low enantioselectivity in the presence of acetonitrile (rows 1 and 2) while excellent enantioselectivity (E >200) was observed when butyl butanoate acted as an acyl donor and as a co-solvent in DIPE (row 4). Enantioselectivity dropped when butylacetate replaced the butanoate (row 4 compared to row 6). TBME gave both lower reactivity (measured as conversion after 2 h) and enantioselectivity than DIPE (row 4 compared to row 5). To this end, the gram-scale resolution of *rac*-**4** with CAL-A in butyl butanoate/DIPE (1:1) was successfully accomplished in 2 h as described in the Experimental. The separated nitrile enantiomers (*R*)-**7** (ee = 95%) and (*S*)-**4** (ee = 99%) were transformed into the amino esters (*R*)- and (*S*)-**5** by refluxing in 0.7 M HCl/EtOH without any change in the original enantiopurities. It

Table 1. *N*-Acylation of *rac*-**4** (0.05 M) by CAL-A preparation (20 mg/mL) at room temperature

Entry	Acyl donor	Solvent	Time (h)	*c* (%)	$Ee^{(S)\text{-}4}$	$Ee^{(R)\text{-}7}$	*E*
1	$PrCO_2CH_2CF_3$	TBME/AN[a] (2:1)	2.5	51	75	72	19
2	$PrCO_2CH_2CF_3$	DIPE/AN[a] (2:1)	1	49	84	89	46
3	$PrCO_2Bu$		3.5	48	86	94	90
4	$PrCO_2Bu$/DIPE (1:1)		2	49	96	98	>200
5	$PrCO_2Bu$/TBME (1:1)		2	34	51	96	81
6	$MeCO_2Bu$/DIPE (1:1)		22	40	62	92	44
7	$PrCO_2Bu$[b]		68	45	30	37	3
8	$PrCO_2CH_2CF_3$[b]	TBME/AN[a] (2:1)	91	17	13	62	5

[a] AN is acetonitrile.
[b] CAL-B (50 mg/mL) as a lipase, temperature 47 °C.

was interesting to recognize that *C. antarctica* lipase B (CAL-B), as one of the most generally used lipase in enantioselective reactions, non-enantioselectively accepted *rac*-**4** as a substrate (rows 7 and 8).

CAL-A has been used for the kinetic resolution of *O*- and *S*-heterocyclic β^3-amino esters before,[11] but this work is the first time when *N*-heterocyclic β^3-amino esters were studied. For this purpose, *rac*-**5** was subjected to acylation in $PrCO_2Bu$/DIPE (1:1) at room temperature (Table 2). The reaction proceeded at excellent enantioselectivity and practically stopped at 50% conversion when the resolution products (*R*)-**6** and (*S*)-**5** were both at ee >99% (the other enantiomer was not observed by the chiral HPLC method). However, the time needed to reach the 50% conversion was considerably longer for the acylation of *rac*-**5** than for *rac*-**4**. The reaction in the presence of CAL-B under otherwise the same conditions was extremely slow (36% conversion was reached after one week) and proceeded at low enantio- and chemoselectivity in the reaction where the *N*-acylation of the amino group and the exchange of the ester group of *rac*-**4** both took place.

Table 2. *N*-Acylation of a substrate (0.05 M) in $PrCO_2Bu$/DIPE (1:1) by CAL-A preparation (20 mg/mL) at room temperature

Substrate	Time (h)	*c* (%)	Ee^S	Ee^R
rac-**4**	2	49	96	98
rac-**5**	16	50	>99	>99

The absolute configuration of the less reactive nitrile enantiomer was confirmed to be (*S*)-**4** by the transformation of L-tryptophan to (*S*)-**5** through the nitrile intermediate (Scheme 1) and by comparing the chromatographic behaviour of the compounds. According to the results, CAL-A furnishes *N*-acylation with high (*R*)-enantiopreference for both the nitrile and ester substrates.

3. Conclusion

In conclusion we have reported an efficient chemoenzymatic method for the preparation of the enantiomers of **5** from racemic α-amino acid, tryptophan. More importantly, the capacity of CAL-A to resolve β-amino nitrile *rac*-**4** with excellent (*R*)-enantiopreference has been accomplished, allowing the preparation of enantiopure amino nitrile synthons (*R*)-**7** and (*S*)-**4** to further synthetic purposes (Scheme 1).

4. Experimental part

4.1. Materials and methods

Tryptophan, 2-nitrobenzenesulfonyl chloride, thiophenol, potassium cyanide, butyl butanoate and the solvents were products of Aldrich or Fluka. 2,2,2-Trifluoroethyl butanoate was prepared from butanoyl chloride and the corresponding alcohol. All solvents were of the highest analytical grade and were dried by standard methods when necessary. CAL-A (lipase A from *C. antarctica*, Chirazyme L5, lyo.) was purchased from Boehringer–Mannheim. Before use, CAL-A was adsorbed on celite by dissolving the enzyme (5 g) and sucrose (3 g) in Tris–HCl buffer (250 mL, 20 mM, pH = 7.9) followed by the addition of celite (17 g). The mixture was dried by allowing the water to evaporate. The preparation containing 20% (w/w) of the enzyme was thus obtained. The enzyme preparation gave the initial rate 0.086 ± 0.001 mmol/min/g for the acylation of racemic valine methyl ester (0.1 M) with 2,2,2-trifluoroethyl butanoate (0.2 M) in TBME (*E* = 13) as a standard reaction. *C. antarctica* lipase B (CAL-B, Novozym 435) was a generous gift from Novozyme. Preparative chromatographic separations were performed by column chromatography on Merck Kieselgel 60 (0.063–0.200 μm). TLC was carried out with Merck Kieselgel $60F_{254}$ sheets. If not otherwise stated, all enzymatic reactions were performed at room temperature (23 °C).

The ^1H and ^{13}C NMR spectra were recorded on a Bruker 500 spectrometer with tetramethylsilane (TMS) as an internal standard. ^1H–^1H COSY, ^1H–^{13}C HQSC and ^1H–^{13}C HMBC spectra were used for the assignments of the chemical shifts. Mass spectra were taken on a VG 7070E mass spectrometer. Optical rotations were determined with a Perkin–Elemer polarimeter, and $[\alpha]_D$ values given in units of 10^{-1} deg cm^2 g^{-1}. Melting points were measured on a Mettler FP80 instrument. The determination of *E* was based on the equation $E = \ln[(1-c)(1-ee_s)]/\ln[(1-c)(1+ee_s)]$ with the use of linear regression, *E* being the slope of a line $\ln[(1-c)(1-ee_s)]$ versus $\ln[(1-c)(1+ee_s)]$.[16]

In a typical small-scale experiment, the lipase preparation was added to the solution of *rac*-**4** or *rac*-**5** (0.1 mmol) and an acyl donor in 2 mL of a solvent. The progress of the reactions and the ee values were followed by taking samples (0.1 mL) at intervals and analyzing them by HPLC. The analyses were conducted with the HP 1090 instrument at the wavelength of 263 nm using a CHIRACEL-OD column (0.46×25 cm) and a mixture of hexane and isopropyl alcohol (9:1) as an eluent at the flow rate of 1 mL/min. Before analysis, unreacted amine was derivatized with propionic anhydride in order to achieve good baseline separation.

4.2. Preparation of *rac*-2-amino-3-(1*H*-3-indolyl)propan-1-ol 1

The known method was followed.[8] Lithium aluminum hydride (3.75 g, 98.7 mmol) and racemic tryptophan (5.00 g, 24.5 mmol) were suspended in dry tetrahydrofuran (250 mL) under reflux for 15 h. The mixture was cooled to 0 °C followed by the treatment with saturated sodium sulfate solution, filtration and evaporation to afford alcohol *rac*-**1** (4.56 g, 24.0 mmol) at 98% yield. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.53–2.57 (dd, J = 7.28, 14.10 Hz, 1H, indole-CH_2); 2.76–2.80 (dd, J = 5.82, 14.09 Hz, 1H, indole-CH_2); 2.94–2.99 (m, 1H, indole-CH$_2$CH); 3.20–3.23 (dd, J = 6.73, 10.29 Hz, 1H, CH_2OH); 3.33–3.36 (dd, J = 4.70, 10.30 Hz, 1H, CH_2OH); 6.95–6.98 (t, J = 7.42 Hz, 1 arom. H); 7.04–7.07 (t, J = 7.48 Hz, 1 arom. H); 7.14 (s, 1 arom. H); 7.33–7.34 (d, J = 8.05 Hz, 1 arom. H); 7.53–7.54 (d, J = 7.84 Hz, 1 arom. H); 10.82 (br s, indole-NH). ^{13}C NMR (DMSO-d_6, 126 MHz): δ = 29.65 (indole-CH$_2$), 53.50 (indole-CH$_2$$C$H), 66.09 ($CH_2$OH), 111.19, 111.71, 118.00, 118.37, 120.65, 123.14, 127.51, 136.12.

4.3. Preparation of *rac*-3-(2-nitrobenzenesulfonyl)amino-4-(3-indolyl)butanenitrile 3

2-Nitrobenzenesulfonyl chloride (2-NsCl) (10.0 g, 45.1 mmol) was added in one portion to a solution of *rac*-**1** (2.85 g, 15.0 mmol) in dry CH_2Cl_2 and pyridine (15 mL, 2:1, v/v) at 0 °C. The mixture was stirred overnight at room temperature, diluted with CH_2Cl_2 (220 mL) and treated with saturated sodium chloride solution (100 mL). The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (3×100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. The resulted crude product **2** was used for next step without further purification.

Potassium cyanide (1.46 g, 22.5 mmol) was added to a solution of the above crude product **2** in MeOH (50 mL) at room temperature. The mixture was gently refluxed until TLC indicated the disappearance of the starting material. The reaction mixture was treated with silica gel (2 g) before the solvent was evaporated. *rac*-**3** (4.67 g, 12.2 mmol, yield 81%, solid, mp 152–154 °C) was purified on silica gel by elution with petroleum ether/ethyl acetate (6:2). HRMS: M^+ found (M^+ calculated for $C_{18}H_{16}N_4O_4S$): 384.08960 (384.08923); MS: m/z (relative intensity) = 384 (10), 186 (4), 130 (100), 103 (4), 77 (6); ^{1}H NMR (acetone-d_6, 500 MHz): δ = 2.92–2.97 (dd, J = 4.20, 15.76 Hz, 1H, CH_2CN); 2.97–3.01 (dd, J = 5.50, 16.86 Hz, 1H, CH_2CN); 3.08–3.13 (dd, J = 9.61, 14.56 Hz, 1H, indole-CH_2); 3.15–3.19 (dd, J = 5.09, 14.54 Hz, 1H, indole-CH_2); 4.05–4.10 (m, 1H, CHCH$_2$CN); 6.83 (br s, 1H, NH); 6.88–6.91 (t, J = 7.19 Hz, 1 arom. H); 7.00–7.04 (t, J = 7.14 Hz, 1 arom. H); 7.19–7.23 (m, 2 arom. H); 7.32–7.38 (m, 2 arom. H); 7.52–7.63 (m, 3 arom. H); 9.85 (br s, 1H, NH). ^{13}C NMR (acetone-d_6, 126 MHz): δ = 25.83 (CH$_2$CN), 30.60 (indole-CH$_2$), 52.84 (CHCH$_2$CN), 109.92, 112.41, 118.15, 118.95, 119.71, 122.07, 125.51, 125.53, 127.71, 130.37, 133.06, 133.52, 134.29, 137.51, 147.60.

4.4. Preparation of *rac*-3-amino-4-(1*H*-3-indolyl)butanenitrile 4

Thiophenol (0.49 g, 4.45 mmol) was added to a mixture of *rac*-**3** (0.34 g, 0.88 mmol) and anhydrous K_2CO_3 (1.22 g, 8.85 mmol) in dry CH_3CN (4 mL). After half an hour, the starting material was totally consumed as indicated by TLC. The solvent was evaporated and the residue purified on silica gel by elution with dichloromethane/methanol (19:1), affording *rac*-**4** (0.17 g, 0.87 mmol) at 99% yield. HRMS: M^+ found (M^+ calculated for $C_{12}H_{13}N_3$): 199.11100 (199.11095); MS: m/z (relative intensity) = 199 (M^+, 10), 130 (100), 103 (7), 77 (10); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.34–2.39 (dd, J = 6.42, 16.57 Hz, 1H, CH_2CN); 2.46–2.50 (dd, J = 5.06, 16.57 Hz, 1H, CH_2CN); 2.88–2.93 (dd, J = 7.23, 14.34 Hz, 1H, indole-CH_2); 2.96–3.00 (dd, J = 6.27, 14.36 Hz, 1H, indole-CH_2); 3.46–3.51 (m, 1H, CHNH$_2$); 7.07 (d, J = 2.08 Hz, 1 arom. H); 7.12–7.15 (t, J = 7.58 Hz, 1 arom. H); 7.20–7.23 (t, J = 7.29 Hz, 1 arom. H); 7.36–7.38 (d, J = 8.14 Hz, 1 arom. H); 7.60 (d, J = 7.92 Hz, 1 arom. H); 8.34 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 26.00 (CH$_2$CN), 32.93 (indole-CH$_2$), 48.81 (CHNH$_2$), 111.32, 111.40, 118.36, 118.65, 119.68, 122.33, 123.02, 127.24, 136.38.

4.5. Preparation of *rac*-3-amino-4-(1*H*-3-indolyl)butanoic acid ethyl ester 5

A solution of *rac*-**4** (0.10 g, 0.50 mmol) in 0.7 M HCl in ethanol was stirred for 48 h at 90 °C followed by the evaporation of the solvent. The residue was dissolved in 10 mL chloroform/aqueous NH_4OH (1%, 1:1). The organic layer was separated and the aqueous layer washed with chloroform (2×8 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated. After column chromatography eluting with dichloromethane/methanol (19:1), the unreacted *rac*-**4** (0.03 g, 0.15 mmol) was recovered and *rac*-**5** (0.08 g, 0.32 mmol) obtained at 65.0% yield as a semi-solid product. HRMS: M^+ found (M^+ calculated for $C_{14}H_{18}N_2O_2$): 246.13710 (246.13683); MS: m/z (relative intensity) = 246 (9), 232 (33), 131 (24), 123 (100), 116 (14), 109 (11), 77 (16); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.24–1.27 (t, J = 7.09 Hz, 3H, CH_3); 2.36–2.41 (dd, J = 8.64, 16.00 Hz, 1H, CH_2CO$_2$); 2.55–2.59 (dd, J = 4.15, 15.99 Hz, 1H, CH_2CO$_2$); 2.77–2.81 (dd, J = 8.06,

14.17 Hz, 1H, indole-CH_2); 2.93–2.97 (dd, J = 5.37, 14.18 Hz, 1H, indole-CH_2); 3.60–3.62 (m, 1H, CHNH$_2$); 4.12–4.16 (q, J = 7.13 Hz, 2H, CO$_2$CH_2CH$_3$); 7.07 (s, 1 arom. H); 7.11–7.14 (t, J = 7.49 Hz, 1 arom. H); 7.19–7.22 (t, J = 7.65 Hz, 1 arom. H); 7.36–7.38 (d, J = 8.10 Hz, 1 arom. H); 7.62–7.64 (d, J = 7.88 Hz, 1 arom. H); 8.14 (br s, 1H, NH). ^{13}C NMR (CDCl$_3$, 126 MHz): δ = 14.18 (CH$_3$), 32.41 (indole-CH$_2$), 40.99 (CH$_2$CO$_2$), 48.70 (CHNH$_2$), 60.45 (CO$_2C$H$_2$CH$_3$), 111.18, 112.53, 119.00, 119.50, 122.16, 122.82, 127.57, 136.38, 172.62 (CO$_2$).

4.6. Gram-scale resolution of *rac*-4

CAL-A preparation (20 mg/mL) was added to a solution of racemic **4** (1.00 g, 5.02 mmol) in PrCO$_2$Bu/DIPE (1:1) (100 mL). The reaction was stopped at 51% conversion by filtering off the enzyme. The filtrate was evaporated and the residue purified on silica gel eluting with dichloromethane/methanol (19:1), affording (*S*)-**4**, 0.47 g, 2.38 mmol, ee = 99% and $[\alpha]_D^{20} = +15.0$ (c 0.9, CHCl$_3$) and semi-solid (*R*)-**7**, 0.67 g, 2.49 mmol, ee = 95%, $[\alpha]_D^{20} = +32.5$ (c 0.9, CHCl$_3$). Spectral data for (*R*)-**7**: HRMS: M$^+$ found (M$^+$ calculated for C$_{16}$H$_{19}$N$_3$O): 269.15260 (269.15281); MS: *m*/*z* (relative intensity) = 269 (12), 182 (90), 130 (100), 103 (7), 77 (9); ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 0.89–0.92 (t, J = 7.39 Hz, 3H, CH_3); 1.59–1.66 (m, 2H, CH_2CH$_3$); 2.14–2.17 (t, J = 7.34 Hz, 2H, COCH_2); 2.47–2.51 (dd, J = 4.20, 16.77 Hz, 1H, CH_2CN); 2.73–2.77 (dd, J = 5.48, 16.77 Hz, 1H, CH_2CN); 3.05–3.09 (dd, J = 8.26, 14.61 Hz, 1H, indole-CH_2); 3.15–3.19 (dd, J = 6.20, 14.61 Hz, 1H, indole-CH_2); 4.45–4.54 (m, 1H, CHNHCO); 5.80 (br s, 1H, NH); 7.11–7.16 (m, 2 arom. H); 7.21–7.24 (t, J = 7.21 Hz, 1 arom. H); 7.34–7.39 (d, J = 8.13 Hz, 1 arom. H); 7.62–7.63 (d, J = 7.91 Hz, 1 arom. H); 8.34 (br s, 1 H). ^{13}C NMR (CDCl$_3$, 126 MHz): δ = 13.65 (CH_3), 19.00 (CH_2CH$_3$), 22.26 (CH_2CN), 28.92 (indole-CH$_2$), 38.53 (COCH$_2$), 46.29 (CHNHCO), 110.09, 111.48, 117.63, 118.50, 119.99, 122.57, 123.06, 127.14, 136.38, 173.20 (NHCO).

The obtained (*S*)-**4** was transformed to (*S*)-**5** at 60% yield, $[\alpha]_D^{20} = -5.4$ (c 1.0, CHCl$_3$), ee = 99% and (*R*)-**7** to (*R*)-**5** at 63% yield, $[\alpha]_D^{20} = +5.2$ (c 1.0, CHCl$_3$), ee = 95% as described above.

4.7. Gram-scale resolution of *rac*-5

CAL-A preparation (20 mg/mL) was added to the solution of racemic **5** (1.00 g, 4.07 mmol) in PrCO$_2$Bu/DIPE (1:1) (81 mL). The reaction was stopped at 50% conversion by filtering off the enzyme. The filtrate was evaporated and the residue purified on silica gel eluting with dichloromethane/methanol (19:1), affording (*S*)-**5**, 0.48 g, 1.95 mmol, ee >99% and $[\alpha]_D^{20} = -5.4$ (c 1.0, CHCl$_3$), and semi-solid (*R*)-**6**, 0.62 g, 1.96 mmol, ee >99%, $[\alpha]_D^{20} = +8.0$ (c 1.0, CHCl$_3$). Spectral data for (*R*)-**6**: HRMS: M$^+$ found (M$^+$ calculated for C$_{18}$H$_{24}$N$_2$O$_3$): 316.17860 (316.17869); MS: *m*/*z* (relative intensity) = 316 (11), 229 (100), 184 (10), 156 (31), 143 (15), 130 (50), 116 (27); ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 0.88–0.91 (t, J = 7.39 Hz, 3H, COCH$_2$CH$_2$CH_3); 1.24–1.27 (t, J = 7.12 Hz, 3H, CO$_2$CH$_2$CH_3); 1.57–1.64 (m, 2H, COCH$_2$CH_2CH$_3$); 2.10–2.13 (t, J = 7.34 Hz, 2H, COCH_2CH$_2$CH$_3$); 2.47–2.51 (dd, J = 4.58, 16.00 Hz, 1H, CHCH_2CO$_2$); 2.52–2.56 (dd, J = 4.37, 16.58 Hz, 1H, CHCH_2CO$_2$); 2.97–3.02 (dd, J = 7.83, 14.54 Hz, 1H, indole-CH_2); 3.08–3.12 (dd, J = 5.87, 14.54 Hz, 1H, indole-CH_2); 4.12–4.16 (q, J = 7.11 Hz, 2H, CO$_2$CH_2CH$_3$); 4.60–4.67 (m, 1H, CHNHCO); 7.03 (d, J = 2.20 Hz, 1 arom. H); 7.10–7.13 (t, J = 7.78 Hz, 1 arom. H); 7.17–7.20 (t, J = 8.03 Hz, 1 arom. H); 7.35–7.37 (d, J = 8.12 Hz, 1 arom. H); 7.64–7.66 (d, J = 7.87 Hz, 1 arom. H); 8.29 (br s, 1 H, NH). ^{13}C NMR (CDCl$_3$, 126 MHz): δ = 13.65 (COCH$_2$-CH$_2C$H$_3$), 14.18 (CO$_2$CH$_2C$H$_3$), 19.07 (COCH$_2$-CH$_2$CH$_3$), 29.48 (indole-CH$_2$), 37.40 (CHCH$_2$CO$_2$), 38.83 (COCH$_2$CH$_2$CH$_3$); 46.70 (CHCH$_2$CO$_2$), 60.67 (CO$_2C$H$_2$CH$_3$); 111.18, 111.62, 118.89, 119.56, 122.11, 122.82, 127.72, 136.23, 172.21 (CO$_2$CH$_2$CH$_3$), 172.76 (COCH$_2$CH$_2$CH$_3$).

4.8. Preparation of *rac*-3-(1*H*-3-indolyl)-2-(tosylamino)-propyl toluene-4-sulfonate 8

Compound **8** was prepared at 85% yield by the known method.[8] ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 2.32 (s, 3H, CH_3); 2.44 (s, 3H, CH_3); 2.77–2.82 (dd, J = 6.98, 14.63 Hz, 1H, indole-CH_2); 2.98–3.02 (dd, J = 7.00, 14.63 Hz, 1H, indole-CH_2); 3.57–3.64 (m, 1H, indole-CH$_2$CH); 3.87–3.90 (dd, J = 5.65, 9.97 Hz, 1H, CH_2O-SO$_2$); 4.08–4.11 (dd, J = 4.42, 9.98 Hz, 1H, CH_2OSO$_2$); 6.88–6.89 (d, J = 2.32 Hz, 1 arom. H); 6.95–6.98 (dt, J = 0.84, 7.87 Hz, 1 arom. H); 7.01–7.03 (d, J = 8.07 Hz, 2 arom. H); 7.12–7.18 (m, 2 arom. H); 7.27–7.29 (d, J = 8.14 Hz, 1 arom. H); 7.31–7.33 (d, J = 8.01 Hz, 2 arom. H); 7.43–7.45 (d, J = 8.29 Hz, 2 arom. H); 7.74–7.76 (d, J = 8.31 Hz, 2 arom. H); 8.16 (br s, 1H, NH). ^{13}C NMR (CDCl$_3$, 126 MHz): δ = 21.52 (CH_3), 21.69 (CH_3), 27.32 (indole-CH$_2$), 52.13 (indole-CH$_2C$H), 70.60 (CH_2OSO$_2$), 109.39, 111.30, 118.23, 119.62, 122.15, 123.45, 126.75, 128.01, 129.45, 130.00, 132.31, 136.21, 136.29, 143.38, 145.19.

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