Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 513–520

TETRAHEDRON: *ASYMMETRY*

Lipase-catalysed resolution of 2-dialkylaminomethylcyclohexanols

Enikõ Forró,[a,b] Liisa T. Kanerva[a,*] and Ferenc Fülöp[b]

[a]*Departments of Chemistry and Biomedicine, University of Turku, FIN-20014 Turku, Finland*
[b]*Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, Szeged, Hungary*

Received 11 December 1997; accepted 15 January 1998

Abstract

The lipase PS- and Novozym 435-catalysed resolutions of 2-dialkylaminomethylcyclohexanols (**A–F**) with various vinyl esters were studied in different organic media. High enantioselectivity (E>200) was observed when vinyl acetate was used as an acylating agent and diethyl ether as a solvent. The (1*R*,2*R*) enantiomers react preferentially in the case of the *cis* isomers, whereas the (1*R*,2*S*) enantiomers do so in the case of the *trans* counterparts. Reaction rates were markedly affected by the solvent and by the quantity of the enzyme.

The 1,2- and 1,3-amino alcohols are compounds of considerable biological and chemical importance. The widespread investigations on alicyclic 1,2- and 1,3-amino alcohols[1–4] prompted us to study the resolution of racemic *cis*- and *trans*-2-dialkylaminomethylcyclohexanols (**A–F**) by using lipase-catalysed acylation in organic media as a tool to attain highly enantiopure products (Scheme 1). The racemates of these compounds[5–14] and some of their derivatives have been examined thoroughly in various pharmacological tests.[5–9,14] The local anaesthetic activities of all four stereoisomers of 2-dialkylaminomethylcyclohexyl benzoate are comparable with that of lidocaine.[5] The *cis*- and *trans*-2-dialkylaminomethylcyclohexyl carbanilates and carbamates, synthesized by phenyl isocyanate addition to the corresponding cyclohexanols, display a strong anaesthetic effect, often accompanied by antiarhythmic activity.[6–8] 2-Dialkylaminomethylcyclohexanols can occur as intermediates in the synthesis of semi-rigid analogues of prothiadene and dithiadene, potential antidepressant and antihistamine agents.[9]

The investigated compounds are also of chemical importance, *e.g.*, hydrogenolysis of the dibenzylamino group of compound **F** provides a 1,3-amino alcohol with a primary amino group. The two functional groups (OH and NH_2) are subject to a wide variety of chemical transformations.[5]

* Corresponding author.

0957-4166/98/$19.00
PII: S0957-4166(98)00019-6

Table 1
Effects of various R–CO_2–CH=CH_2 (0.2 M) on the acylation of **B** (0.1 M) in the presence of Novozym 435 (30 mg ml^{-1}) in diethyl ether at room temperature

R	Time (h)	Conversion (%)	$ee_{alcohol}$[a] (%)	ee_{ester}[b] (%)
CH_3	48	24	32	>99
	62	31	44	>99
$CH_3(CH_2)_2$	48	18	22	>99
	62	20	24	>99
$CH_3(CH_2)_9$	48	6	6	>99
	62	7	8	>99

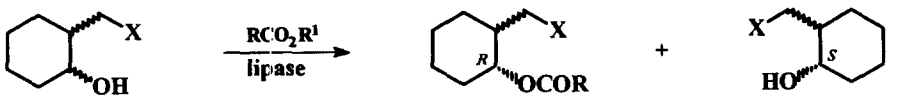
[a]According to chiral GC after derivatization of the substrate with propionic anhydride.
[b]According to chiral GC.

1. Results and discussion

In previous studies, lipase PS from *Pseudomonas cepacia* proved applicable for the resolution of secondary alcohols in general, and for that of cycloalkanols in particular.[15–21] Some doubts arose about the possibilities for the resolution of **A–F**, because *N*-isopropyl-2-amino-1-phenylethanol was shown to be a nonsubstrate for lipase PS-catalysed acylation in toluene.[17] The size of the *N*-alkyl substituent occupying the pocket R_{small} is clearly critical according to the proposed dimensions for the two hydrophobic pockets at the active site of the lipase.[22,23] Extensive lipase screening in diethyl ether indicated that, besides lipase PS, Novozym 435 (lipase from *Candida antarctica* B) is also a promising catalyst for the asymmetric acylation of the present cycloalkanols with *N*-substituents at the position β to the stereocentre. The two catalysts lead to excellent enantioselectivity (enantiomeric ratio, *E*, usually over 200).[24] The resolution conditions were subsequently optimized for lipase PS- and Novozym 435-catalysed acylations by using **B** as a model compound.

The enzymatic reactions of R^1OH (originating from RCO_2R^1) with the products $\mathbf{A_1–F_1}$, which can accompany the asymmetric acylation of cycloalkanols **A–F** (Scheme 1), yielded $\mathbf{A_2–F_2}$ in decreasing enantiopurity with time. For this reason and on the basis of previous experience with lipase PS catalysis,[15] vinyl esters were used as irreversible acyl transfer reagents (vinyl alcohol as R^1OH irreversibly tautomerizes to acetaldehyde) throughout the work. Moreover, acetate was shown to be a better acyl donor than esters with longer carbon chains.[15,25] Vinyl acetate is also a choice for the Novozym 435-catalysed acylation of **B** (Table 1). As a drawback, the Schiff base formation of the liberated acetaldehyde and the free amino groups of a lipase may lead to partial deactivation and a loss of selectivity. In this respect, some caution was necessary in the present work. It turned out that the acetylation of **B** (0.1 M) in diethyl ether in the presence of Novozym 435 (30 mg ml^{-1}) proceeded somewhat more slowly and less enantioselectively with vinyl acetate (0.4 M; conversion 40% after 120 h; $ee_{alcohol}$ 64%, ee_{ester} 96%) than when vinyl acetate (0.2 M; conversion 46% after 120 h; $ee_{alcohol}$ 84%, ee_{ester} ~99%, C) was used. Acetaldehyde is produced by enzymatic acylation with vinyl acetate and possibly by enzymatic hydrolysis of the ester with the water present in the enzyme preparation.

The quantitative basis of solvent effects on reactivity (the time needed to reach a certain conversion) and enantioselectivity is unclear and often unpredictable. Ether solutions are generally preferable for work with lipase PS.[25] In the present work, selected solvent screening for the Novozym 435-catalysed resolution of **B** was performed (Table 2). The enzyme was practically inactive in acetone and tetrahydrofuran. Diethyl ether was chosen as the most favourable solvent for further studies.



A, B, C, D, F A_1, B_1, C_1, D_1, F_1 A_2, B_2, C_2, D_2, F_2

	A	B	C	D	F
X	$-NMe_2$	$-NMe_2$	-N⟨ ⟩	-N⟨ ⟩	-N(Ph)(Ph)
configuration	*cis*	*trans*	*cis*	*trans*	*trans*

Scheme 1.

Table 2
The Novozym 435-catalysed (30 mg ml^{-1}) acetylation of **B** (0.1 M) with vinyl acetate (0.2 M) in different organic solvents at room temperature

Solvent	log P[a]	Time (h)	Conversion (%)	E (%)
Acetone	-0.23	84	no reaction	
Tetrahydrofuran	0.49		no reaction	
Diethyl ether	0.85		41	> 200
tert-Amyl alcohol	1.40		21	62
Isopropyl ether	1.90		25	> 200
Toluene	2.50		20	61

[a]P is the partition coefficient of the solvent between water and 1-octanol.

The enzymatic reactions can also be controlled via the amount of enzyme. Even though the enantioselectivity in the lipase PS- and Novozym 435-catalysed acetylations of alcohols **A–F** is generally excellent (usually E>200), the reactivity for the acetylation of alcohol **B** clearly passes through a maximum at an enzyme content of *ca* 30 mg ml^{-1}, the effect being less pronounced in the case of lipase PS (Table 3).

One of the benefits of biocatalytic reactions over conventional chemical ones is that elevated temperatures are not needed. Rather, the reactions proceed effectively at room temperature. Additionally, the enantioselectivity can often be enhanced at lower temperatures.[26] Enhancement of the enantioselectivity is not necessary in the present work. On the other hand, at room temperature the time needed to reach the theoretical 50% conversion is relatively long in the case of Novozyme 435 (*e.g.* a conversion of 21% after 62 h; Table 3, row 5). In order to decrease the reaction time, the Novozym 435-catalysed acetylation of **B** was performed at 40°C. Surprisingly, a slower reaction (conversion 19% after 108 h) was observed without any effect on the enantioselectivity.

The above optimizations were mostly based on previous work with lipase PS[15–21,25] and on the Novozym 435-catalysed acetylation of **B** (Tables 1–3). The applicability of the optimal conditions was tested for the acetylation of alcohols **A–F**. Although E>200 throughout the substrate screening, only lipase PS effectively catalyses the asymmetric acetylation of the *cis* compounds **A** and **C** (Table 4). Successful enantioselective acetylation of the *trans* compounds **B**, **D** and **F** is possible (with different reaction rates) when either lipase PS or Novozym 435 is used. Since the real protein contents and

Table 3
Effects of the quantity of Novozym 435 (i) and lipase PS preparation[a] (ii) on the acetylation of **B** (0.1 M) with vinyl acetate (0.2 M) in diethyl ether at room temperature

Enzyme preparation (mg ml^{-1})	Time (h)	Conversion (%)	$ee_{alcohol}$[b] (%)	ee_{ester}[c] (%)
10 (i)	64	13	15	>99
20 (i)	64	30	42	>99
30 (i)	62	31	44	>99
30(ii)	46	50	98	98
50 (i)	62	21	26	>99
50 (ii)	46	47	88	98
75 (i)	96	8	9	>99

[a]Contains 20% (w/w) of lipase adsorbed on Celite in the presence of sucrose. [b]According to chiral GC after derivatization of the substrate with propionic anhydride. [c]According to chiral GC.

Table 4
Activity of Novozym 435 (i) 30 mg ml^{-1} and lipase PS (ii) 50 mg ml^{-1} in the acetylation of **A–F** (0.1 M) with vinyl acetate (0.2 M) in diethyl ether at room temperature

Substrate	Enzyme	Time (h)	$ee_{alcohol}$[b] (%)	ee_{ester}[c] (%)	Conversion (%)
A	ii	96	86	97	47
	i	116	10	>99	9
B	ii	46	99	98	50
	i	92	81	99	45
C	ii	16	72	>99	42
	i	144	4	>99	4
D	ii	116	98	97	50
	i	142	91	98	48
F	ii	10	>99	99	~50
	i	20	>99	99	~50

[a]Contains 20% (w/w) of lipase adsorbed on Celite in the presence of sucrose. [b]According to chiral GC after derivatization of the substrate with propionic anhydride. [c]According to chiral GC.

specific activities of the two enzyme preparations are unknown, a straightforward comparison between their reactivities is impossible. It can be concluded, however, that lipase PS is the more favourable of the two because, as stated above (Table 3), it is not possible to enhance the reactivity of Novozyme 435 to the level shown for lipase PS in Table 4 by increasing the enzyme content under the present reaction conditions.

Gram-scale resolutions of compounds **A–F** were performed in diethyl ether in the presence of lipase PS or Novozym 435 and the results are summarized in Table 5. The esters ($\mathbf{A_1}$–$\mathbf{F_1}$) produced by the (*R*)-selective acetylation of cyclohexanols underwent spontaneous deacylation to the corresponding alcohols ($\mathbf{A_3}$–$\mathbf{F_3}$) in methanol at room temperature, without loss of enantiopurity.

It is interesting that recrystallization from diisopropyl ether was accompanied by the spontaneous res-

Table 5
The enzyme-catalysed resolution of **A–F** in the presence of Novozym 435 (i) 30 mg ml^{-1} or lipase PS preparation[a] (ii) 50 mg ml^{-1} and vinyl acetate (0.2 M) in diethyl ether at room temperature

Substrate	Enzyme	Time (h)	Conversion (%) E	Recovered alcohol (A_2-F_2) and (A_3-F_3, second row) Yield[b] (%)	Isomer	ee (%)	$[\alpha]_D^{20}$	Produced ester (A_1 - F_1) Yield[b] (%)	Isomer	ee (%)	$[\alpha]_D^{20}$
A	ii	162	50 E>200	98	*1S,2S* *1R,2R*	96.2[c] 98.9[c]	+19.0[d] −20.0[f]	76	*1R,2R*	98.9[e]	−34.0[d]
B	i	214	50 E>200	67	*1S,2R* *1R,2S*	96.0[c] 96.6[c]	−9.2[g,h] +12.5[i]	84	*1R,2S*	97.9[e]	−67.6[g]
C	ii	46	50 E>200	91	*1S,2S* *1R,2R*	96.8[c] 98.3[c]	+15.0[d] −15.0[f]	97	*1R,2R*	98.4[e]	−40.0[d]
D	i	255	50 E>200	98	*1S,2R* *1R,2S*	97.0[c] 97.5[c]	−37.6[g] +39.0[f]	91	*1R,2S*	99.0	−47.2[g]
F	ii	20	50 E>200	99	*1S,2R* *1R,2S*	99.0[j] 99.0[j]	−44.5[d] +45.0[e]	81	*1R,2S*	>99.0[j]	−76.0[d]

[a]Contains 20% (w/w) of lipase adsorbed on Celite in the presence of sucrose. [b]Yield 100% at 50% conversion. [c]According to chiral GC after derivatization with propionic anhydride. [d](c = 1, MeOH). [e]According to chiral GC. [f](c = 0.8, MeOH). [g](c = 2.5, MeOH). [h]The ester impurity lowers the value of $[\alpha]_D^{20}$. [i](c=2, MeOH). [j]According to chiral HPLC.

olution of racemic *trans*-2-dibenzylaminomethylcyclohexanol (**F**), yielding different crystal structures. Well-developed crystals with high enantiopurities (ee>90%) were sorted for the two enantiomers.

1.1. Determination of absolute configurations

Chiral chromatography indicated that the corresponding enantiomers of compounds **A–F** react preferentially with lipase PS or Novozym 435 catalysts. According to the Kazlauskas model for the active site of lipases, the (1*R*) configuration was predicted for these enantiomers. The validity of this was proved in the case of 2-dibenzylaminomethylcyclohexanol (**F**). For this purpose, the enantiomer $\mathbf{F_2}$ was reduced catalytically to the corresponding aminoalcohol. The value of $[\alpha]_D^{20}$=+31.9 (c=1.77, MeOH) for the reduced product is in good agreement with the literature value ($[\alpha]_D^{20}$=+33.9 (c=2, MeOH).[27] Thus, the absolute configuration of the unreactive cyclohexanols $\mathbf{A_2}$–$\mathbf{F_2}$ is (1*S*,2*S*) for the *cis* and (1*S*,2*R*) for the *trans* isomers.

2. Experimental

2.1. Materials and methods

Racemic *cis*- and *trans*-2-dialkylaminomethylcyclohexanols **A–F** were obtained by means of the Mannich reaction and subsequent reduction. The Mannich reaction was carried out in excess cyclohexanone

with paraformaldehyde and the corresponding amine. The resulting ketones were reduced with $NaBH_4$. 2-Dimethylaminomethyl- and 2-(1-piperidinylmethyl)cyclohexanols were obtained as isomeric mixtures (**A**:**B**=2:3; **C**:**D**=1:2), which were separated by column chromatography [**A**: mp 38–41°C (lit.[11] mp 40–41°C); **B**: oil; **C**: mp 48–51°C; **D**: oil], elution being performed with ethyl acetate for the *trans* and with methanol for the *cis* isomers. The reduction of 2-dibenzylaminomethylcyclohexanone hydrochloride under the same conditions resulted exclusively in **F** with the *trans* configuration (mp 93–94°C).

Vinyl acetate and vinyl decanoate were purchased from Aldrich Co., and vinyl butyrate from Tokyo Kasei Kogyo Co. Lipase PS was obtained from Amano Pharmaceuticals, and Novozym 435 as an immobilized preparation from Novo Nordisk. Before use, lipase PS was 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 preparation thus obtained contained 20% (w/w) of lipase.

The solvents were of the best analytical grade and were dried over molecular sieves (3 Å). For gram-scale resolution, diethyl ether was distilled just before use.

In a typical small-scale experiment, one of the 2-dialkylaminomethylcyclohexanols **A–F** (0.1 M solution) in diethyl ether (3 ml) was added to the lipase PS preparation (50 mg ml^{-1}) or Novozym 435 (30 mg ml^{-1}). A vinyl ester (0.2 M in the reaction mixture) was added. The mixture was shaken at room temperature (22–24°C). The progress of the reaction was followed by taking samples (0.1 ml) from the reaction mixture at intervals. In some cases, the unreacted alcohol in the sample was derivatized with propionic anhydride in the presence of 4-dimethylaminopyridine and pyridine before the gas chromatographic analysis. The ee values of the unreacted alcohol ($\mathbf{A_2}$–$\mathbf{D_2}$) and the produced ester ($\mathbf{A_1}$–$\mathbf{D_1}$) enantiomers were determined by gas chromatography on a Chrompack CP-Cyclodextrin-β-2,3,6-M-9 column (25 m). The ee values for $\mathbf{F_1}$ and $\mathbf{F_2}$ were determined by using high-pressure liquid chromatography with a Chiralcel OG column (25 cm).

2.2. *Gram-scale resolution of* cis-*2-dimethylaminomethylcyclohexanol (A)*

Racemic **A** (2.35 g; 15 mmol) and vinyl acetate (2.81 ml; 30 mmol) in diethyl ether (150 ml) were added to the lipase PS preparation (4.50 g, 50 mg ml^{-1}). The mixture was stirred at room temperature for 162 h. The reaction stopped at 50% conversion with 96% ee for unreacted (1*S*,2*S*)-$\mathbf{A_2}$ and 99% ee for the produced (1*R*,2*R*)-$\mathbf{A_1}$. The enzyme was filtered off and the solvent was evaporated. The resolved products were separated on silica gel, by elution with ethyl acetate for $\mathbf{A_2}$ (1.14 g oil, 7.28 mmol, ee 96%) and with methanol for $\mathbf{A_1}$ (1.32 g oil, 6.6 mmol, ee 99%). Within 2 to 3 days, the ester enantiomer $\mathbf{A_1}$ underwent quantitative deacylation to the corresponding alcohol $\mathbf{A_3}$ (ee 99%) on standing in methanol at room temperature. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for $\mathbf{A_1}$: 1.2–1.9 (9H, m, 4×CH_2 and remaining CH), 2.0 (3H, s, CH_3), 2.1–2.2 (2H, dd, CH_2N), 2.18 (6H, s, 2×CH_3), 5.0 (H, m, C*H*O$COCH_3$). Analysis: calculated for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03; found: C, 65.55; H, 11.23; N, 6.94.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for $\mathbf{A_2}$ and $\mathbf{A_3}$: 1.25–2.1 (9H, m, 4×CH_2 and remaining CH), 2.2 (1H, dd, *J*=8.8, 3.9 Hz, CH_2N), 2.38 (6H, s, 2×CH_3), 3.0 (1H, dd, *J*=10.8, 1.7 Hz, CH_2N), 3.9 (1H, m, C*H*OH), 7.2 (1H, brs, OH). MS analysis for $\mathbf{A_2}$: M=157. Analysis: calculated for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91; found for $\mathbf{A_3}$: C, 68.73; H, 12.27; N, 8.71.

2.3. *Gram-scale resolution of* trans-*2-dimethylaminomethylcyclohexanol (B)*

With the procedure described above and in the presence of Novozym 435 (30 mg ml^{-1}), racemic **B** (1.88 g; 12 mmol) afforded the unreacted (1*S*,2*R*)-$\mathbf{B_2}$ (0.60 g oil, 3.83 mmol, ee 96.0%) and the ester (1*R*,2*S*)-$\mathbf{B_1}$ (1.00 g oil, 5.02 mmol, ee 97.9%) in 214 h.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **B_1**: 0.9–2.01 (9H, m, 4×CH_2 and remaining CH), 2.03 (3H, s, CH_3), 2.10 (1H, dd, *J*=12.1, 4.4 Hz, CH_2N), 2. 17 (6H, s, 2×CH_3), 2.19 (1H, dd, *J*=12.1, 8.9 Hz, CH_2N), 4.5 (1H, m, C*H*OCOCH_3). Analysis: calculated for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03; found: C, 65.50; H, 10.41; N, 7.19). MS analysis for **B_2**: M=157. **B_3** (ee 96.6%). Analysis: calculated for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91; found: C, 67.98; H, 12.56; N, 8.60. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **B_2** and **B_3**: 0.8–2.0 (9H, m, 4×CH_2 and remaining CH), 2.2 (1H, dd, *J*=9.52, 2.68 Hz, CH_2N), 2.4 (1H, dd, CH_2N), 3.38 (1H, m, C*H*OH), 5.83 (1H, brs, OH).

2.4. *Gram-scale resolution of* cis-*2-(1-piperidinylmethyl)cyclohexanol (**C**)*

With the procedure described above and in the presence of lipase PS (50 mg ml^{-1}), racemic **C** (1.35 g; 6.8 mmol) afforded the unreacted (1*S*,2*R*)-**C_2** (0.61 g oil, 3.00 mmol, ee 97%) and the ester (1*R*,2*S*)-**C_1** (0.79 g oil, 3.30 mmol, ee 98%) in 46 h.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **C_1**: 1.0–2.3 (19H, m, 9×CH_2 and remaining CH), 2.05 (3H, s, CH_3), 2.3 (2H, dd, CH_2N), 5.0 (1H, m, C*H*OCOCH_3). Analysis: calculated for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85; found: C, 70.31; H, 11.21; N, 5.81.

C_2: Analysis: calculated for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10; found: C, 72.67; H, 12.05; N, 6.97.

C_3 (ee 98%). Analysis: calculated for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10; found: C, 72.49; H, 11.89; N, 7.16.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **C_2** and **C_3**: 1.2–2.8 (19H, m, 9×CH_2 and remaining CH), 2.2 (1H, dd, *J*=9.37, 3.6 Hz, CH_2N), 3.0 (1H, dd, *J*=10.9, 1.9 Hz, CH_2N), 3.9 (1H, m, C*H*OH), 7.1 (1H, brs, OH).

2.5. *Gram-scale resolution of* trans-*2-(1-piperidinylmethyl)cyclohexanol (**D**)*

With the procedure described above and in the presence of Novozym 435 (30 mg ml^{-1}), racemic **D** (2.35 g; 12 mmol) afforded the unreacted (1*S*,2*R*)-**D_2** (1.15 g oil, 5.83 mmol, ee 97%) and the ester (1*R*,2*S*)-**D_1** (1.29 g oil, 5.38 mmol, ee 99%) in 255 h.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **D_1**: 0.9–2.4 (19H, m, 9×CH_2 and remaining CH), 2.0 (3H, s, CH_3), 2.28–2.35 (2H, dd, CH_2N), 4.55 (1H, m, C*H*OCOCH_3). Analysis: calculated for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85; found: C, 70.29; H, 10.46; N, 5.85.

D_2: Analysis: calculated for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10; found: C, 72.64; H, 12.17; N, 7.05.

D_3 (ee 97.5%). Analysis: calculated for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10; found: C, 72.56; H, 11.45; N, 6.81.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **D_2** and **D_3**: 0.8–2.6 (19H, m, 9×CH_2 and remaining CH), 2.29 (1H, dd, *J*=9.28, 3.2 Hz, CH_2N), 2.38 (1H, dd, *J*=12.4, 11.48 Hz, CH_2N), 3.38 (1H, m, C*H*OH).

2.6. *Gram-scale resolution of* trans-*2-dibenzylaminomethylcyclohexanol (**F**)*

With the procedure described above and in the presence of lipase PS (50 mg ml^{-1}), racemic **F** (1.84 g, 5.9 mmol) afforded the unreacted (1*S*,2*R*)-**F_2** (0.91 g crystalline product, 2.94 mmol, mp 134–136°C, ee 99%) and the ester (1*R*,2*S*)-**F_1** (0.85 g oil, 2.4 mmol, ee>99%) in 34 h. Separation of the resolved products occured on elution with diethyl ether.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **F_1**: 0.7–2.2 (9H, m, 4×CH_2 and remaining CH), 2.0 (3H, s, CH_3), 2.1 (1H, dd, *J*=10.0, 2.32 Hz, CH_2N), 2.4 (1H, dd, *J*=8.92, 3.6, Hz, CH_2N), 3.1–3.3 (4H, d,

2×CH_2), 4.45 (1H, m, C*H*OCOCH$_3$), 7.2–7.4 (10H, m, 10×CH). Analysis: calculated for $C_{23}H_{29}NO_2$: C, 78.60; H, 8.32; N, 3.98; found: C, 78.66; H, 8.88; N, 3.93.

F$_2$: Analysis: calculated for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53; found: C, 81.60; H, 9.23; N, 4.51.

F$_3$ (Crystalline product, mp 132–134°C, ee 99%). Analysis: calculated for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53; found: C, 81.58; H, 9.11; N, 4.49.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.7–2.0 (9H, m, 4×CH_2 and remaining CH), 2.2–2.6 (2H, dd, CH_2N), 3.0 (1H, m, C*H*OH), 3.1–4.2 (4H, d, 2×CH_2), 6.9 (1H, brs, OH), 7.2–7.4 (10H, m, 10×CH).

Acknowledgements

One of us (E. F.) is grateful for a grant from the Centre for International Mobility (CIMO). Support from MKM (FKFP 0910/1997) Hungary is also gratefully acknowledged.

References

1. Hayashi, Y.; Rohde, J. J.; Corey, E. J. *J. Am. Chem. Soc.* **1996,** *118*, 5502.
2. Eliel, E. L.; He, X. *J. Org. Chem.* **1990**, *55*, 2114.
3. Maestro, A.; Astorga, C.; Gotor, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3153.
4. Fülöp, F.; Bernáth, G.; Pihlaja, K. *Adv. Heterocyclic Chem.* **1998**, *69*, 349.
5. Nemes, P.; Kajtár, J.; Kajtár, M.; Kárpáti, E.; Nádor, K. *Arzneim.-Forsch./Drug Res.* **1988,** *38*, 1081.
6. Gregan, F.; Racanska, E.; Remko, M. *Pharmazie* **1995,** *50*, 772.
7. Gregan, F.; Kettmann, V.; Novomesky, P.; Sivy, J. *Collect. Czech. Chem. Commun.* **1994,** *59*, 675.
8. Bradlerova, A.; Pronayova, N.; Misikova, E.; Durinda, J. *Collect. Czech. Chem. Commun.* **1990,** *55*, 1854.
9. Polivka, Z.; Holubek, J.; Svatek, E.; Metys, J.; Protiva, M. *Collect. Czech. Chem. Commun.* **1985,** *50*, 1078.
10. Traynelis, V. J.; Dadura, J. G. *J. Org. Chem.* **1961**, *26*, 1813.
11. Möhrle, H.; Baumann, H. *Arch. Pharm.* **1966**, *299*, 355.
12. Möhrle, H.; Baumann, H. *Arch. Pharm.* **1968**, *301*, 219.
13. Ratonis, R.; Combes, G. *Bull. Soc. Chim. France* **1959**, 576.
14. Risch, N.; Esser, A. *Liebigs Ann. Chem.* **1992**, 233.
15. Forró, E.; Lundell, K.; Fülöp, F.; Kanerva, L. T. *Tetrahedron: Asymmetry* **1997**, *8*, 3095.
16. Kanerva, L. T.; Sundholm, O. *Acta Chem. Scand.* **1993**, *47*, 823.
17. Kanerva, L. T.; Rahiala, K.; Vänttinen, E. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1759.
18. Lundell, K.; Kanerva, L. T. *Tetrahedron: Asymmetry* **1995**, *6*, 2281.
19. Kanerva, L. T.; Rahiala, K.; Sundholm, O. *Biocatalysis*, **1994**, *10*, 169.
20. Lundell, K.; Raijola, T.; Kanerva, L. T. *Enzyme Microb. Technol.* **1997**, in press.
21. Sundholm, O.; Kanerva, L. T. *Acta Chim. Hung. —Models in Chemistry*, **1997**, in press.
22. According to the model, a lipase distinguishes the two enantiomers on the basis of the size of the substituents R_{large} and R_{small} at the alcoholic stereocentre [$R_{small}CH(OH)R_{large}$] in such a way that the more reactive enantiomer bears the (*R*) absolute configuration when the Cahn–Ingold–Prelog priority of the group R_{large} is higher than that of the group R_{small} and H is behind the plain. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656. Cygler, M.; Grochulski, P.; Kazlauskas, R. J.; Schrag, J. D.; Bouthillier, F.; Rubin, B.; Serreqi, A. N.; Gupta, A. K. *J. Am. Chem. Soc.* **1994**, *116*, 3180.
23. Lemke, K.; Lemke, M.; Theil, F. *J. Org. Chem.* **1997**, *62*, 6268.
24. $E=\{\ln[(1-ee_s)/(1+ee_s/ee_p)]\}/\{\ln[(1+ee_s)/(1+ee_s/ee_p)]\}$ where ee_s and ee_p refer to the enantiomeric excess of the unreacted substrate and product fractions, respectively, and $c=ee_S/(ee_S+ee_P)$; Rakels, J. L. L.; Straathof, J. J.; Heijnen, J. J. *Enzyme Microb. Technol.* **1993**, *15*, 1051.
25. Kanerva, L. T.; Csomós, P.; Sundholm, O.; Bernáth, G.; Fülöp, F. *Tetrahedron: Asymmetry* **1996**, *7*, 1705.
26. Holmberg, E.; Hult, K. *Biotechnol. Lett.* **1991**, *13*, 323.
27. Fülöp, F.; Huber, I.; Bernáth, G.; Hönig, H.; Seufer-Wasserthal P. *Synthesis* **1991,** 43.