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Preparation of (1*R*,8*S*)- and (1*S*,8*R*)-9-azabicyclo[6.2.0]dec-4-en-10-one: potential starting compounds for the synthesis of anatoxin-*a*

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Abstract—9-Azabicyclo[6.2.0]dec-4-en-10-one (±)-**2**, obtained from cyclooctadiene by addition of chlorosulfonyl isocyanate, was *N*-hydroxymethylated to (±)-**3** and then resolved by lipase-catalysed asymmetric acylation of the primary OH group at the (*S*)-stereogenic centre. High enantioselectivity ($E=94$) was observed when lipase PS and vinyl butyrate were used in di-*iso*-propyl ether at −15°C, resulting in the enantiomerically enriched ester **3a** and alcohol **3b** (e.e. ≥92%). Treatment of **3a** and **3b** with NH_4OH/MeOH afforded the corresponding β-lactams (1*R*,8*S*)-**2a** and (1*S*,8*R*)-**2b** (e.e. ≥93%), potential starting compounds in anatoxin-*a* synthesis. The ring opening of lactams (±)-**2**, (±)-**7**, **3a** and **3b**, followed by reduction, resulted in racemic **4**–**6** and **8** and enantiomeric **4a**, **4b**, **5a** and **5b** eight-membered cyclic β-amino acid derivatives. © 2001 Published by Elsevier Science Ltd.

1. Introduction

Anatoxin-*a*, a neurotoxic alkaloid, is one of the most toxic of the cyanobacterial toxins, but a potent and stereospecific agonist at nicotinic acetylcholine receptors.[1–3] It has been isolated from strains of *Anabaena flos aqua*, a freshwater blue–green algae. The presence of cyanobacteria in lakes and drinking water[4,5] creates a major problem worldwide. Intense pharmacological interest[3,6,7] has led to a number of syntheses of anatoxin-*a* in both racemic and enantiomerically pure form.[1,8–12] (+)-Anatoxin-*a* has been efficiently synthesised from (−)-cocaine hydrochloride,[8] whilst Trost and Oslob reported a new synthetic route to (−)-anatoxin-*a* via a palladium-catalysed asymmetric cyclisation.[9] A recently published efficient total synthesis of (±)-anatoxin-*a* starts from β-lactam (±)-**2**.[11] β-Lactam **2** can also be a precursor to valuable β-amino acids. It is well known that β-amino acids are important compounds from both pharmacological and chemical aspects[13] (e.g. (1*R*,2*S*)-aminocyclopentanecarboxylic acid, *cis*-*pentacin*,[14] an antifungal antibiotic); cyclic β-amino acids can be used as building blocks in the synthesis of biologically active peptides; the two functional groups are subject to a wide variety of chemical transformations.[15]

Our aims in this study were to prepare the enantiomerically pure alicyclic β-lactams **2a** and **2b**, potential starting compounds for enantiopure anatoxin-*a* synthesis, and to use β-lactam **2** for the synthesis of both racemic and enantiomeric eight-membered cyclic β-amino acids and esters.

2. Results and discussion

2.1. Synthesis of (±)-2 and its transformations into racemic alicyclic β-amino acids

The racemic β-lactam **2** was prepared from cyclooctadiene **1** by chlorosulfonyl isocyanate (CSI) addition.[10] It was transformed with paraformaldehyde under sonication into *N*-hydroxymethylated β-lactam (±)-**3**, the starting material for the enzymatic resolution (Scheme 1). (±)-**2** could then be transformed by ring opening with HCl/EtOH into *cis*-amino ester (±)-**4** or into *cis*-amino acid (±)-**6** with concentrated aqueous HCl. The unsaturated cyclooctene derivatives (±)-**2** and (±)-**4** were reduced catalytically under H_2 or in the presence of cyclohexene as a hydrogen donor to cyclooctanes (±)-**5** and (±)-**7**, respectively. It is important to note that the synthesis starting from cyclooctadiene is more economical as compared to that starting from cyclooctene.

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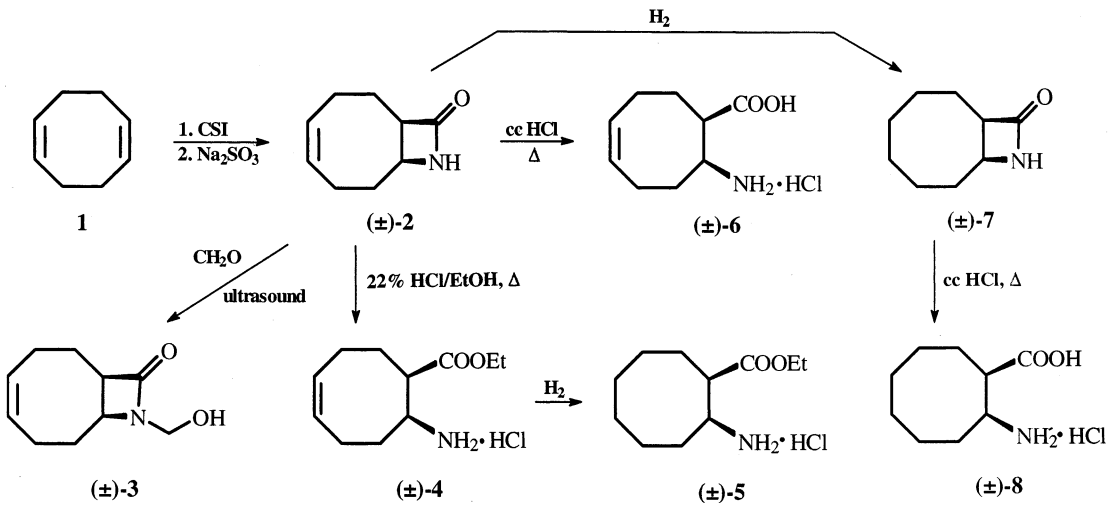
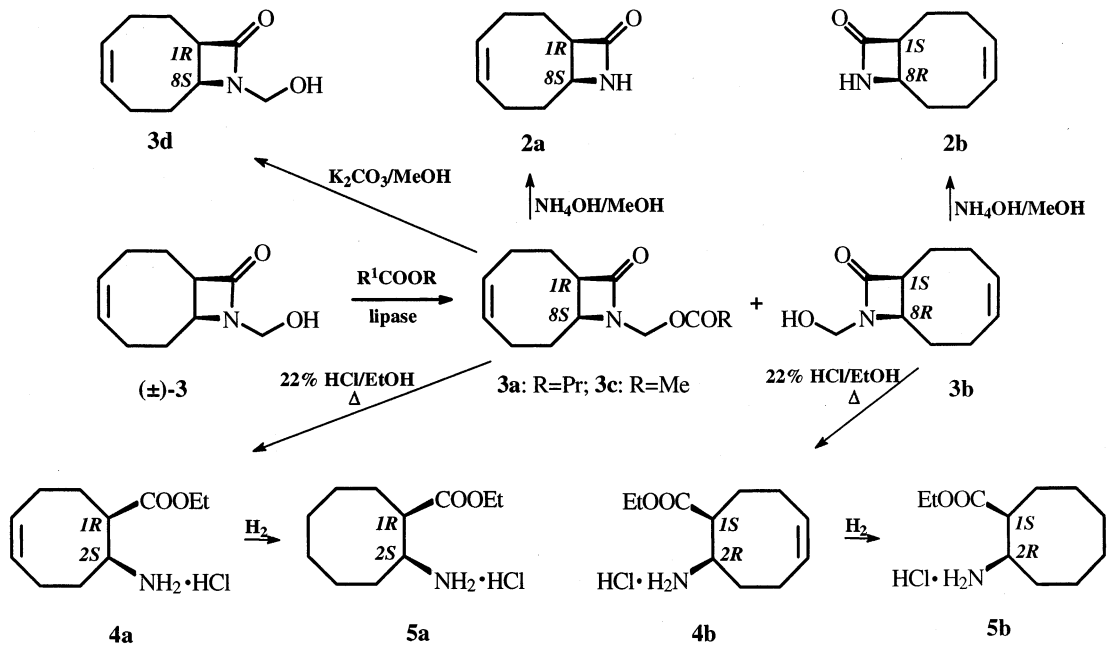


Scheme 1.

2.2. Enzymatic resolution of (±)-3 and transformations of its enantiomers

Lipase PS (*Pseudomonas cepacia*) and lipase AK (*Pseudomonas fluorescens*) are the enzymes most commonly used in the resolution of primary alcohols.[16,17] In previous studies, both lipase PS and lipase AK proved to be applicable for the asymmetric acylation of monocyclic and bicyclic *N*-hydroxymethylated β-lactams.[18–22] In the lipase AK-catalysed acylation of *N*-hydroxymethyl-6-azabicyclo[3.2.0]heptan-7-one, using vinyl butyrate in acetone, the occurrence of the reverse enzymatic reaction was observed, resulting in a considerable decrease in enantioselectivity ($E=90$).[20] Successful gram-scale resolutions of some recently investigated related substrates (*N*-hydroxymethyl-7-azabicyclo[4.2.0]octan-8-one, -7-azabicyclo[4.2.0]oct-3-en-8-one and -7-azabicyclo[4.2.0]oct-4-en-8-one), based on asymmetric acylation, were performed in acetone by using lipase PS as catalyst and vinyl butyrate as the acyl donor ($E>200$).[21] High selectivities ($E>200$) were observed for the lipase PS- or lipase AK-catalysed asymmetric acylation of 3,4-benzo-6-hydroxymethyl-6-azabicyclo[3.2.0]heptan-7-one.[22] These previous results in the enzymatic resolution of alicyclic β-lactams suggested the possibility of selective *N*-acylation of (±)-**3** (Scheme 2).

The lipase PS- and lipase AK-catalysed butyrylations of (±)-**3** in acetone at 25°C did not lead to the same high *E* values as those observed earlier for the six-membered analogues[21] and at conversions around 50% or higher, they tended to drop dramatically (Table 1, rows 1 and



Scheme 2.

Table 1. Effects of solvent, acyl donor (0.1 M), enzyme (30 mg mL^{-1}) and temperature on the enantioselectivity in acylation of (±)-**3**

Row	Enzyme	Acyl donor	Solvent	Reaction time (h)	e.e.$_s$ (%)	e.e.$_p$ (%)	Conv. (%)
1	Lipase PS[a]	VB	Acetone[b]	7	81	83	49
2	Lipase PS[a]	VB	Di-*iso*-propyl ether[b]	0.75	88	71	55
3	Lipase PS[a]	VB	Di-*iso*-propyl ether[b]	0.25	78	94	45
			Et_3N	0.75	93	83	53
4	Lipase PS[a]	VB	Acetonitrile[b]	72	8	80	9
5	Lipase PS[a]	VB	Chloroform[b]	72	*rac*		
6	Lipase PS[a]	VB	Toluene[b]	1	92	91	50
				3	88	43	67
7	Lipase PS[a]	VA	Acetone[b]	2.7	73	77	49
8	Lipase PS[a]	VA	Di-*iso*-propyl ether[b]	0.25	74	91	45
				0.75	89	74	55
9	Lipase PS[a]	VA	Di-*iso*-propyl ether Et_3N[b]	0.75	92	86	52
10	Lipase PS[a]	VA	Di-*iso*-propyl ether[c]	1	89	91	49
				1.5	91	84	52
11	Lipase PS[a]	VA	Di-*iso*-propyl ether[d]	1	88	94	48
				2.5	95	93	51
12	Lipase PS[a]	VA	Tetrahydrofuran[b]	0.5	36	61	37
				1	62	58	52
13	Lipase PS[a]	Vpr	Di-*iso*-propyl ether[b]	0.25	72	90	44
				0.75	89	69	56
14	Lipase PS[a]	Vpiv	Di-*iso*-propyl ether[b]	53	71	82	46
				96	94	62	60
15	Lipase PS[a]	IA	Di-*iso*-propyl ether[b]	2.25	64	88	42
				4	82	55	60
16	Novozym 435	VB	Acetone[b]	0.25	30	33	48
17	Novozym 435	VB	Di-*iso*-propyl ether[b]	0.25	50	32	61
18	Lipase AK[a]	VB	Acetone[b]	2.5	36	84	30
19	Lipase AK[a]	VB	Di-*iso*-propyl ether[b]	0.25	66	84	44
				0.75	87	50	64
20	CAL-A[a]	VB	Acetone[b]	48	*rac*		
21	CAL-A[a]	VB	Di-*iso*-propyl ether[b]	1.7	37	38	49
22	PPL	VB	Di-*iso*-propyl ether[b]	1.5	23	61	28
23	Lipolase[a]	VB	Acetone[b]	48	*rac*		
24	Lipolase[a]	VB	Di-*iso*-propyl ether[b]	0.25	41	61	40
				0.75	60	41	59

[a] Contains 20% (w/w) lipase adsorbed on Celite in the presence of sucrose.
[b] 25°C.
[c] 0°C.
[d] –15°C.
VA, vinyl acetate; VB, vinyl butyrate; Vpr, vinyl propionate; Vpiv, vinyl pivalate; and IA, *iso*-propenyl acetate.

18). Accordingly, preliminary experiments were needed to find the optimal conditions for gram-scale resolution. The effects of enzyme, acyl donor, solvent and temperature on the enantioselectivity were investigated (Table 1).

Initially, we examined the butyrylation reactions with vinyl butyrate in acetone and di-*iso*-propyl ether at 25°C in the presence of various commercially available lipases, including Novozym 435 (lipase from *Candida antarctica* B), CAL-A (lipase from *Candida antarctica* A), PPL (porcine pancreatic lipase) and Lipolase (*Thermomices lanuginosus*). These lipases did not exhibit higher selectivity than lipase PS; probably the reverse enzymatic reaction yielded the products **3a** and **3b** with enantiopurities that decreased rapidly with time. Acylation was not observed even after 24 h. It is notable that Lipolase, a lipase for fat hydrolyses, catalysed the butyrylation of (±)-**3** in di-*iso*-propyl ether at higher *E* (Table 1, row 24) than did Novozym, which is more frequently used for the esterification of primary and secondary alcohols (Table 1, row 17).[16,17]

In an attempt to enhance the enantioselectivity, vinyl butyrate was replaced by other vinyl esters (vinyl acetate, vinyl propionate, vinyl pivalate and *iso*-propenyl acetate). The acylation reactions performed in di-*iso*-propyl ether at 25°C did not stop at 50% conversion. Nearly the same *E* values were observed around 50% conversion for the reactions and the e.e. values for products **3a** and **3b** then began to drop dramatically in all cases (Fig. 1). It was demonstrated earlier that in transesterification reactions the water adsorbed on the enzyme preparation can serve as a nucleophile, leading to ester hydrolysis and considerably reducing the enantioselectivity of the reaction.[20] To demonstrate the occurrence of ester hydrolysis, racemic butyrate was left in di-*iso*-propyl ether in the presence of lipase PS,

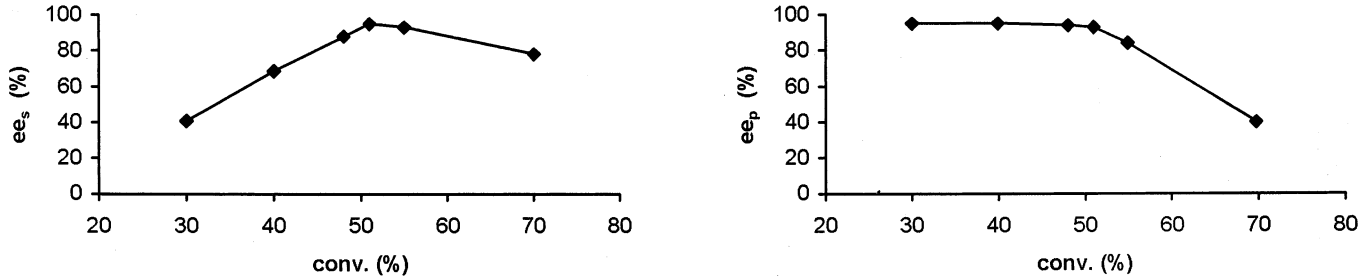


Fig. 1. Experimental e.e. values vs conversion for lipase PS-catalysed butyrylation of (±)-**3** in di-*iso*-propyl ether at −15°C.

without any added nucleophile except for the water adsorbed on the enzyme. The ester was found to be reacted to alcohol (21% conversion in 15 min, 79% conversion in 1.5 h; $E \sim 2$).

It is known that the nature of the solvent usually influences the enantioselectivity of enzymatic reactions. Ethereal solutions are generally preferable for work with lipase PS.[17,23] In order to find a solvent where the enzymatic hydrolysis of the ester is minimised and where the enzymatic acylation proceeds with high enantioselectivity, several solvents were examined for the lipase PS-catalysed acylation of (±)-**3**. Of the solvents used (acetone, di-*iso*-propyl ether, acetonitrile, chloroform, tetrahydrofuran and toluene at 25°C) the enzyme was practically inactive in chloroform (Table 1, entry 5), and with acetonitrile the reaction time was extremely long (Table 1, entry 4). Low enantioselectivity was observed with tetrahydrofuran solvent (Table 1, entry 12). Di-*iso*-propyl ether and toluene gave the best results (Table 1, entries 2, 6 and 8) with e.e.s of 74–89% with di-*iso*-propyl ether and 88–92% in the reactions with toluene solvent. When a few drops of Et_3N was added to di-*iso*-propyl ether solvated reactions, the *E* value was increased slightly at conversions close to 50% (Table 1, entries 3 and 9).

Manipulation of the enantioselectivity by decreasing the reaction temperature of the enzyme-catalysed acylation proved possible (Table 1, entries 8, 10 and 11). The *E* value for the lipase PS-catalysed acetylation with vinyl acetate in di-*iso*-propyl ether was clearly enhanced when the reaction was conducted at −15°C ($E_{\text{apparent}} =$ 102 at 51% conversion).

On the basis of the above results, the gram-scale resolution of (±)-**3** was performed in di-*iso*-propyl ether with lipase PS catalyst and vinyl acetate or vinyl butyrate as acyl donor at −15°C. The results are presented in Table 2 and in the experimental section.

Treatment of **3a** and **3b** with NH_4OH/MeOH afforded **2a** and **2b**, potential starting compounds for enantiopure anatoxin-*a* synthesis. The ester **3a** was transformed with K_2CO_3/MeOH to alcohol **3d**, the antipode of **3b**, obtained from the enzymatic reaction. Transformations of **3a** and **3b** by ring opening with HCl/EtOH followed by catalytic reduction resulted in enantiomers of β-amino acid esters **4a**, **4b**, **5a** and **5b** (Scheme 2). The physical data on the enantiomers prepared are reported in Table 2.

2.3. Absolute configurations

The analysed chromatograms indicated the same enantiopreference in the reactions of all of the lipases examined. With lipase PS catalysis, the corresponding enantiomers of (±)-**3** react similarly as in the case of the homologue 7-hydroxymethyl-7-azabicyclo[4.2.0]oct-3-en-8-one.[21] The lipase-catalysed acylations of (±)-**3** occurred at the (*S*)-stereocentre. Thus, the (1*R*,8*S*)-configuration is accepted for the resulting ester **3a**, and the (1*S*,8*R*)-configuration is assigned to the unreacted alcohol **3b**.

3. Experimental

3.1. Materials and methods

Vinyl acetate and butyrate were purchased from Fluka, vinyl propionate, pivalate and *iso*-propenyl acetate from Aldrich Co., lipase PS and lipase AK from Amano Pharmaceuticals, PPL (type II) from Sigma, and CAL-A, Lipolase and Novozym 435 (as an immobilised preparation) from Novo Nordisk. Before use lipase PS, lipase AK, CAL-A and Lipolase (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.

Table 2. Physical data on enantiomers prepared

Compound	Abs. config.	e.e. (%)	$[\alpha]_D^{20}$
2a	(1*R*,8*S*)	93	+19.8 (c=0.35, MeOH)
2b	(1*S*,8*R*)	99	−20.2 (c=0.35, MeOH)
3a	(1*R*,8*S*)	92	−29.5 (c=1, MeOH)
3b	(1*S*,8*R*)	97	−27.0 (c=1, MeOH)
3c	(1*R*,8*S*)	83	−27.9 (c=1, MeOH)
3d	(1*R*,8*S*)	90	+24.7 (c=1, MeOH)
4a	(1*R*,2*S*)	81	−1.5 (c=1, EtOH)
4b	(1*S*,2*R*)	98	+1.8 (c=1, EtOH)
5a	(1*R*,2*S*)	86	+6.3 (c=0.5, EtOH)
5b	(1*S*,2*R*)	97	−7.0 (c=0.5, EtOH)

In a typical small-scale experiment, racemic **3** (0.1 M solution) in an organic solvent (3 mL) was added to the lipase tested (30 mg mL^{-1}). A vinyl ester (0.2 M in the reaction mixture) was added. The mixture was shaken continuously at −15, 0 or 25°C. The progress of the reaction was followed by taking samples from the reaction mixture at intervals and analysing them by gas chromatography. The e.e. values of the unreacted alcohol **3b** and the ester enantiomers **3a** or **3c** produced were determined by gas chromatography on a Chrompack CP-Chirasil-DEX CB column (25 m). Amino esters **4a**, **4b**, **5a** and **5b** were derivatised with hexanoic anhydride in the presence of 4-dimethylaminopyridine and pyridine before gas chromatographic analysis on a Chirasil-*L*-Val column (25 m).

Specific 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. Racemic 9-azabicyclo[6.2.0]dec-4-en-10-one (±)-2

1,5-Cyclooctadiene (24.5 mL, 0.2 mol), anhydrous Na_2CO_3 (3.2 g, 0.08 mol) and CH_2Cl_2 (15 mL) were added to a flask equipped with an argon inlet adaptor and cooled to 0°C. Chlorosulfonyl isocyanate (17 mL, 0.2 mol) was added dropwise to the stirred reaction mixture over 15 min. After stirring at 0°C for a further 2 h, the mixture was allowed to warm to room temperature overnight. The resulting liquid was diluted with CH_2Cl_2 (25 mL) and then added dropwise to a vigorously stirred two-phased mixture of Na_2SO_3 (73 g) and Na_2HPO_4 (82 g) in H_2O (400 mL) underlaid with $CHCl_3$ (300 mL). The organic layer was separated and the aqueous phase was extracted with chloroform. The combined organic layers were dried (Na_2SO_4) and, after filtration, concentrated. The resulting white solid, racemic **2** (7.5 g, 24%), was recrystallised from di-*iso*-propyl ether/acetone mp 109–113°C (lit.[10] 112–113°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.91–2.09 and 2.37–2.42 (8H, m, 4×CH_2), 3.28–3.29 (1H, m, H-1), 3.82–3.85 (1H, m, H-8), 5.68–5.70 (2H, m, C*H*C*H*), 6.01 (1H, bs, NH). Anal. calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.23; H, 8.59; N, 9.28%.

3.3. Racemic ethyl *cis*-2-aminocyclooct-5-enecarboxylate hydrochloride (±)-4

β-Lactam (±)-**2** (2 g, 13.22 mmol) was stirred under reflux in ethanol (25 mL) containing 22% dry hydrogen chloride for 10 h. The solvent was completely evaporated and the resulting white crystals of (±)-**4** were recrystallised from *n*-hexane/ethyl acetate (1.3 g, 42%); mp 112–117°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.30–1.33 (3H, t, J=7.1, CH_3), 1.78–2.66 (8H, m, 4×CH_2), 3.21–3.23 (1H, m, H-1), 3.77–3.78 (1H, m, H-2), 4.25–4.30 (2H, m, CH_2CH$_3$), 5.57–5.76 (2H, m, C*H*C*H*), 8.42 (3H, bs, N^+H_3). Anal. calcd for $C_{11}H_{20}ClNO_2$: C, 56.53; H, 8.62; N, 5.99. Found: C, 56.39; H, 8.68; N, 5.87%.

3.4. Racemic ethyl *cis*-2-aminocyclooctanecarboxylate hydrochloride (±)-5

Palladium-on-carbon (0.1 g) was added to ethyl *cis*-2-aminocyclooct-5-enecarboxylate hydrochloride **4** (0.5 g, 2.14 mmol) dissolved in methanol (20 mL) under a H_2 atmosphere. After stirring for 3 h, the catalyst was filtered off and the filtrate evaporated to dryness. The resulting white crystalline product was recrystallised from di-*iso*-propyl ether (0.29 g, 58%); mp 91–94°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.27–1.31 (3H, t, J=7.1, CH_3), 1.57–2.24 (12H, m, 6×CH_2), 3.13–3.15 (1H, m, H-1), 3.73–3.75 (1H, m, H-2), 4.23–4.24 (2H, m, CH_2CH$_3$), 8.41 (3H, bs, N^+H_3). Anal. calcd for $C_{11}H_{22}ClNO_2$: C, 56.04; H, 9.41; N, 5.94. Found: C, 56.13; H, 9.46; N, 5.90%.

3.5. (±)-*cis*-2-Aminocyclooct-5-enecarboxylic acid hydrochloride (±)-6

The β-Lactam (±)-**2** (0.5 g, 3.3 mmol) was dissolved in cc HCl (6 mL) and stirred under reflux for 2 h at 70°C. The solvent was evaporated off and the residue was recrystallised from methanol/acetone affording white crystals of (±)-**6** (0.3 g, 44%); mp 218–220°C; ^{1}H NMR (400 MHz, D_2O) δ (ppm): 1.80–2.52 (8H, m, 4×CH_2), 3.06–3.09 (1H, m, H-1), 3.80–3.89 (1H, m, H-2), 5.69–5.79 (2H, m, C*H*C*H*). Anal. calcd for $C_9H_{16}ClNO_2$: C, 52.56; H, 7.84; N, 6.81. Found: C, 52.51; H, 7.84; N, 6.78%.

3.6. Racemic 9-azabicyclo[6.2.0]decan-10-one (±)-7

Palladium-on-carbon (0.3 g) was added to (±)-9-azabicyclo[6.2.0]dec-4-en-10-one **2** (0.5 g, 3.3 mmol) dissolved in a mixture of MeOH (20 mL) and cyclohexene (4 mL). The mixture was refluxed for 4 h and the catalyst was then filtered off. After evaporation, the white crystalline product was recrystallised from *n*-hexane (0.24 g, 47%; mp 71–73°C), lit.[24] mp 71–72°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.29–2.09 (12H, m, 6×CH_2), 3.02–3.06 (1H, m, H-1), 3.63–3.68 (1H, m, H-8), 5.89 (1H, bs, NH). Anal. calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.28; H, 9.88; N, 9.17%.

3.7. Racemic *cis*-2-aminocyclooctanecarboxylic acid hydrochloride (±)-8

β-Lactam (±)-**7** (0.5 g, 3.26 mmol) was dissolved in cc HCl (6 mL) with gently warming for 2 h. The solvent was evaporated off and the residue was recrystallised from H_2O/acetone, affording white crystals of (±)-**8** (0.28 g, 41%); mp 214–216°C; ^{1}H NMR (400 MHz, D_2O) δ (ppm): 1.52–1.97 (12H, m, 6×CH_2), 3.06–3.10 (1H, m, H-1), 3.77–3.81 (1H, m, H-2). Anal. calcd for $C_9H_{18}ClNO_2$: C, 52.05; H, 8.74; N, 6.74. Found: C, 52.11; H, 8.59; N, 6.71%.

3.8. Racemic 9-hydroxymethyl-9-azabicyclo[6.2.0]dec-4-en-10-one (±)-3

9-Azabicyclo[6.2.0]dec-4-en-10-one (±)-**2** (4 g, 26.45 mmol) was dissolved in THF (35 mL). Paraformaldehyde (0.8 g, 26.6 mmol), K_2CO_3 (0.22 g, 1.59 mmol) and H_2O (1.5 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 recrystallised from di-*iso*-propyl ether to afford a white crystalline product, (±)-**3** (3 g, 62%); mp 96–97°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.86–2.21 and 2.36–2.43 (8H, m, 4×CH_2), 3.26–3.30 (1H, m, H-1), 3.70 (1H, bs, OH), 3.93–3.97 (1H, m, H-8), 4.45–4.48 (1H, d, CH_2OH, J=11.6), 4.74–4.77 (1H, d, CH_2OH, J=11.6), 5.66–5.71 (2H, m, C*H*C*H*). Anal. calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.19; H, 8.33; N, 7.70%.

3.9. Gram-scale resolution of racemic 9-hydroxymethyl-9-azabicyclo[6.2.0]dec-4-en-10-one (±)-3

Racemic **3** (1.5 g, 8.27 mmol), vinyl acetate (1.53 mL, 16.56 mmol), Et_3N (a few drops) and Na_2SO_4 (0.3 g) in di-*iso*-propyl ether (100 mL) were added to lipase PS (3 g, 30 mg mL^{-1}) and the mixture was shaken at −15°C for 3 h, the enzyme was filtered off at 53% conversion (e.e.-**3b**=95%, e.e.-**3c**=83%). Di-isopropyl ether was evaporated. The residue was chromatographed on silica, eluting with ethyl acetate; this afforded unreacted (1*S*,8*R*)-**3b** [0.5 g, 34%; $[\alpha]_D^{25}$ =−27.0 (c=1, MeOH); mp 48–49°C (recrystallised from di-*iso*-propyl ether); e.e.=97%] and the ester (1*R*,8*S*)-**3c** (0.81 g, 44%; $[\alpha]_D^{25}$=−27.9 (c=1, MeOH); e.e.=83%) as a pale-yellow oil. The gram-scale resolution of (±)-**3** (1.5 g) was repeated with vinyl butyrate (1.89 mL, 16.56 mmol) instead of vinyl acetate. Intense shaking (4 h) of the mixture (conversion 51%) afforded the unreacted (1*S*,8*R*)-**3b** (e.e.=96%) and the ester (1*R*,8*S*)-**3a** (e.e.=92%). The column chromatographic separation on silica, eluting with ethyl acetate, furnished **3b** (0.46 g, 31%; e.e.=97%) and **3a** (0.9 g, 43%; $[\alpha]_D^{25}$=−29.5 (c=1, MeOH); e.e.=92%) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **3a**: 0.93–0.97 (3H, t, J=7.6, CH_3), 1.62–1.68 (2H, m, $CH_2CH_2CH_3$), 1.81–2.42 (10H, m, $CH_2CH_2CH_3$ and 4×CH_2 from ring), 3.29–3.32 (1H, m, H-1), 3.84–3.88 (1H, m, H-8), 5.04–5.06 (1H, d, CH_2OCOPr, J=11.2), 5.12–5.15 (1H, d, CH_2OCOPr, J=11.2), 5.68–5.70 (2H, m, C*H*C*H*). Anal. calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.13; H, 8.53; N, 5.51.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **3b**: similar to that for (±)-**3**. Anal. calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.39; H, 8.24; N, 7.73%.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **3c**: 1.83–2.26 and 2.37–2.43 (8H, m, 4×CH_2), 2.09 (3H, bs, CH_3), 3.30–3.34 (1H, m, H-1), 3.84–3.89 (1H, m, H-8), 5.02–5.05 (1H, d, CH_2OCOMe, J=11.3), 5.12–5.15 (1H, d, CH_2OCOMe, J=11.3), 5.67–5.71 (2H, m, C*H*C*H*). Anal. calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.33; H, 7.64; N, 6.31%.

3.10. Methanolysis of 3a to the corresponding alcohol enantiomer 3d

A mixture of **3a** (0.13 g, 0.52 mmol) and K_2CO_3 (0.17 g, 1.2 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 (3×30 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated. The product (1*R*,8*S*)-**3d** was obtained as a slowly crystallising oil (0.06 g, 63%; $[\alpha]_D^{25}$=+24.7 (c=1, MeOH); e.e.=90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **3d**: similar to that for (±)-**3**. Anal. calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.20; H, 8.25; N, 7.75%.

3.11. (1*R*,8*S*)- and (1*S*,8*R*)-9-Azabicyclo[6.2.0]dec-4-en-10-one 2a and 2b

The ester (1*R*,8*S*)-**3a** (0.2 g, 0.79 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 afforded white crystals of (1*R*,8*S*)-**2a** [0.08 g, 65%; $[\alpha]_D^{25}$=+19.8 (c=0.35, MeOH); mp 117–119°C (recrystallised from di-*iso*-propyl ether); e.e.=93%].

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **2a**: similar to that for (±)-**2**. Anal. calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26; found: C, 71.31; H, 8.62; N, 9.26%.

Similarly, (1*S*,8*R*)-**3b** (0.2 g, 1.1 mmol) afforded white crystals of (1*S*,8*R*)-**2b** [0.12 g, 72%; $[\alpha]_D^{25}$=−20.2 (c=0.35, MeOH); mp 122–123°C (recrystallised from di-*iso*-propyl ether); e.e.=99%].

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **2b**: similar to that for (±)-**2**. Anal. calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.43; H, 8.69; N, 9.30%.

3.12. Ethyl (1*R*,2*S*)- and (1*S*,2*R*)-2-aminocyclooct-5-enecarboxylate hydrochloride 4a and 4b

The ester (1*R*,8*S*)-**3a** (0.2 g, 0.79 mmol) was dissolved in 22% HCl/EtOH (10 mL) and refluxed for 5 h at 70°C. The solvent was evaporated off and the product, (1*R*,2*S*)-**4a**, was obtained as a pale-yellow oil (0.08 g, 43%; $[\alpha]_D^{25}$=−1.5 (c=1, EtOH); e.e.=81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **4a**: similar to that for (±)-**4**. Anal. calcd for $C_{11}H_{20}ClNO_2$: C, 56.53; H, 8.62; N, 5.99. Found: C, 56.50; H, 8.72; N, 5.99%.

Similarly, (1*S*,8*R*)-**3b** (0.2 g, 1.1 mmol) afforded (1*S*,2*R*)-**4b** as a pale-yellow oil (0.11 g, 43%; $[\alpha]_D^{25}$=+1.8 (c=1, EtOH); e.e.=98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **4b**: similar to that for (±)-**4**. Anal. calcd for $C_{11}H_{20}ClNO_2$: C, 56.53; H, 8.62; N, 5.99. Found: C, 56.41; H, 8.61; N, 6.09.

3.13. Ethyl (1*R*,2*S*)- and (1*S*,2*R*)-2-aminocyclooctanecarboxylate hydrochloride 5a and 5b

With the method described in Section 3.4, the ester (1*R*,8*S*)-**4a** (0.08 g, 0.32 mmol) afforded the product (1*R*,2*S*)-**5a** as white crystals [0.05 g, 62%; $[\alpha]_D^{25}=+6.3$ ($c=0.5$, EtOH); mp 101–105°C (recrystallised from *n*-hexane/ethyl acetate); e.e. = 86%].

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **5a**: similar to that for (±)-**5**. Anal. calcd for $C_{11}H_{22}ClNO_2$: C, 56.04; H, 9.41; N, 5.94. Found: C, 56.31; H, 9.40; N, 5.89.

Similarly, (1*S*,8*R*)-**4b** (0.1 g, 0.43 mmol) afforded (1*S*,2*R*)-**5b** as white crystals [0.06 g, 59%; $[\alpha]_D^{25}=-7.0$ ($c=0.5$, EtOH); mp 111–115°C (recrystallised from *n*-hexane/ethyl acetate); e.e. = 97%].

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **5b**: similar to that for (±)-**5**. Anal. calcd for $C_{11}H_{22}ClNO_2$: C, 56.04; H, 9.41; N, 5.94; found: C, 56.11; H, 9.66; N, 5.94%.

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References

1. Mansell, H. L. *Tetrahedron* **1996**, *52*, 6025.
2. Wonnacott, S.; Kaiser, S.; Mogg, A.; Soliakov, L.; Jones, I. W. *Eur. J. Pharmacol.* **2000**, *393*, 51.
3. Sharples, C. G. V.; Kaiser, S.; Soliakov, L.; Marks, M. J.; Collins, A. C.; Washburn, M.; Wright, E.; Spencer, J. A.; Gallagher, T.; Whiteaker, P.; Wonnacott, S. *J. Neurosci.* **2000**, *20*, 2783.
4. Bumke-Vogt, C.; Mailahn, W.; Chorus, I. *Environ. Toxicol.* **1999**, *14*, 117.
5. Fromme, H.; Kohler, A.; Krause, R.; Fuhrling, D. *Environ. Toxicol.* **2000**, *15*, 120.
6. Durany, N.; Riederer, P.; Deckert, J. *Alzheimers Rep.* **1999**, *2*, 263.
7. Fawell, J. K.; Mitchell, R. E.; Hill, R. E.; Everett, D. J. *Hum. Exp. Toxicol.* **1999**, *18*, 168.
8. Wegge, T.; Schwarz, S.; Seitz, G. *Tetrahedron: Asymmetry* **2000**, *11*, 1405.
9. Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057.
10. Parsons, P. J.; Camp, N. P.; Underwood, J. M.; Harvey, D. M. *J. Chem. Soc., Chem. Commun.* **1995**, 1461; *Tetrahedron* **1996**, *52*, 11637.
11. Parsons, P. J.; Camp, N. P.; Edwards, N.; Sumoreeah, L. R. *Tetrahedron* **2000**, *56*, 309.
12. Aggarwal, V. K.; Humphries, P. S.; Fenwick, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 1985.
13. Porter, E. A.; Wang, X.; Lee, H. S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565.
14. Fülöp, F. In *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed. The Chemistry of 2-Aminocyclopentanecarboxylic Acid. Elsevier Science: New York, 2000; Vol. 22, pp. 273–306.
15. Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1.
16. Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis*; Wiley-VCH Verlag: Weinheim, 1999; pp. 65–107.
17. (a) Forró, E.; Lundell, K.; Fülöp, F.; Kanerva, L. T. *Tetrahedron: Asymmetry* **1997**, *8*, 3095; (b) Forró, E.; Kanerva, L. T.; Fülöp, F. *Tetrahedron: Asymmetry* **1998**, *9*, 513; (c) Forró, E.; Fülöp, F. *Tetrahedron: Asymmetry* **1999**, *10*, 1985; (d) Forró, E.; Szakonyi, Z.; Fülöp, F. *Tetrahedron: Asymmetry* **1999**, *10*, 4619.
18. Nagai, H.; Shiozawa, T.; Achiwa, K.; Terao, Y. *Chem. Pharm. Bull.* **1993**, *41*, 1933.
19. Hongo, H.; Iwasa, K.; Kabuto, C.; Matsuzaki, H.; Nakano, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1747.
20. Csomós, P.; Kanerva, L. T.; Bernáth, G.; Fülöp, F. *Tetrahedron: Asymmetry* **1996**, *7*, 1789.
21. Kámán, J.; Forró, E.; Fülöp, F. *Tetrahedron: Asymmetry* **2000**, *11*, 1593.
22. Fülöp, F.; Palkó, M.; Kámán, J.; Lázár, L.; Sillanpää, R. *Tetrahedron: Asymmetry* **2000**, *11*, 4179.
23. Kanerva, L. T.; Csomós, P.; Sundholm, O.; Bernáth, G.; Fülöp, F. *Tetrahedron: Asymmetry* **1996**, *7*, 1705.
24. Hoechst, A. G. NL 6504300 (*Chem. Abstr.* **1966**, *64*, 8134c); Bestian, H.; Biener, H.; Clauss, K.; Heyn, H. *Liebigs Ann. Chem.* **1968**, *718*, 94.