Chemoenzymatic Preparation of Enantiopure Homoadamantyl β-Amino Acid and β-Lactam Derivatives

Zsuzsanna Cs. Gyarmati,[a,b] Arto Liljeblad,[a] Gyula Argay,[c] Alajos Kálmán,[c] Gábor Bernáth,[b] Liisa T. Kanerva[a,*]

[a] Laboratory of Synthetic Drug Chemistry and Department of Chemistry, University of Turku, Lemminkäisenkatu 2, 20520 Turku, Finland
Fax: (+358)-2-3337955, e-mail: lkanerva@utu.fi
[b] Institute of Pharmaceutical Chemistry, University of Szeged and Research Group for Heterocyclic Chemistry, Hungarian Academy of Sciences, P.O. Box 121, 6701 Szeged, Hungary
[c] Institute of Chemistry, Chemical Research Center of the Hungarian Academy of Sciences, P.O. Box 17, 1525 Budapest, Hungary

Received: November 11, 2003; Accepted: March 10, 2004

Abstract: Racemic *cis*-10-azatetracyclo[7.2.0.$1^{2,6}$.$1^{4,8}$]-tridecan-11-one was prepared from homoadamant-4-ene by chlorosulfonyl isocyanate addition. The transformation of the β-lactam to the corresponding β-amino ester followed by *Candida antarctica* lipase A-catalyzed enantioselective ($E >> 200$) *N*-acylation with 2,2,2-trifluoroethyl butanoate afforded methyl (1*R*,4*R*,5*S*,8*S*)-5-aminotricyclo[4.3.1.$1^{3,8}$]undecane-4-carboxylate and the (1*S*,4*S*,5*R*,8*R*)-butanamide with >99% ee at 50% conversion. Alternatively, transformation of the β-lactam to the corresponding *N*-hydroxymethyl-β-lactam and the following *Pseudomonas cepacia* (currently *Burkholderia cepacia*) lipase-catalyzed enantioseletive *O*-acylation provided the (1*S*,4*S*,6*R*,9*R*)-alcohol (ee = 87%) and the corresponding (1*R*,4*R*,6*S*,9*S*)-butanoate (ee > 99%). In the latter method, competition for the enzyme between the (1*R*,4*R*,6*S*,9*S*)-butanoate, 2,2,2-trifluoroethyl butanoate and the hydrolysis product, butanoic acid, tended to stop the reaction at about 45% conversion and finally gave racemization in the (1*S*,4*S*,6*R*,9*R*)-alcohol with time.

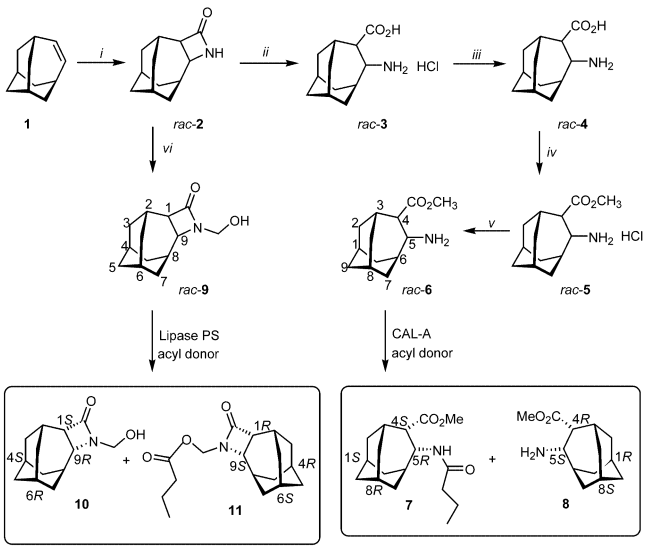
Keywords: β-amino acid; enantioselective acylation; homoadamantyl derivative; β-lactam; lipase catalysis

Introduction

A number of derivatives of adamantane are bioactive. Thus, 1-aminoadamantane is a dopaminergic, noradrenergic and serotonergic substance and some of its analogues with enhanced antioxidant activity have been reported to have potential for blocking or reducing neuronal damage and death in the treatment of Parkinsonian syndromes.[1,2] The symmetrical and lipophilic tricyclic adamantane skeleton in 1-aminoadamantane facilitates the penetration of the protonated compound ($pK_a = 10.8$) across the blood-brain barrier.[1] 1-Aminoadamantane is also an effective antiviral agent against influenza, the adamantane skeleton promoting passage of the compound through the cell membrane to attack a virus within.[3] As compared with the thoroughly studied adamantane derivatives, much less is known about the highly interesting homoadamantane compounds, which possess a spatially similar homologous structure. Both adamantane and homoadamantane skeletons are found, for instance, in the plant metabolites of *Hypericum sampsonii* (a Chinese herbal medicine).[4] Some of these metabolites have been evaluated for their cytotoxic effect against the P388 cancer cell line.

Our interest has long been in the preparation of β-amino acid derivatives.[5,6] The present work describes the preparation of the homoadamantane-*cis*-fused β-lactam intermediate *rac*-**2** and its transformation into enantiopure β-amino acid derivatives **7**, **8**, **10** and **11** *via* chemoenzymatic pathways (Scheme 1). The lipase-catalyzed kinetic resolutions of *rac*-**6** and *rac*-**9** have been in key positions when enantiopurity has been introduced in the products. Chemoenzymatic methods earlier proved successful for the preparation of highly enantiopure monocyclic (the ring containing 5–8 or 12 carbon atoms) and bicyclic (bicyclo[2.2.1]-heptane or -heptene) β-amino acid derivatives.[5–10] A difference in the present work is the large and compact structure of the spherical homoadamantane system. Our main motivation continues to be the preparation of enantiopure β-amino acids as starting materials for the synthesis of fused-skeleton 1,3-heterocycles and bioactive molecules.[11–13]

  DOI: 10.1002/adsc.200303205



Scheme 1. *i*: 1. CSI, CH_2Cl_2, 2. Na_2SO_3, NaOH; *ii*: concentrated HCl; *iii*: propylene oxide, EtOH; *iv*: $SOCl_2$, MeOH; *v*: NH_3; *vi*: paraformaldehyde, cat. K_2CO_3, cat. H_2O, sonication in THF.

Results and Discussion

Synthesis of Substrates *rac*-6 and *rac*-9

The regio- and stereoselective 1,2-dipolar cycloaddition of chlorosulfonyl isocyanate (CSI) to cycloalkenes is a method that is widely used for the preparation of racemic cycloalkane-fused β-lactams[14–16] and their transformation into *N*-hydroxymethyl-β-lactams and alicyclic β-amino acids and esters (Scheme 1).[8–13] For the preparation of β-lactam *rac*-**2**, 4-homoadamantene (**1**) was needed. The preparation followed the literature procedure:[17] ring expansion of commercially available adamantan-2-one into homoadamantan-4-one by reaction with diazomethane, subsequent reduction into homoadamantan-4-ol and dehydration with hexamethylphosphoramide. The addition of CSI to **1** in dichloromethane proceeded without difficulty while the formation of *rac*-**2** from the resulting azetidinone derivative by slow reductive hydrolysis with Na_2SO_3 (in 2 days the chemical yield was 37%) was the bottle-neck in the synthesis. The hydrolysis of *rac*-**2** in concentrated HCl followed by reaction with propylene oxide in EtOH provided easy access to the corresponding free β-amino acid, *rac*-**4**. Traditional esterification with MeOH/$SOCl_2$ and treatment with NH_3 finally gave *rac*-**6** as a substrate for enzymatic kinetic resolution. Although not studied in the present work, the direct transformation of *rac*-**2** into *rac*-**5** in MeOH/HCl is also possible.[8,9] We rather wished to prepare and characterize the acid (*rac*-**4**) as a new compound. Transformation of the β-lactam (*rac*-**2**) with paraformaldehyde under sonication gave *N*-hydroxymethyl-β-lactam *rac*-**9** as previously described for azetidinones.[6–10]

Enzymatic Kinetic Resolution of *rac*-6

A CAL-A (calcium-dependent, thermostable lipase A from *Candida antarctica*)[18,19] preparation (the lipase was adsorbed on Celite in the presence of sucrose)[20] was earlier found to display excellent (2*R*)-enantioselectivity for the *N*-acylation of monocyclic (rings containing 5–8 or 12 carbon atoms) and bicyclic (bicyclo[2.2.1]heptane or -heptene) β-amino esters with 2,2,2-trifluoroethyl esters of butanoic and longer carboxylic acids in ethereal solutions.[5,10] It was essential that the functional groups in these β-amino carboxylates were in the *cis*, or in the di-*endo* or di-*exo* orientation. With the sterically less restricted *trans* isomers, low enantioselectivity was observed. In the present work, *rac*-**6** as a racemic *cis* isomer was subjected to *N*-acylation with 2,2,2-trifluoroethyl butanoate in diisopropyl ether in the presence of the CAL-A preparation. Excellent enantioselectivity in terms of the *E* values is obvious from the results (Table 1). The high enantioselectivity is also indicated by the fact that the reaction stops at 50% conversion with ee values ~99% for both the unreacted **8** and the amide **7** formed. Interestingly, the reactivity (reflected by the conversion achieved after a certain time) of the bulky homoadamantyl derivative (the amino and ester functions attached to the 7-membered ring) is relatively high compared to the reactivities of methyl 2-aminocycloheptanecarboxylate (entry 4) and 2-aminocyclododecanecarboxylate (entry 5).

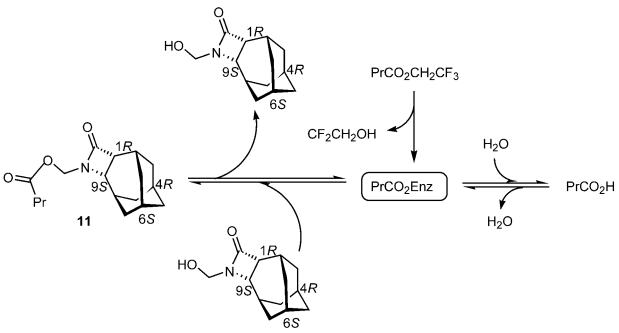
For the *N*-acylation of *rac*-**6** with 2,2,2-trifluoroethyl butanoate in diisopropyl ether, the CAL-A content was optimized. As shown in Table 1, 50 mg/mL of the enzyme preparation led to 50% conversion in 5 h (entry 3) while 10 h was needed when 10 mg/mL of the preparation was applied (entry 1). As described in the Experimental Section, 10 mg/mL (corresponding to

Table 1. Acylation of *rac*-**6** (0.05 M) with 2,2,2-trifluoroethyl butanoate (0.1 M) in diisopropyl ether (2 mL) in the presence of the CAL-A preparation at room temperature.

Entry	CAL-A [mg/mL]	Time [h] preparation	Conversion [%]	*E*
1	10	5 (10)	38 (50)	≫200
2	25	5	46	≫200
3	50	5	50	≫200
4	50	1	48[a]	>200
5	50	24	50[b]	>200

[a] Methyl 2-aminocycloheptanecaboxylate as a substrate (Ref.[10]).
[b] Methyl 2-aminocyclododecanecarboxylate as a substrate (Ref.[10]).

2 mg/mL of CAL-A) was chosen for the gram-scale resolution. For economic reasons, low enzyme content was preferred at the expense of reaction time. Work-up after 10 h gave enantiopure (1*S*,4*S*,5*R*,8*R*)-**7** and (1*R*,4*R*,5*S*,8*S*)-**8** in close to quantitative isolated chemical yields (47% of each, the theoretical yields being 50%). Thus, in accordance with expectations, the amino group at the stereogenic (5*R*) center was enzymatically acylated. The present results confirm the earlier suggestion that *N*-acylations mediated by CAL-A provide an excellent method for the resolution of sterically hindered alicyclic and aliphatic β-amino esters.[5,10,21,22]



Scheme 2. Competitive enzymatic reactions leading to equilibria at the end of the kinetic resolution of *rac*-**9**.

Enzymatic Resolution of *rac*-9

The lipase-catalyzed *O*-acylation of various alicyclic *N*-hydroxymethyl-β-lactams as precursors for β-amino acids is a widely used method for the preparation of β-amino acid or β-lactam enantiomers, lipase PS and lipase AK (lipase from *Pseudomonas fluorescens*) proving to be most suitable as catalysts and dry acetone as a solvent.[6–10] Accordingly, *rac*-**9** was subjected to lipase-catalyzed acylation with 2,2,2-trifluoroethyl and vinyl butanoate in dry acetone in the presence of the lipase PS preparation (the lipase was adsorbed on Celite in the presence of sucrose;[20] Scheme 1, Table 2). The results show that the acylation tends to stop at approximately 45% conversion, especially at higher lipase PS contents (entries 2–4). Alicycle-fused-*N*-hydroxymethyl β-lactam substrates have shown the same tendency before.[6,9,10] As explanation, enzymatic hydrolysis of the produced ester enantiomer or a reaction between the product ester and unreacted primary alcohol enantiomers were suggested although not studied in detail. When (1*R*,4*R*,6*S*,9*S*)-**11** (0.1 M) in acetone was subjected to the presence of the lipase PS preparation (50 mg/mL) 13% (after 1 h) and 15% (after 6 h) of the substrate was hydrolyzed into the corresponding alcohol. When a mixture of **10** (0.05 M, ee = 87 or 94%) and **11** (0.05 M, ee = 99%) as such or in the presence of 2,2,2-trifluoroethyl butanoate was treated under the same conditions, **10** was racemized over time while the enantiopurity of **11** was almost unchanged (Table 3). The system was stable without the enzyme. These results turn attention to enzymatic hydrolysis as an explanation. However, the question about the origin of water can be raised because the detected partial hydrolysis of alkyl-activated achiral esters (2,2,2-trifluoroethyl or vinyl butanoate used in molar excess) can be assumed to consume the water in the seemingly dry enzyme preparation already at the beginning of the resolution reaction. On the other hand, esterification is known to produce water. When a mixture of the more reactive (1*R*,4*R*,6*S*,9*S*)-alcohol (0.05 M) and butanoic acid (0.05 M) in acetone was subjected to the presence of the lipase PS preparation (50 mg/mL) the formation of (1*R*,4*R*,6*S*,9*S*)-**11** was clear although the reaction seemed to stop at 3% conversion. Competing ester hydrolysis is evident in this test reaction, which is ascribed to water in the enzyme preparation. On the above basis, butanoic acid producing water while reacting with the enzyme and the hydrolysis of (1*R*,4*R*,6*S*,9*S*)-**11** are involved in complicated equilibria and explain the difficulty in reaching the theoretical 50% conversion and the racemization of **10** for the enzymatic resolution of *rac*-**9** (Scheme 2).

The gram-scale resolution of *rac*-**9** with 2,2,2-trifluoroethyl butanoate was performed in dry acetone with 12.5 mg/mL of the lipase PS preparation in 2 mL of dry acetone (see Experimental Section). After 10 h 47% conversion was reached and the work-up afforded (1*S*,4*S*,6*R*,9*R*)-**10** (ee = 87%) and (1*R*,4*R*,6*S*,9*S*)-**11** (ee > 99%) in almost quantitative chemical yields.

Table 2. Enzymatic acylation of *rac*-**9** (0.05 M) with achiral acyl donors (0.2 M) in dry acetone (2 mL) at room temperature.

Entry	Acyl donor	Enzyme preparation [mg/mL]	Time [h]	Conversion [%]	ee (**10**) [%]	ee (**11**) [%]
1	$PrCO_2CH_2CF_3$	lipase PS [12.5]	3 (10)	47 (48)[a]	89 (93)	>99
2	$PrCO_2CH_2CF_3$	lipase PS [25]	3 (5)	43 (44)[a]	76 (78)	>99
3	$PrCO_2CH_2CF_3$	lipase PS [50]	3 (10)	34 (45)[a]	52 (81)	>99
4	$PrCO_2CH{=}CH_2$	lipase PS [25]	3 (5)	43 (44)[a]	76 (78)	>99
5	$PrCO_2CH{=}CH_2$	CAL-B [2.5]	5	55[b]	60	50

[a] Estimated $E >> 200$; reaction stops before 50% conversion is reached.
[b] $E = 5$.

Table 3. Enantiopurities in dry acetone in the presence of lipase PS preparation (50 mg/mL) in the mixture of (a) **10** (0.05 M) and **11** (0.05 M), (b) **10** (0.05 M), **11** (0.05 M) and 2,2,-trifluoroethyl butanoate (0.2 M) and (c) **10** (0.05 M) and 2,2,-trifluoroethyl butanoate (0.2 M) followed by the addition of **11** (0.05 M) after 2 h room temperature.

Time [h]	ee (**10**) [%]			ee (**11**) [%]		
	(a)	(b)	(c)	(a)	(b)	(c)
0	95	87	87	99	99	99
3	–	68	–	–	98	–
5	68	–	54	98	–	99
10	59	46	–	98	98	–
24	52	–	–	96	–	–

Absolute Configuration

The absolute configuration of **10** was elucidated by an X-ray structure determination. For this purpose, *N*-hydroxymethyl-β-lactam **10** was transformed into the dimer **12** as described in the Experimental Section by stirring in aqueous HCl (18%) solution for 24 h at room temperature. Under such conditions, the corresponding β-lactam enantiomer is formed and reacts with the **10** present in the reaction mixture, leading to the formation of dimer **12**. The X-ray structure (Fig. 1) clearly indicates the (1*S*,4*S*,6*R*,9*R*) configuration for **10**. Thus, in accordance with the earlier cases,[6–10] the enantiomer that reacts is the one in which the *N*-hydroxymethyl group is attached to the carbon with the (*S*) absolute configuration.

Opposite enantiodiscrimination was previously reported[5,6,10] for the acylation of alicyclic β-amino esters and the corresponding *N*-hydroxymethyl-β-lactams by lipases. This likewise holds in the present work, where **10** after separation was transformed into the butanamide methyl ester by treatment with MeOH/HCl and NH_3 followed by the reaction with butanoic anhydride, the positions of the peaks in the GC chromatograms then being compared with those for the CAL-A-catalyzed resolution of *rac*-**6**. The results confirm the absolute configuration (1*S*,4*S*,5*R*,8*R*) for **7** and (1*R*,4*R*,5*S*,8*S*) for **8**.

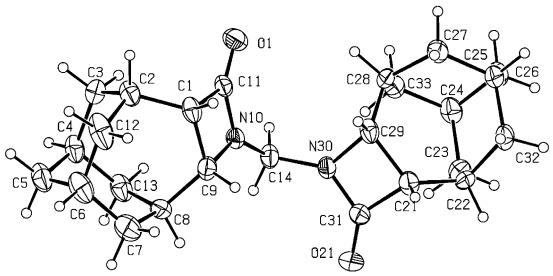


Figure 1. ORTEP plot of the X-ray structure for dimer **12**. The thermal ellipsoids are drawn at the 30% probability level.

Conclusion

In the present work, the enantiomers **7**, **8**, **10** and **11** of *cis*-5-aminotricyclo[4.3.1.1^{3,8}]undecane-4-carboxylic acid derivatives were prepared in a chemoenzymatic manner by using the CAL-A-catalyzed *N*-acylation of the β-amino ester and the lipase PS-catalyzed *O*-acylation of the *N*-hydroxymethyl-β-lactam (Scheme 1). The present work, in accordance with the earlier works, strikingly indicates that the CAL-A-catalyzed *N*-acylation of β-amino esters reliably leads to the enantiomers (1*S*,4*S*,5*R*,8*R*)-**7** and (1*R*,4*R*,5*S*,8*S*)-**8** with $E > > 200$.[5,10] On the other hand, enzymatic *O*-acylation of the *N*-hydroxymethyl-β-lactam involves two general drawbacks. First, hydrolysis of (1*R*,4*R*,6*S*,9*S*)-**11** in the resolution mixture tends to prevent the resolution from going to completion and to the formation of the less reactive enantiomer in an enantiopure form. As another drawback, treatment of **10** in aqueous HCl forms the dimer **12**. Dimer formation is always possible in a reaction mixture containing both β-lactam and *N*-hydroxymethyl-β-lactam under acidic conditions, necessary for the hydrolysis or alcoholysis of a β-lactam derivative into the corresponding amino acid or amino ester.[23]

Experimental Section

General Remarks

Adamantan-2-one, CSI, propylene oxide, vinyl butanoate and the solvents were products of Aldrich or Fluka. 2,2,2-Trifluoroethyl butanoate was prepared from butanoyl chloride and 2,2,2-trifluoroethanol by a standard procedure. Homoadamant-4-ene was prepared from adamantan-2-one by a known method.[17] All solvents were of the highest analytical grade and were dried over molecular sieves (3 Å) before use. Lipase PS (lipase from *Pseudomonas cepacia*) was purchased from Amano Europe, England, and CAL-A (lipase A from *Candida antarctica*, Chirazyme L5, lyo.) from Roche. Before use, the lipases were adsorbed on celite (17 g) by dissolving the enzyme (5 g) and sucrose (3 g) in Tris-HCl buffer (250 mL, 20 mM, pH = 7.9) as described previously.[20] The final lipase content was 20% (w/w) in the enzyme preparation. 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. Spots were visualized with 5% ethanolic phosphomolybdic acid solution and heating. All enzymatic reactions were performed at room temperature (23–24 °C).

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 spectrometer operating at 400 MHz and 100 MHz, respectively, and were referenced to TMS as internal standard. Mass spectra were taken on a VG 7070E mass spectrometer. For X-ray crystallography, intensity data were collected on an En-

raf-Nonius CAD4 diffractometer, with graphite-monochromated Cu-Kα radiation (λ = 1.54180 Å) at 293 K in the range $3.58 = \theta = 75.92°$, using ω-2θ scans. Cell parameters were determined by least-squares refinements of 25 ($25.00 = \theta = 29.76°$) reflections. 5101 reflections were collected for 12. The intensities of the standard reflections indicated a crystal decay of 1% (the data were corrected for decay). A psi-scan absorption correction was applied to the data (the minimum and maximum transmission factors were 0.8263 and 0.9704). Optical rotations were determined with a JASCO Model DIP-360 digital polarimeter. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. The determination of E was based on the equation $E = \ln[(1-c)(1-ee_S)]/\ln[(1-c)(1+ee_S)]$[24] with the use of linear regression, E being the slope of a line $\ln[(1-c)(1-ee_S)]$ *vs.* $\ln[(1-c)(1+ee_S)]$. Melting points were determined by a hot plate method and are uncorrected.

In a typical small-scale experiment, *rac*-**6** (0.1 mmol) in diisopropyl ether or *rac*-**9** (0.1 mmol) in dry acetone (2 mL) was added to a lipase preparation (10–50 mg/mL), followed by the addition of an achiral acyl donor (2–4 equivalents) to the substrate. The progress of the reactions and the ee values were followed by taking samples (0.1 mL) at intervals and analyzing them by gas chromatography. For good baseline separation, the unreacted amino group (*rac*-**6**) in the sample was derivatized with acetic anhydride in the presence of pyridine containing 1% 4-*N*,*N*-dimethylaminopyridine (DMAP) before injection. The GC was equipped with a Chrompack CP-Chirasil-L-Valine column [conditions: 190 °C; retention times (min): 13.72 and 14.72 for *rac*-**6** acetamide and 20.01 and 21.62 for the butanamide enantiomers] or with a Chrompack CP-Chirasil-DEX CB column [conditions: 190 °C; retention times (min): 40.20 and 41.56 for *rac*-**9** and 73.72 and 76.10 for the butanoate enantiomers].

cis-10-Azatetracyclo[7.2.0.1^{2,6}.1^{4,8}]tridecan-11-one (*rac*-2)

Homoadamant-4-ene (**1**; 4.0 g, 27 mmol) and absolute CH_2Cl_2 (25 ml) were added to a 4-necked-flask and cooled to 0 °C. CSI (2.8 mL, 4.6 g, 32 mmol) in CH_2Cl_2 (10 mL) was added dropwise to the stirred mixture over 1.5 h. The mixture was refluxed for 1 day and thereafter stirred at room temperature for 2 days. The reaction mixture was cooled to 0 °C and Na_2SO_3 (0.01 mol in 15 mL H_2O) was added dropwise over 8 h. The pH was held at 8–9 by parallel addition of 20% aqueous KOH (*ca.* 20 mL). The mixture was stirred at room temperature for 2 days. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was dried on Na_2SO_4 and $CaCl_2$. After filtration, the solvent was evaporated. *rac*-**2** (yield: 1.9 g, 37%; m.p. 208–210 °C) was purified by column chromatography with *n*-hexane:ethyl acetate (1:1) as eluent; HRMS: M^+ found: 191.13087 (M^+ calculated: 191.13101); MS: *m/z* (relative intensity) = 192 (1), 191 (2), 190 (1); $[M]^+$: 164 (1), 163 (2), 162 (2), 149 (12), 148 (100); ^{1}H NMR ($CDCl_3$): δ = 1.26–2.32 (14H, m, 5C$\underline{H}_2$, 4C$\underline{H}$), 3.36–3.38 (1H, m, C$\underline{H}$CO), 3.84–3.86 (1H, m, C$\underline{H}$NH), 6.64 (1H, bs, N$\underline{H}$); ^{13}C NMR ($CDCl_3$): δ = 26.28, 27.36, 29.01, 29.90, 32.78, 33.09, 33.33, 36.17, 36.23, 57.23, 60.38, 170.73.

cis-5-Aminotricyclo[4.3.1.1^{3,8}]undecane-4-carboxylic Acid (*rac*-4)

A solution of *rac*-**2** (1.90 g, 10 mmol) in concentrated aqueous HCl (30 ml) was stirred at room temperature for 8 h. The resulting white hydrochloride crystals were filtered off, washed with Et_2O and recrystallized from MeOH:Et_2O (10:1), affording *rac*-**3**; yield: 2.21 g (90%); mp 299–301 °C; ^{1}H NMR (D_2O): δ = 1.58–2.19 (14H, m, 5C$\underline{H}_2$, 4C$\underline{H}$), 3.43–3.47 (1H, m, C$\underline{H}$CO), 3.75–3.77 (1H, m, C$\underline{H}$NH$_3^+$); ^{13}C NMR (D_2O): δ = 25.32, 25.39, 28.34, 32.97, 33.54, 33.65, 36.04, 36.17, 37.42, 50.56, 56.35, 177.28.

Propylene oxide (1.13 mL, 0.94 g, 16.2 mmol) was added to a solution of *rac*-**3** (2.0 g, 8.1 mmol) in absolute EtOH (60 mL) and the mixture was refluxed for 4 h. The solvent was evaporated and *rac*-**4** (yield: 1.69 g, 81%; mp 213–215 °C) was recrystallized from diethyl ether; HRMS: M^+ found: 209.14165 (M^+ calculated: 209.14158); MS: *m/z* (relative intensity) = 209 (1), 208 (2), $[M]^+$, 193 (2), 192 (4), 191 (1), 190 (1), 182 (4), 175 (2), 173 (1), 168 (1), 164 (2), 163 (3), 162 (3), 150 (5), 149 (13), 148 (100), 147 (5), 146 (2); ^{1}H NMR (D_2O): δ = 1.58–2.20 (14H, m, 5C$\underline{H}_2$, 4C$\underline{H}$), 3.38–3.40 (1H, m, C$\underline{H}$CO), 3.73–3.75 (1H, m, C$\underline{H}$NH$_2$); ^{13}C NMR (D_2O): δ = 26.05, 26.10, 28.98, 33.05, 33.88, 34.00, 35.63, 36.36, 37.98, 50.26, 56.06, 177.21.

Methyl *cis*-5-Aminotricyclo[4.3.1.1^{3,8}]undecane-4-carboxylate (*rac*-6)

To a solution of *rac*-**4** (0.7 g, 3.3 mmol) in MeOH (10 mL) distilled $SOCl_2$ (0.3 mL, 3.7 mmol) was added dropwise at −5 °C. The reaction mixture was stirred at −5 °C for 1 h, and thereafter at room temperature for 24 h, and finally refluxed for 8 h. The solvent was evaporated and the product was crystallized from diethyl ether, affording *rac*-**5**; yield: 0.84 g, (98%); mp 198–200 °C; ^{1}H NMR (D_2O): δ = 1.59–2.22 (14H, m, 5C$\underline{H}_2$, 4C$\underline{H}$), 2.54–2.57 (1H, m, C$\underline{H}$CO), 3.51–3.54 (1H, m, C$\underline{H}$NH$_3^+$), 3.75 (3H, s, C$\underline{H}_3$); ^{13}C NMR (D_2O): δ = 26.13, 26.16, 29.08, 33.33, 34.00, 34.13, 35.66, 36.33, 37.81, 50.24, 52.60, 56.03, 175.60.

The free amino ester was obtained by bubbling gaseous NH_3 into a solution of *rac*-**5** in $CHCl_3$ (20 ml) for 0.5 h. The reaction mixture was extracted with distilled water (3 × 10 mL) and the organic layer was dried on Na_2SO_4 and concentrated under vacuum affording *rac*-**6**; yield: 0.71 g (97%); HRMS: M^+ found: 223.15672 (M^+ calculated: 223.15723); MS: *m/z* (relative intensity) = 224 (16), 223 (100), 222 (17), $[M]^+$, 208 (14), 208 (84), 207 (8), 206 (46), 193 (6), 192 (30), 191 (7), 190 (10), 180 (7), 176 (4), 175 (6), 174 (22), 166 (4), 165 (8), 164 (41), 163 (39), 162 (19), 152 (4), 151 (4), 150 (18), 149 (5), 148 (12), 147 (19), 146 (11), 145 (8); ^{1}H NMR ($CDCl_3$): δ = 1.44–2.11 (14H, m, 5C$\underline{H}_2$, 4C$\underline{H}$), 3.05–3.07 (1H, m, C$\underline{H}$CO), 3.54–3.56 (1H, m, C$\underline{H}$NH$_2$), 3.70 (3H, s, C$\underline{H}_3$); ^{13}C NMR ($CDCl_3$): δ = 27.19, 27.47, 30.83, 32.60, 32.66, 34.82, 36.52, 39.91, 39.97, 51.02, 55.52, 55.74, 175.18.

Lipase-Catalyzed Resolution of *rac*-6

Racemic **6** (0.33 g, 1.5 mmol) and 2,2,2-trifluoroethyl butanoate (0.45 ml, 3.0 mmol) in diisopropyl ether (30 mL) were added to a CAL-A preparation (300 mg). The mixture was stirred for 10 h at room temperature. The reaction was stopped by

filtering off the enzyme at 50% conversion with ee > 99% for both the produced **7** and the unreacted **8**. The temperature was lowered to 0 °C and gaseous HCl was bubbled through the solution for 30 minutes. After evaporation, the residue was dissolved in diethyl ether (20 mL) and the less reactive enantiomer was allowed to precipitate as the white hydrochloride (1*R*,4*R*,5*S*,8*S*)-**8**; yield: 0.18 g (0.81 mmol); mp 214–216 °C; $[\alpha]_D^{22}$: −10.5 (*c* 1, H_2O); ee = > 99%.

The solvent was evaporated and recrystallization from diisopropyl ether afforded *cis*-methyl 5-propoxycarbonylaminotricyclo[4.3.1.1^{3,8}]-undecane-4-carboxylate (1*S*,4*S*,5*R*,8*R*)-**7** as colorless crystals; yield: 0.20 g (0.68 mmol); mp 122–125 °C; $[\alpha]_D^{22}$: +13.8 (*c* 1, $CHCl_3$); ee > 99%; HRMS: M^+ found: 293.19986 (M^+ calculated: 293.19909); MS: *m/z* (relative intensity) = 294 (4), 293 (14), $[M]^+$, 265 (3), 263 (2), 262 (5), 261 (2), 250 (3), 234 (6), 233 (29), 224 (2), 223 (16), 222 (97), 207 (2), 206 (10), 205 (4), 193 (6), 192 (8), 191 (15), 190 (26), 176 (2), 175 (6), 174 (4), 166 (2), 165 (8), 164 (12), 163 (24), 162 (15), 161 (3), 149 (2), 148 (4), 147 (7), 146 (5); ^{1}H NMR ($CDCl_3$): δ = 0.92 (3H, t, *J* = 7 Hz, $CH_2CH_2CH_3$), 1.55–1.98 (14H, m, 5CH_2, 4CH), 2.11 (2H, t, *J* = 7 Hz, $CH_2CH_2CH_3$), 3.24–3.28 (1H, m, CHCO), 3.64 (3H, s, $COOCH_3$), 4.56–4.60 (1H, m, CHNH), 6.65 (1H, bs, NH); ^{13}C NMR ($CDCl_3$): δ = 13.63, 19.13, 26.83, 27.03, 30.83, 33.35, 33.65, 36.64, 36.84, 37.45, 38.05, 39.03, 51.48, 52.60, 52.75, 171.35, 175.49.

cis-*N*-Hydroxymethyl-10-azatetracyclo[7.2.0.1^{2,6}.1^{4,8}]-tridecan-11-one (*rac*-9)

rac-**2** (3.00 g, 15.7 mmol) was dissolved in tetrahydrofuran (40 mL), and paraformaldehyde (0.57 g, 19.0 mmol), K_2CO_3 (0.22 g, 1.59 mmol) and distilled water (3 mL) were added. The solution was sonicated for 8 h. The solvent was evaporated off and the residue was dissolved in diethyl ether (100 mL). The solution was dried over Na_2SO_4 for 12 h. The solvent was evaporated and recrystallization from diisopropyl ether afforded *rac*-**9** as colorless crystals; yield: 2.6 g (75%); mp 139–140 °C; HRMS: M^+ found: 221.14100 (M^+ calculated: 221.14158); MS: *m/z* (relative intensity) = 222 (2), 221 (3), 220 (1), $[M]^+$, 205 (2), 204 (5), 192 (1), 191 (1), 190 (1), 176 (2), 175 (1), 174 (1), 163 (1), 162 (4), 150 (5), 149 (17), 148 (100), 147 (5); ^{1}H NMR ($CDCl_3$): δ = 1.39–2.37 (14H, m, 5CH_2, 4CH), 3.36–3.39 (1H, m, CHCO), 3.50 (1H, t, *J* = 4 Hz, OH), 3.96–3.99 (1H, m, CHN), 4.32 (1H, d, *J* = 11 Hz, CH_2OH), 4.92 (1H, d, *J* = 11 Hz, CH_2OH); ^{13}C NMR ($CDCl_3$): δ = 26.59, 27.65, 29.42, 30.71, 31.37, 33.69, 36.54, 60.11, 60.47, 64.11, 68.37, 69.23, 170.78.

Lipase-Catalyzed Resolution of *rac*-9

rac-**9** (0.44 g, 1.99 mmol) was dissolved in dry acetone (40 mL), and lipase PS (0.50 g) and 2,2,2-trifluoroethyl butanoate (8.0 mmol, 1.2 mL) were added. The mixture was stirred for 10 h at room temperature. The enzyme was filtered off at 47% conversion with 87% ee for the unreacted **10** and > 99% ee for the **11** produced. The acetone was evaporated and the residue was chromatographed on silica, with elution with CH_2Cl_2:acetone (4:1), affording (1*S*,4*S*,6*R*,9*R*)-**10** {yield: 0.22 g, 0.99 mmol, mp 130–132 °C; $[\alpha]_D^{22}$: −41.5 (*c*1, $CHCl_3$); ee = 87%) and (1*R*,4*R*,6*S*,9*S*)-11 {yield: 0.27 g, 0.93 mmol, mp 58–60 °C; $[\alpha]_D^{22}$: −36.3 (*c* 1, $CHCl_3$); ee > 99%}; HRMS: M^+ found: 291.18378 (M^+ calculated: 291.18344); MS: *m/z* (relative intensity) = 291 (1), $[M]^+$, 221 (1), 220 (3), 206 (2), 205 (4), 204 (16), 203 (2), 176 (2), 175 (1), 163 (1), 162 (2), 161 (1), 160 (1), 150 (1), 149 (12), 148 (100), 147 (2), 146 (1); ^{1}H NMR ($CDCl_3$): δ = 0.95 (3H, t, *J* = 7 Hz, $CH_2CH_2CH_3$), 1.26–2.42 (14H, m, 5CH_2, 4CH), 2.31 (2H, t, *J* = 7 Hz, $CH_2CH_2CH_3$), 3.40–3.42 (1H, m, CHCO), 3.84–3.86 (1H, m, CHN), 4.99 (1H, d, *J* = 10 Hz, NCH_2O), 5.24 (1H, d, *J* = 10 Hz, NCH_2O); ^{13}C NMR ($CDCl_3$): δ = 13.53, 18.13, 26.19, 27.23, 29.03, 30.17, 30.88, 33.24, 33.31, 35.78, 36.06, 36.12, 60.60, 61.51, 62.95, 170.00, 173.47. The products were obtained as white crystals.

Preparation of Enantiopure 12

For determination of the absolute configurations of **10** and **11**, enantiopure **10** was dimerized to form **12** (Figure 1). For this purpose, **10** (0.1 g, 0.45 mmol) was stirred in aqueous HCl (18%, 2 mL) at room temperature for 24 h. The solvent was evaporated and the product was recrystallized from MeOH, affording 12; yield: 51%; mp 251–254 °C; HRMS: M^+ found: 394.26178 (M^+ calculated: 394.26203); MS: *m/z* (relative intensity) = 395 (1), 394 (6), $[M]^+$, 367 (2), 366 (9), 248 (1), 247 (10), 220 (1), 206 (2), 205 (16), 204 (70), 203 (6), 192 (1), 190 (2), 177 (1), 176 (8), 175 (10), 174 (1), 163 (1), 162 (2), 161 (1) 149 (12), 148 (100), 147 (8); ^{1}H NMR ($CDCl_3$): δ = 1.40–1.95 (24H, m, 8CH_2, 8CH), 2.32–2.41 (4H, m, 2CH_2), 3.39–3.41 (2H, m, 2CHCO), 3.75–3.77 (2H, m, 2CHN), 4.38 (2H, s, NCH_2N); ^{13}C NMR ($CDCl_3$): δ = 25.45, 26.47, 28.34, 29.55, 29.64, 32.32, 32.46, 35.23, 35.35, 43.10, 58.75, 59.37, 168.85.

X-Ray Crystallographic Study

Crystal data for **12**: $C_{25}H_{34}N_2O_2$, M = 394.54, orthorhombic, space group $P2_12_12_1$, unit cell dimensions: *a* = 7.256(1) Å, *b* = 11.652(1) Å, *c* = 24.666(1) Å, *Z* = 4, *V* = 2085.4(3) Å^3, D_c = 1.257 Mg/m^3, μ(Cu-Kα) = 0.618 mm^{-1}, *F*(000) = 856, *T* = 293(2) K; a colorless prism with crystal dimensions 0.50 × 0.35 × 0.06 mm.

The structure was solved by direct methods (*SHELXS-97*)[25] and refined by anisotropic full-matrix least-squares on F^2 techniques (*SHELXL-97*)[26] to an R_1 value of 0.0450 (wR_2 = 0.1457). These final *R* values are based on the reflections with $I > 2\sigma$. Hydrogen atom positions were calculated from assumed geometries. Hydrogen atoms were included in structure factor calculations, but were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the *U*(eq) value of the atom they were bonded to, incorporated into PLATON[27] crystallographic software. Figure 1 was drawn with ORTEP-3 for Windows.[28]

Acknowledgements

Zs. Cs. Gy. is grateful for a grant from the Center of International Mobility (CIMO) in Finland. The authors acknowledge receipt of OTKA grant T030647, OTKA grant T034422 and ETT grant 556/2000 in Hungary. They also thank Ágota Buttásné Kiss and Attila Bokros for synthetic work.

References

[1] J. L. Neumeyer, R. G. Booth, in: *Principles of Medicinal Chemistry*, (Eds.: W. O. Foye, T. L. Lemke, D. A. Williams), Lippincott Williams & Wilkins: New York, **1995**; pp. 240–241.
[2] J. Skolimowski, A. Kochman, L. Gebicka, D. Metodiewa, *Bioorg. Med. Chem.* **2003**, *11*, 3529–3539.
[3] M. Jones Jr., *Organic Chemistry*, Norton, New York, **1997**, p. 227.
[4] Li-H. Hu, K.-Y. Sim, *Tetrahedron* **2000**, *56*, 1379–1386.
[5] L. T. Kanerva, P. Csomós, O. Sundholm, G. Bernáth, F. Fülöp, *Tetrahedron: Asymmetry* **1996**, *7*, 1705–1716.
[6] P. Csomós, L. T. Kanerva, G. Bernáth, F. Fülöp, *Tetrahedron: Asymmetry* **1996**, *7*, 1789–1796.
[7] J. Kámán, E. Forró, F. Fülöp, *Tetrahedron: Asymmetry* **2000**, *11*, 1593–1600.
[8] F. Fülöp, M. Palkó, J. Kámán, L. Lázár, R. Sillanpää, *Tetrahedron: Asymmetry* **2000**, *11*, 4179–4187.
[9] E. Forró, J. Árva, F. Fülöp, *Tetrahedron: Asymmetry* **2001**, *12*, 643–649.
[10] Zs. Cs. Gyarmati, A. Liljeblad, M. Rintola, G. Bernáth, L. T. Kanerva, *Tetrahedron: Asymmetry* **2003**, *14*, 3805–3814.
[11] G. Bernáth, *Bull. Soc. Chim. Belg.* **1994**, *103*, 509–530.
[12] F. Fülöp, G. Bernáth, K. Pihlaja, *Adv. Heterocycl. Chem.* **1998**, *69*, 349–477.
[13] F. Fülöp, *Chem. Rev.* **2001**, *101*, 2181–2204.
[14] E. Nativ, P. Rona, *Isr. J. Chem.* **1972**, *10*, 55–58.
[15] J. K. Rasmussen, A. Hassner, *Chem. Rev.* **1976**, *76*, 389–408.
[16] R. Singh, R. D. G. Cooper, *Tetrahedron* **1994**, *50*, 12049–12064.
[17] R. M. Black, G. B. Gill, *J. Chem. Soc. C* **1970**, 671–676.
[18] T. B. Nielsen, M. Ishii, O. Kirk, *Biotechnol. Appl. Cold-Adapted Org.* **1999**, 49–61.
[19] E. M. Anderson, K. M. Larsson, O. Kirk, *Biotrans.* **1998**, *16*, 181–204.
[20] L. T. Kanerva, O. Sundholm, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2407–2410.
[21] S. Gedey, A. Liljeblad, L. Lázár, F. Fülöp, L. T. Kanerva, *Tetrahedron: Asymmetry* **2001**, *12*, 105–110.
[22] M. Solymár, F. Fülöp, L. T. Kanerva, *Tetrahedron: Asymmetry* **2002**, *13*, 2383–2388.
[23] A. R. Katritzky, G. Yao, L. Xiangfu, Z. Xiaohong, *J. Org. Chem.* **1993**, *58*, 2086–2093.
[24] C.-S. Chen, Y. Fujimoto, G. Girdaukas, C. J. Sih, *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
[25] G. M. Sheldrick, *SHELXS-97*, University of Göttingen, Germany, **1997**.
[26] G. M. Sheldrick, *SHELXL-97*, University of Göttingen, Germany, **1997**.
[27] PLATON Windows implementation by L. J. Farrugia, Department of Chemistry, University of Glasgow, UK, **1998**.
[28] L. J. Farrugia, *J. Appl. Crystallogr.* **1997**, *30*, 565.

