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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 19 (2008) 1114–1119

Lipase-catalysed N-acylation of β²-amino esters

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Received 19 March 2008; accepted 1 April 2008

Dedicated to Professor Gábor Bernáth on the occasion of his 75th birthday

Abstract—The *Candida antarctica* lipase A-catalysed N-acylation of ethyl 3-amino-2-ethylpropanoate *rac*-**3** and methyl 3-amino-2-isopropylpropanoate *rac*-**6** was performed with ethyl butanoate in *tert*-amyl alcohol at 4 °C. The resulting enantiomerically enriched derivatives were isolated as *N*-Boc-protected amino esters (*R*)-**9** and (*R*)-**10** and butyramides (*S*)-**7** and (*S*)-**8** (ee: 76–95%).

1. Introduction

Cyclic[1] and acyclic[2–5] β-amino acids are of key importance in the organic chemistry. These are the constituents of both naturally occurring and synthetic derivatives with valuable physiological effects,[6] for example, taxoids.[4,7] β-Peptides and α-peptides containing β-amino acids are not degradable by proteases, and may lead to protease inhibitors, which are currently important targets in pharmaceutical chemistry.[6] The folding properties and three-dimensional structures of β-peptides have already been explored,[3,8–10] while interest has recently turned to the preparation of enantiomerically pure β-amino acids and their derivatives;[1,11] many different methods have been described for the preparation of β²-amino acid enantiomers.[12–16]

Lipase-catalysed kinetic resolution has proven to be an excellent method for the preparation of β³- and β²,³-amino acid enantiomers, for which, unlike the β² derivatives, low enantioselectivities were described.[17] Enzymes can catalyse the transformations on both functional groups of amino esters: N-acylation[18–20] of the amino group, and ester hydrolysis[21] of the ester function. As far as we are aware, only three enzymatic resolutions of β²-amino esters have been reported.[22–24] *N*-Phenylacetylated α-methyl-β-alanine has been successfully hydrolysed with penicillin G amidase.[22] The enantiomers of α-methyl-β-alanine ethyl ester have been prepared through a two-step sequential resolution (N-acylation and interesterification) catalysed by CAL-A and CAL-B, respectively.[23] Various hydrolytic enzymes have been applied for the resolution of β²-amino acid esters, resulting in enantiomerically enriched β²-amino acids and esters.[24]

Herein, we report an N-acylation-based enzymatic resolution method for the preparation of 2-ethyl- and 2-isopropyl-3-aminopropanoic acid enantiomers.

2. Results and discussion

2.1. Syntheses of racemic β²-amino esters 3 and 6

Model racemic compounds were synthesised by a combination of literature procedures for the preparation of analogous α-substituted β-amino esters.[20,25,26] The addition of benzylamine to ethyl ethacrylate[27] **1** furnished the corresponding *N*-benzylamino ester **2**, which was transformed to ethyl 3-amino-2-ethylpropanoate *rac*-**3** by catalytic hydrogenolysis. The condensation of methyl cyanoacetate **4** and acetone under reductive conditions resulted in the isopropyl-substituted malononitrile derivative **5**,[28] the cyano group of which was reduced by catalytic hydrogenation to yield methyl 3-amino-2-isopropylpropanoate *rac*-**6** (Scheme 1).

2.2. Lipase-catalysed enantioselective N-acylation of (±)-3 and (±)-6

Enzyme screening was first performed on model compound (±)-**3**. Ethyl 3-amino-2-ethylpropanoate was subjected to

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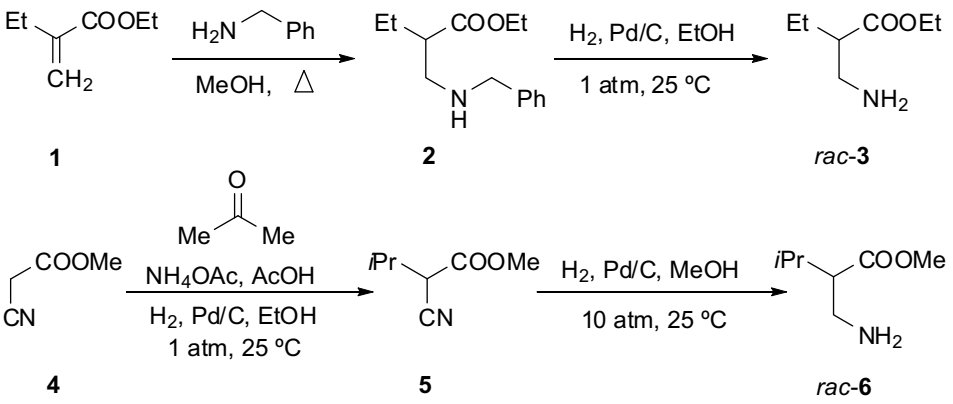
doi:10.1016/j.tetasy.2008.04.002



Scheme 1.

an enzyme-catalysed reaction in iPr$_2$O (0.05 M solution) by the addition of vinyl acetate (2 equiv) in the presence of different lipase preparations (50 mg/mL) at 25 °C. The lipases tested were CAL-A, CAL-B (Lipolase), and lipases AY, AK, PS and PPL. CAL-A and CAL-B were previously used in the resolution of α-methyl-β-alanine ethyl ester[23] and β-substituted analogues;[19,29] CAL-B also catalyses N-acylation and interesterification. Our preliminary experiments indicated that the CAL-B-catalysed reaction led rapidly to multiple products, while the enantiomeric excess of the substrate remained low. During the enzyme screening, the enantioselectivities were under 2 in all the cases (conversions between 43% and 58%), except for CAL-A, which displayed a slightly higher enantioselectivity ($E = 4$), and accordingly was chosen for further optimisation.

In order to find a more appropriate acyl donor for the CAL-A-catalysed (50 mg/mL) resolution, six achiral esters (ethyl butanoate, butyl butanoate, vinyl butanoate, 2,2,2-trifluoroethyl butanoate, vinyl acetate and 2,2,2-trifluoroethyl chloroacetate) were tested. The reactions were started in a 0.05 M iPr$_2$O solution of (±)-**3** at room temperature (25 °C) by the addition of 0.55 or 1 equiv of an acyl donor. The selectivities were low (E up to 6); the most promising E values were obtained when using butanoates. As a result of the low E values, new reactions were started at 4 °C (cold room) using 0.55 equiv of ethyl butanoate and 2,2,2-trifluoroethyl butanoate. The results led us to continue our studies with ethyl butanoate.

Table 1. CAL-A-catalysed (25 mg/mL) N-acylation of (±)-**3** (0.05 M) with ethyl butanoate (0.55 equiv) in different solvents at 4 °C

Solvent	Time (day)	ee$_s$[a] (%)	ee$_p$[b] (%)	Conv. (%)	E
MeCN	25	45	>99	26	>200
tert-AmOH	25	68	>99	40	>200
DCM	25	4	40	9	2
THF	25	8.7	45	16	2.9
Et$_2$O	3	14	24	37	2
iPr$_2$O	10	52	58	47	6

[a] According to GC after derivatisation with trifluoroacetic anhydride in the presence of 4-dimethylaminopyridine and pyridine.
[b] Calculated by using an internal standard (octadecane).

We next optimised the solvent, with reactions in MeCN, *tert*-amyl alcohol (*tert*-AmOH), DCM, THF, Et$_2$O and iPr$_2$O, the most commonly used organic solvents for lipase-catalysed resolutions (Table 1). The reactions were highly enantioselective ($E > 200$), but extremely slow in polar solvents (MeCN and *tert*-amyl alcohol). The other solvents proved to be useless due to their low selectivity.

In an attempt to shorten the reaction time, a higher reaction temperature and an increased amount of enzyme were applied. At 25 °C, the selectivity of the reaction was lowered dramatically, both in *tert*-amyl alcohol and in MeCN. An increased amount of enzyme (50 mg/mL) accelerated the reaction while E decreased (Table 2).

Table 2. Effects of temperature and enzyme amount on CAL-A-catalysed resolution of (±)-**3**[a]

Temperature (°C)	Solvent	Enzyme amount (mg/mL)	Time (day)	ee$_s$[b] (%)	ee$_p$[c] (%)	Conv. (%)	E
4	MeCN	25	25	45	>99	26	>200
	tert-Amyl alcohol	25	25	68	>99	40	>200
		50	14	80	93	46	63
25	MeCN	25	21	30	67	32	17
	tert-Amyl alcohol	25	7	50	83	37	18
		50	3	49	77	39	12

[a] 0.05 M substrate, ethyl butanoate (0.55 equiv).
[b] According to GC after derivatisation with trifluoroacetic anhydride in the presence of 4-dimethylaminopyridine and pyridine.
[c] Calculated by using an internal standard (octadecane).

Another possibility to enhance the reaction rate is the use of various additives, which can also change the selectivity of lipase-catalysed reactions, especially in the case of lipase PS.[30–32] Selected additives ($CuCl_2$ 0.1 equiv; TEA 0.1 equiv; and 15-Crown-5, 0.33 equiv) were tested with lipase PS (25 mg/mL) under the above-described conditions in *tert*-amyl alcohol at 4 °C. However, both the reaction rate and the selectivity were low in all the cases (31–61% conversion after 10–28 days; *E*: 2–4). The same additives were next used in CAL-A-catalysed (25 mg/mL) reactions, when these lowered not only the selectivity, but also the reaction rate: the reactions reached 36–44% conversion after 35 days, while *E* was between 20 and 74. Unfortunately, LiCl (0.1 equiv) inactivated the CAL-A.

Following the preliminary results, the gram-scale resolutions of (±)-**3** and (±)-**6** were performed in *tert*-amyl alcohol (0.05 M) with 0.55 equiv of ethyl butanoate in the presence of 50 mg/mL CAL-A preparation at 4 °C. The less reactive enantiomers were transformed into their *N*-Boc-protected derivatives (*R*)-**9** and (*R*)-**10**, and separated from butyramides (*S*)-**7** and (*S*)-**8** by column chromatography.

Since the selectivity was relatively low ($E = 9$) in the case of (±)-**6**, the gram-scale reaction was stopped when the product ee was 78%, and the separated enantiomerically enriched substrate (ee = 58%) was then subjected to a second enzymatic reaction under the above conditions. The physical data on the enantiomers prepared are reported in Table 3.

To determine the selectivity of the enzyme, *N*-Boc-protected amino ester **9** was hydrolysed with $LiOH \cdot H_2O$,[33] resulting in 3-*tert*-butoxycarbonylamino-2-ethylpropanoic acid **11**. The specific rotation for **11** was $[\alpha]_D^{25} = -13.2$ (*c* 1.0, CH_2Cl_2); the literature values for (*R*)-**11** {$[\alpha]_D^{26} = -17.3$ (*c* 1.3, MeOH);[33] $[\alpha]_D^{20} = -18.2$ (*c* 1.0, CH_2Cl_2), ee >95%[34]} confirmed the (*S*)-selectivity.

Table 3. Physical data on enantiomers prepared

Compound	Yield (%)[a]	ee (%)	$[\alpha]_D^{25}$
(*S*)-**7**	36	95[b]	+26.0 (*c* 1.0, MeOH)
(*R*)-**9**	25	85[c]	−20.6 (*c* 0.5, MeOH)
(*S*)-**8**	38	78[c]	+26.4 (*c* 1.0, MeOH)
(*R*)-**10**	18	76[c]	−13.4 (*c* 1.0, MeOH)

[a] Maximum yield 50% at 50% conversion.
[b] From a comparison of the specific rotation with that of (*R*)-**7**, synthesised from unreacted (*R*)-**3** with ee = 88%.
[c] Determined by GC.

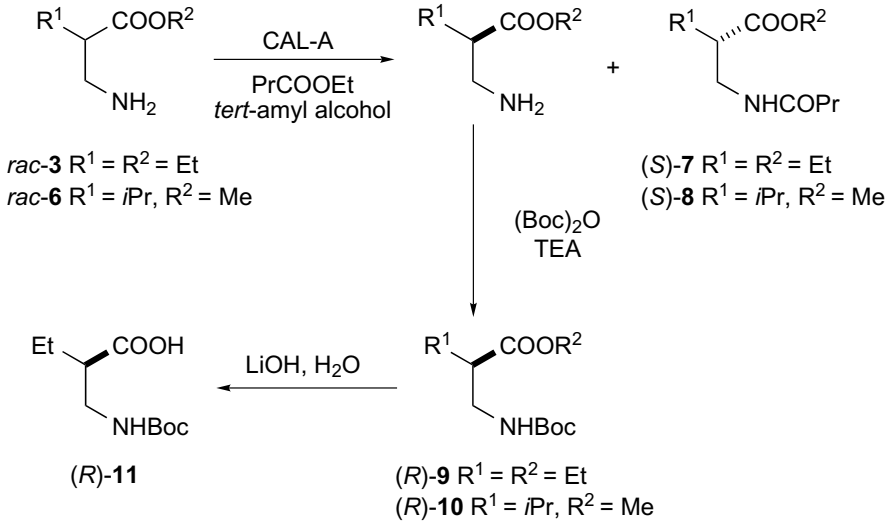
3. Conclusion

In conclusion, ethyl 3-amino-2-ethylpropanoate (±)-**3** and methyl 3-amino-2-isopropylpropanoate (±)-**6** were resolved via *Candida antarctica* lipase-A-catalysed (50 mg/mL) N-acylation in *tert*-amyl alcohol (0.05 M) with 0.55 equiv of ethyl butanoate at 4 °C (Scheme 2). The enzymatic reactions, followed by *N*-Boc protection of the less reactive amino ester enantiomers, led to butyramides (*S*)-**7** and (*S*)-**8** and *N*-Boc-protected amino esters (*R*)-**9** and (*R*)-**10**, which were separated by column chromatography with moderate to good ee values (ee: 76–95%) (Table 3).

4. Experimental

4.1. Materials and methods

CAL-A (*C. antarctica* lipase A, Chirazyme L-5) was purchased from Roche. Lipases AK (*Burkholderia* sp.) and PS (*Burkholderia cepacia*) were from Aldrich. Lipase AY (*Candida rugosa*) was from Amano Pharmaceuticals. CAL-B (from *C. antarctica*, Chyrazime L-2) immobilised on acrylic resin, known by the trade name Lipolase, was from Sigma Aldrich. Before use, CAL-A and lipases PS,



Scheme 2.

AK and AY were adsorbed on Celite in the presence of sucrose.[35] 2,2,2-Trifluoroethyl butanoate, butyl butanoate and 2,2,2-trifluoroethyl chloroacetate were prepared from the corresponding acid chlorides and alcohols. The solvents were of the highest analytical grade. ^{1}H NMR spectra were recorded on a Bruker AM 400 spectrometer. Optical rotations were measured with a Perkin Elmer 341 polarimeter.

4.2. Preparation of ethyl 3-amino-2-ethylpropanoate, (±)-3

A mixture of ethyl ethacrylate (**1**, 9.00 g, 70.2 mmol) and benzylamine (5.00 g, 46.7 mmol) was refluxed in EtOH (7 mL) for 4 h and then allowed to stand at room temperature for 2 days. The solvent was evaporated off and the residue was distilled to give **2** [7.36 g (31.3 mmol, 68%), bp: 120–135 °C (6 mm Hg)] as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.91 (3H, t, $J = 7.4$ Hz, CH_3CH_2CH), 1.26 (3H, t, $J = 7.1$ Hz, OCH_2CH_3), 1.51–1.72 (2H, m, CH_3CH_2CH), 2.53–2.62 (1H, m, CH_3CH_2CH), 2.72 (1H, dd, $J = 4.9$, 11.9 Hz, CH_2NHCH_2-Ph), 2.90 (1H, dd, $J = 8.9$, 11.9 Hz, CH_2NHCH_2Ph), 3.79 (1H, d, $J = 13.4$ Hz, CH_2Ph), 3.85 (1H, d, $J = 13.4$ Hz, CH_2Ph), 4.13–4.19 (2H, m, OCH_2–CH_3), 7.20–7.40 (5H, m, Ar).

A stirred mixture of ethyl 3-benzylamino-2-methylpropanoate (**2**, 11.00 g, 46.7 mmol), abs. EtOH (80 mL) and Pd catalyst (10 wt % on activated charcoal, 1.00 g) was hydrogenated at ambient temperature at atmospheric pressure for 20 h. The catalyst was then filtered off and washed with EtOH. The combined filtrates were evaporated and the residue was purified by distillation to give *rac*-**3** [3.60 g (24.8 mmol, 53%), bp: 85–90 °C (28 mm Hg)] as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.93 (3H, t, $J = 7.5$ Hz, CH_3CH_2CH), 1.27 (3H, t, $J = 7.1$ Hz, OCH_2CH_3), 1.50–1.73 (2H, m, CH_3CH_2CH), 2.36–2.45 (1H, m, CH_3CH_2CH), 2.85 (1H, dd, $J = 4.8$, 12.9 Hz, CH_2NH), 2.96 (1H, dd, $J = 8.4$, 12.9 Hz, CH_2NH), 4.13–4.22 (2H, m, $J = 7.1$ Hz, OCH_2CH_3).

4.3. Preparation of methyl 3-amino-2-isopropylpropanoate, (±)-6

A stirred mixture of methyl cyanoacetate **4** (10.00 g, 100.9 mmol), abs. acetone (8.1 mL, 109.8 mmol), NH_4OAc (0.78 g, 10.0 mmol), glacial AcOH (1.15 mL, 19.7 mmol) and EtOH (20 mL) was hydrogenated at ambient temperature and atmospheric pressure in the presence of Pd catalyst (5 wt % on activated charcoal, 0.40 g) for 5 h. The catalyst was then filtered off and the solvent evaporated off. The crude oily product **5** was purified by distillation [8.72 g (61.8 mmol, 61%), bp: 112–115 °C (28 mm Hg)]. The ^{1}H NMR spectrum of **5** was in accordance with the literature[36] data.

A stirred mixture of methyl 2-cyano-3-methylbutanoate **5** (8.70 g, 0.06 mol), MeOH (60 mL), 36% aqueous HCl (3.15 mL) and Pd catalyst (5 wt % on activated charcoal, 0.50 g) was hydrogenated at ambient temperature at 10 atm for 20 h. The catalyst was then filtered off and washed with MeOH and the filtrate was evaporated. The oily residue was dissolved in water (150 mL) and washed with EtOAc (3 × 30 mL). The aqueous phase was made alkaline with concd NH_3 solution and extracted with EtOAc (3 × 70 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated. The oily residue was converted to the crystalline hydrochloride salt *rac*-**6**·HCl by treatment with 22% ethanolic HCl and Et_2O. Recrystallisation of the crude product from a mixture of MeOH and Et_2O resulted in *rac*-**6**·HCl [1.34 g (7.4 mmol, 15%), mp: 144–145 °C] as colourless crystals. ^{1}H NMR (400 MHz, D_2O): δ (ppm) 0.96 (6H, d, $J = 6.9$ Hz, $(CH_3)_2CH$), 2.13 (1H, m, $(CH_3)_2CH$), 2.73 (1H, m, $(CH_3)_2CHCH$), 3.19 (1H, td, $J = 3.5$, 13.1, CH_2NH), 3.34 (1H, ddd, $J = 1.9$, 10.3, 13.1 Hz, CH_2NH), 3.79 (3H, s, OCH_3).

Amino ester base *rac*-**6** was obtained from the above hydrochloride salt by treatment with NH_3 solution, extraction (EtOAc) and evaporation.

4.4. Small-scale resolutions

In a typical small-scale experiment, the acyl donor (0.1 M) was added to a mixture of racemic amino ester (0.05 M) and enzyme preparation (25 or 50 mg/mL) in an organic solvent (1 mL), and the reaction mixture was then shaken at 4 °C (cold room) or at 25 °C (room temperature). The progress of the reaction and the ee values were determined by taking samples (0.05 mL) at intervals, filtering off the enzyme and analysing them by GC, on a Chrompack CP-Chirasil-DEX CB column (25 m). For a good baseline separation, the unreacted amino group was acylated with acetic or trifluoroacetic anhydride in the presence of pyridine containing 1% 4,4-dimethylaminopyridine.

Since the enantiomers of (±)-**3** could be separated by GC only as the trifluoroacetamide, but not as the *N*-acetyl, *N*-chloroacetyl, *N*-propionyl or *N*-butyryl derivatives, octadecane was used as the internal standard to follow the N-acylation of (±)-**3**.

4.5. Preparative-scale resolution of ethyl 3-amino-2-ethylpropanoate, (±)-3

Racemic **3** (0.80 g, 6.88 mmol) was dissolved in *tert*-amyl alcohol (70 mL). The CAL-A preparation (5.40 g) and ethyl butanoate (0.50 mL, 3.78 mmol) were added in order to start the reaction, with shaking at 4 °C. The reaction mixture was stopped after 42 days, at 52% conversion, by filtering off the enzyme. Evaporation of the solvent resulted in a mixture of (*R*)-**3** (ee = 88%) and (*S*)-**7** (ee = 95%).

Half of the residue was dissolved in MeCN (15 mL). Next TEA (0.14 g, 1.4 mmol, 0.19 mL) and di-*tert*-butoxycarbonyl (0.23 g, 1.05 mmol) were added and the reaction mixture was stirred at room temperature overnight. After evaporation and separation on silica [acetone/hexane (1:19)], butyramide (*S*)-**7** {260 mg (1.21 mmol, 36%); $[\alpha]_D^{25} = +26.0$ (*c* 1.0, MeOH); ee = 95%} and the *N*-Boc-protected amino ester (*R*)-**9** {210 mg (0.86 mmol, 25%); $[\alpha]_D^{25} = -20.6$ (*c* 0.5, MeOH); ee = 85%} were obtained as colourless oils. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for (*S*)-**7**: 0.94 (6H, m, $CH_3CH_2CH + COCH_2CH_2CH_3$), 1.26 (3H, t, $J = 7.10$ Hz, OCH_2CH_3), 1.55–1.70 (4H, m, CH_3-

$CH_2CH + COCH_2CH_2CH_3$), 2.13 (2H, t, $J = 7.46$ Hz, $COCH_2CH_2CH_3$), 2.55 (1H, m, CH_3CH_2CH), 3.35 (1H, m, CH_2NH), 3.51 (1H, m, CH_2NH), 4.16 (2H, q, $J = 7.20$ Hz, OCH_2CH_3), 5.89 (1H, s, NH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for (*R*)-**9**: 0.94 (3H, t, $J = 7.46$ Hz, CH_3CH_2CH), 1.26 (3H, t, $J = 7.10$ Hz, OCH_2CH_3), 1.43 (9H, s, $(CH_3)_3O$), 1.53–1.69 (2H, m, CH_3CH_2CH), 2.52 (1H, m, CH_3CH_2CH), 3.23–3.35 (2H, m, CH_2NH), 4.17 (2H, q, $J = 7.13$ Hz, OCH_2CH_3), 4.85 (1H, br s, NH).

The other half of the residue was dissolved in EtOAc (30 mL) and extracted with 4% aqueous HCl (20 mL). The aqueous phase was basified with aqueous KOH (8%) and the free amino ester (*R*)-**3** was extracted with EtOAc (3×30 mL). The organic phase was dried over Na_2SO_4 and evaporated. This residue was used without further purification to synthesise butyramide (*R*)-**7**, the antipode of (*S*)-**3** obtained from enzymatic resolution. The butyrylation was carried out in pyridine (8 mL) with butanoic anhydride (1.80 mL, 11.2 mmol; 2 equiv). The reaction mixture was stirred overnight at room temperature. The next day, 20 mL of toluene was added to accelerate the evaporation. Purification by column chromatography [acetone/hexane (2:8)] gave (*R*)-**7** {260 mg (1.21 mmol, 89%); $[\alpha]_D^{25} = -24.0$ (*c* 1.0, MeOH); ee = 88%; ee did not decrease during the reaction} as a colourless oil. The comparison of the specific rotations of (*R*)-**7** and (*S*)-**7** confirmed the calculations involving the use of an internal standard, which gave ee (*S*)-**7** = 95%. The ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data for (*R*)-**7** were similar to those for (*S*)-**7**.

4.6. Preparative-scale resolution of methyl 3-amino-2-isopropylpropanoate, (±)-6

Racemic **6** (0.60 g, 4.8 mmol) was dissolved in *tert*-amyl alcohol (80 mL). CAL-A preparation (4.80 g) and ethyl butanoate (0.36 mL, 2.7 mmol) were added and the reaction mixture was shaken at 4 °C. The reaction was stopped after 26 days, at 40% conversion (ee (*R*)-**6** = 52%, ee (*S*)-**8** = 78%), by filtering off the enzyme. After evaporation, the residue was dissolved in 4% aqueous HCl and extracted with EtOAc to obtain butyramide (*S*)-**8** {390 mg (1.8 mmol, 38%); $[\alpha]_D^{25} = +26.4$ (*c* 1.0, MeOH); ee = 78%} as a colourless oil. Aqueous KOH (8%) was added to the aqueous phase and the free amino ester (*R*)-**6** was extracted with EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for (*S*)-**8**: 0.94 (9H, m, $(CH_3)_2CH + COCH_2CH_2CH_3$), 1.64 (2H, m, $COCH_2CH_2CH_3$), 1.97 (1H, m, $(CH_3)_2CH$), 2.12 (2H, t, $J = 7.42$ Hz, $COCH_2CH_2CH_3$), 2.47 (1H, m, $(CH_3)_2CHCH$), 3.35 (1H, m, CH_2NH), 3.59 (1H, m, CH_2NH), 3.70 (3H, s, OCH_3), 5.87 (1H, br s, NH).

The enantiomerically enriched substrate (*R*)-**6** (250 mg, 1.7 mmol) was subjected to enzymatic reaction (without further purification) under the above conditions. After 24 days (ee (*R*)-**6** = 76%, ee (*S*)-**8** = 56%), the reaction was stopped by filtering off the enzyme. After evaporation, the free amino ester was transformed into the *N*-Boc-protected form by the method described above and (*R*)-**10** {210 mg (0.86 mmol, 18%); $[\alpha]_D^{25} = -13.4$ (*c*1.0, MeOH); ee = 76%} was separated from (*S*)-**8** by column chromatography [acetone/hexane (1:19)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for (*R*)-**10**: 0.96 (6H, d, $J = 6.88$ Hz, $(CH_3)_2CH$), 1.44 (9H, s, $(CH_3)_3CO$), 1.96 (1H, m, $(CH_3)_2CH$), 2.43 (1H, m, $(CH_3)_2CHCH$), 3.24 (1H, m, CH_2NH), 3.41 (1H, m, CH_2NH), 3.70 (3H, s, OCH_3), 4.81 (1H, br s, NH).

Acknowledgements

The authors acknowledge the receipt of OTKA Grants K 71938 and T 049407.

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