Chemoenzymatic Preparation of Optically Active *trans*-Cyclohexane-1,2-diamine Derivatives: An Efficient Synthesis of the Analgesic U-(−)-50,488

Javier González-Sabín, Vicente Gotor,* and Francisca Rebolledo*[a]

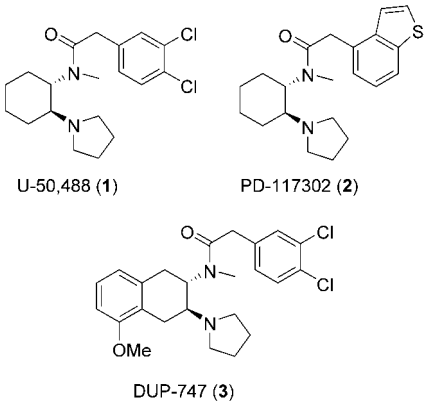
Abstract: Stereoespecific syntheses of (±)-*trans*-*N*,*N*-cyclohexane-1,2-diamines ((±)-**4a**–**g**) were carried out from the corresponding (±)-*trans*-*N*,*N*-dialkylaminocyclohexanols by successive treatment with mesyl chloride and aqueous ammonia. The stereochemical outcome indicates the formation of a *meso*-aziridinium ion intermediate. Kinetic resolutions of diamines (±)-**4** were efficiently accomplished in aminolysis reactions catalyzed by lipase B from *Candida antarctica* with ethyl acetate as the solvent and acyl donor. Acetamides and the remaining diamines, isolated as the benzyloxycarbonyl derivatives, were obtained with very high *ee* values (92–99%). One of the carbamates was used as a precursor of the analgesic U-(−)-50,488.

Keywords: asymmetric synthesis · chemoenzymatic synthesis · diamines · kinetic resolution · lipases

Introduction

Optically active *trans*-cyclohexane-1,2-diamine derivatives are an important class of compounds due to their use as chiral reagents, scaffolds, and ligands for asymmetric catalysis.[1] Moreover, the cyclohexane-1,2-diamine unit can be found in various compounds displaying a broad spectrum of biological activity.[1b,2] For example, compound U-50,488[3] (**1**) and other structural analogues[4] (such as **2** and **3**; Scheme 1) have been reported to be highly selective κ-opioid agonists, free from the adverse side effects of μ-opioid agonists like morphine.[5] As for the majority of pharmacologically active compounds, their properties are related to the configuration of their stereogenic centers. Thus, (1*S*,2*S*)-(−)-**1** exhibits greater κ agonist activity than its enantiomer, and the *cis* diastereomer of U-50,488 has practically no affinity for κ receptors.[6]

The wide ranging applicability of cyclohexane-1,2-diamine derivatives in various areas of chemistry makes the design of efficient methods for their preparation of great interest. Whereas the synthesis of nonracemic *N*,*N*′-disubstituted *trans*-cyclohexane-1,2-diamines can be readily achieved from the commercial but expensive (1*R*,2*R*)- or (1*S*,2*S*)-cyclohexane-1,2-diamine,[7] the methods for obtaining the corresponding *N*,*N*-disubstituted derivatives involve several additional steps: initial monoprotection of the diamine—a step which often takes place with moderate to low yield—and eventual removal of the protecting group.[8]



Scheme 1. Selected κ-opioid analgesics.

Here we wish to report a very simple and efficient method for preparing optically active *N*,*N*-disubstituted cyclohexane-1,2-diamines by using cyclohexene oxide as the starting material. Two key steps are involved in this method, namely, stereospecific transformation of (±)-*trans*-2-(*N*,*N*-dialkylamino)cyclohexanols into (±)-*trans*-1,2-diamines and subsequent enzymatic resolution. Some of these diamines were chosen for their importance as precursors of pharmacologically active compounds. This is the case, for instance, with **4a**, a chemically versatile intermediate for the synthesis of analogues of **1**. Diamines **4d** and **4e** bear additional methoxycarbonyl and formamide functions, respectively, there-

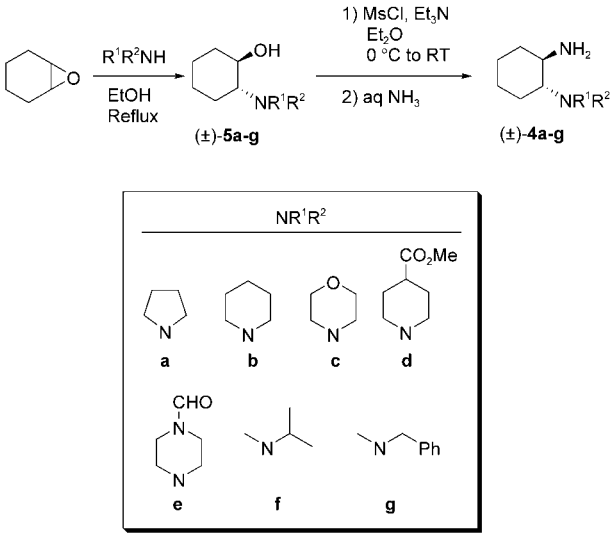
[a] J. González-Sabín, Prof. V. Gotor, Dr. F. Rebolledo
Departamento de Química Orgánica e Inorgánica
Facultad de Química, Universidad de Oviedo, Oviedo (Spain)
Fax: (+34) 9851-03448
E-mail: vgs@fq.uniovi.es
frv@fq.uniovi.es

© 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim
DOI: 10.1002/chem.200400607

by allowing their transformation into other interesting compounds such as diamino acids or polyamines. Moreover, diamine **4g** bears a benzyl group, which could be easily removed to render the corresponding monomethylate derivative, a difficult task to accomplish from the unsubstituted cyclohexane-1,2-diamine.

Results and Discussion

Syntheses of racemic diamines (±)-**4** were achieved by applying the methodology previously described for acyclic diamines.[9] Reaction of cyclohexene oxide with a secondary amine provides the corresponding (±)-*trans*-2-aminocyclohexanol **5** in quantitative yield.[10] One-pot reaction of the β-amino alcohols with mesyl chloride and subsequently with aqueous ammonia yielded the (±)-*trans*-cyclohexane-1,2-diamines (±)-**4** in 70–90% overall yields (Scheme 2).

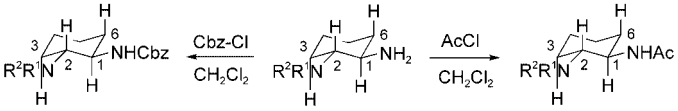


Scheme 2. Preparation of racemic diamines (±)-**4a**–**g**. Ms = mesyl = methane sulfonate.

Abstract in Spanish: *Se ha llevado a cabo la síntesis estereoespecífica de diversas (±)-trans-*N,N*-cyclohexano-1,2-diaminas ((±)-**4a**–**g**) a partir de los correspondientes (±)-trans-*N,N*-dialquilaminociclohexanoles, mediante el tratamiento sucesivo con cloruro de mesilo y amoníaco acuoso. La estereoquímica de los productos sugiere la formación de un ion meso-aziridinio intermedio. La resolución cinética de las diaminas (±)-**4** ha sido realizada eficazmente mediante reacciones de aminólisis catalizadas por la lipasa-B de Candida antarctica, utilizando acetato de etilo como disolvente y como dador de acilo. Las acetamidas producidas y las diaminas, aisladas como sus derivados carbamatos, se obtuvieron con altos excesos enantioméricos (92–99%). Uno de los carbamatos se ha empleado como precursor del analgésico U-(−)-50,488.*

Reactions were stereospecific in all cases. Thus, the *trans* configuration for diamines (±)-**4a** and (±)-**4g** was established by the value of the coupling constants $^3J_{1,2}$, $^3J_{1,6ax}$, or $^3J_{2,3ax}$ in their respective ^{1}H NMR spectra being greater than 10 Hz (Table 1, entries 1 and 2). The *trans* configuration for

Table 1. Selected coupling constants [Hz] measured in the ^{1}H NMR spectra of (±)-**4**, (±)-**6**, or (±)-**7**.[a]

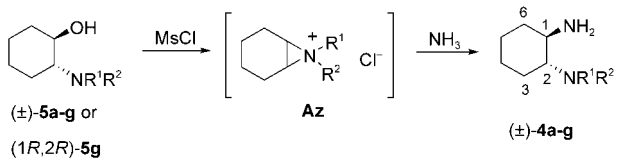


(±)-**7c** (±)-**4a-g** (±)-**6a,b,d-g**

Entry	Compound	Solvent	$^3J_{1,2}$	$^3J_{1,6ax}$	$^3J_{1,6eq}$	$^3J_{2,3ax}$	$^3J_{2,3eq}$
1	(±)-**4a**	$CDCl_3$	10.3			10.3	3.0
2	(±)-**4g**	$CDCl_3$	10.3	10.3	4.3		
3	(±)-**6a**[b]	$CDCl_3$	10.4	10.4	3.9		
4	(±)-**6b**[b]	$CDCl_3$	10.8	10.8	3.0		
5	(±)-**6d**	$CDCl_3+D_2O$	10.6	10.6	3.9		
6	(±)-**6e**	CD_3OD	10.3	10.3	4.3		
7	(±)-**6f**	$CDCl_3+D_2O$	10.6	10.6	3.9		
8	(±)-**7c**	$CDCl_3+D_2O$	10.2	10.2	4.7		

[a] Cbz = benzyloxycarbonyl. [b] *J* values were measured after decoupling of the NH signal.

the other diamines was established by analysis of the ^{1}H NMR spectra of their corresponding acetamide or carbamate derivatives (Table 1, entries 4–8). In all cases, the large *J* values are indicative of a *trans*-diaxial arrangement between H-1 and H-2, and H-1 and H-6ax. This *trans* configuration indicates that the reaction proceeds through a *meso*-



Scheme 3. The conversion of (±)-*trans*-2-aminocyclohexanols **5** into racemic diamines (±)-**4a**–**g** proceeds through a *meso*-aziridinium ion intermediate (**Az**).

aziridinium ion[11] intermediate (**Az**, Scheme 3), which is stereospecifically opened by the ammonia present in the reaction medium. Additional proof supports the notion that *trans*-diamines are only formed through the *meso*-aziridinium ion: when enantiopure amino alcohol (1*R*,2*R*)-**5g**[10b] was submitted to the same reaction conditions, a complete loss of optical activity took place and racemic *trans*-diamine (±)-**4g** was isolated. This result also demonstrates that optically active *trans*-2-*N*,*N*-dialkylaminocyclohexanols cannot be used as precursors of their analogous optically active diamines.

Enzymatic resolution of diamines (±)-**4** was carried out by using lipase B from *Candida antarctica* (CAL-B) as a catalyst. So far, CAL-B (Novozyme SP-435) has proven to be

 © 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

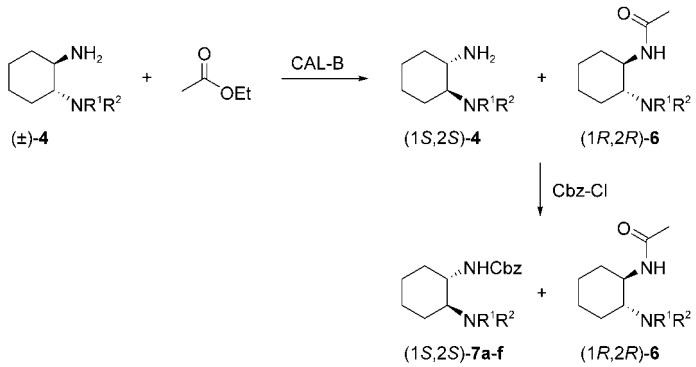
the most effective catalyst for the aminolysis reaction in organic solvents.[12] In particular, this enzyme has shown great efficiency in catalyzing the kinetic sequential resolution of (±)-*trans*-cyclohexane-1,2-diamine, thereby resulting in a useful route for the preparation of optically active symmetrically *N*,*N*′-disubstituted derivatives.[13]

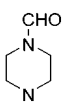
We performed the CAL-B-catalyzed resolution of diamines (±)-**4** under the simplest of reaction conditions, that is, by using ethyl acetate as the acyl donor and solvent. The results presented in Table 2 show that lipase is a very efficient catalyst, and all reactions proceeded with very high values of enantiomer selectivity.[14] In the enzymatic reaction of (±)-**4g**, the resulting mixture formed by the acetamide (1*R*,2*R*)-**6g** and the diamine (1*S*,2*S*)-**4g** was easily separated by flash chromatography. In the other cases, the isolation of both diamine and acetamide was facilitated by the reaction mixtures being previously treated with benzylchloroformate. Thus, diamines (1*S*,2*S*)-**4** were transformed into the corresponding Cbz derivatives (1*S*,2*S*)-**7**, and the resulting mixtures of carbamate and acetamide were also separated by flash chromatography. A base was not required in this derivatization process because benzyloxycarbonylation of the primary amino group of the diamine was catalyzed by the vicinal tertiary amino group. The use of an additional base such as sodium carbonate led to the formation of a mixture of mono- and di-Cbz derivatives, with the di-Cbz derivative being the major compound.

As can be seen in Table 2, yields of both remaining substrate and product were high, especially in the reaction of diamine (±)-**4g**. The high enantioselectivities observed in all cases allowed us to obtain the acetamides (1*R*,2*R*)-**6** with very high *ee* values. The remaining diamines (1*S*,2*S*)-**4**, in most cases isolated as their carbamates, were also mostly obtained with very high *ee* values at conversions (*C*) near to 50%. Although only moderate enantiomeric excess was observed for the remaining substrates of the reactions of (±)-**4d**,**e**,**g** ($C<50\%$, see Table 2), longer reactions times (13, 14, and 9 h, respectively) allowed us to isolate (1*S*,2*S*)-**7d**, (1*S*,2*S*)-**7e**, and (1*S*,2*S*)-**4g** with $ee>99\%$, albeit lower yields. In addition, free diamines (1*S*,2*S*)-**4a**–**f** (*ee*: 93–99%) were obtained in very high yields after removal of the Cbz group (H_2, 10% Pd/C).

In all cases, enantiomeric excess was determined by HPLC with a chiral column. The configuration (1*S*,2*S*) for

Table 2. Enzymatic resolution of racemic diamines (±)-**4**.[a]



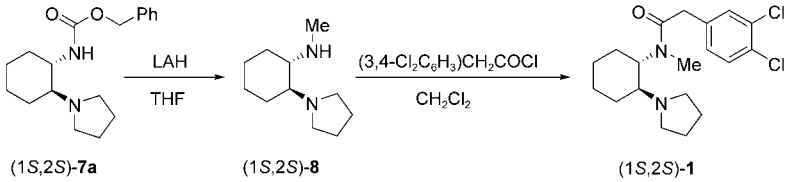
Diamine	NR^1R^2	*t* [h]	*C*[b] [%]	Remaining substrate: diamine or carbamate	yield [%]	*ee* [%]	Product: amide	yield [%]	*ee* [%]	*E*[c]
(±)-**4a**		7	51	(1*S*,2*S*)-**7a**	44	99	(1*R*,2*R*)-**6a**	41	94	170
(±)-**4b**		8	50	(1*S*,2*S*)-**7b**	45	98	(1*R*,2*R*)-**6b**	43	98	>200
(±)-**4c**		8	49	(1*S*,2*S*)-**7c**	46	95	(1*R*,2*R*)-**6c**	45	98	>200
(±)-**4d**		7	44	(1*S*,2*S*)-**7d**	50	77	(1*R*,2*R*)-**6d**	43	98	>200
(±)-**4e**		8	44	(1*S*,2*S*)-**7e**	40	78	(1*R*,2*R*)-**6e**	38	98	>200
(±)-**4f**		6	50	(1*S*,2*S*)-**7f**	38	93	(1*R*,2*R*)-**6f**	43	92	82
(±)-**4g**		5	46	(1*S*,2*S*)-**4g**	49	86	(1*R*,2*R*)-**6g**	45	>99	>200

[a] Reactions were carried out with CAL-B at 28°C and 200 rpm. [b] Conversion: $C=ee_s/(ee_s+ee_p)$. ee_s = substrate *ee* value, ee_p = product *ee* value. [c] Enantiomeric ratio calculated according to ref. [14].

© 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

the remaining diamine **4a** was established after transformation into the analgesic **1** (see below) by comparison of the optical rotation with the reported value for (1*S*,2*S*)-(−)-**1**.[15] This means that CAL-B follows the rule of Kazlauskas et al.,[16] with the diamine with the 1*R*,2*R* configuration being the one preferentially transformed. Taking into account the stereochemical preference shown by CAL-B towards primary amines bearing the steregenic center in the α position,[12] as well as the structural resemblance between diamines reported here, we have tentatively assigned the configurations (1*S*,2*S*) to the other remaining diamines **4b–g** and (1*R*,2*R*) to the corresponding acetamides **6b–g**.

As mentioned above, optically active diamine (1*S*,2*S*)-**4a** is a suitable precursor of the analgesic U-(−)-50,488 ((1*S*,2*S*)-(−)-**1**, see Scheme 1). We carried out the synthesis of this compound from the optically active carbamate (1*S*,2*S*)-**7a**, isolated after benzyloxycarbonylation of the remaining substrate from the enzymatic aminolysis of (±)-**4a**. Thus, reduction of **7a** with $LiAlH_4$ yielded the *N*-methyl derivative (1*S*,2*S*)-**8**, which was treated with 3,4-dichlorophenylacetyl chloride to give (1*S*,2*S*)-**1** in 88% overall yield (Scheme 4).



Scheme 4. Synthesis of analgesic U-(−)-50,488 ((1*S*,2*S*)-**1**). LAH = lithium aluminum hydride.

Previously, compound U-(−)-50,488 was synthesized from *N*-methylcyclohexaneaziridine.[15] The strategy consisted of the opening of the aziridine ring with pyrrolidine to yield (±)-**8** and further fractional crystallization of the diastereomeric salts formed from (±)-**8** and an optically active carboxylic acid. Although (1*S*,2*S*)-**1** was also obtained with a very high *ee* value, we believe that the chemoenzymatic synthesis described herein is an interesting alternative to that previously reported. We use diamine (±)-**4a**, which is obtained from an *N*-dialkylated aziridinium ion (**Az**, Scheme 3) generated in situ under mild conditions. In contrast, the opening of a *N*-alkylaziridine for the preparation of diamine (±)-**8** requires activation by an acidic agent. Moreover, enzymatic resolution of (±)-**4a** is a very simple method, with the compounds being easy to separate by flash chromatography. However, a tedious series of recrystallizations were needed to prepare optically active (1*S*,2*S*)-**8**.

Conclusion

We have developed an efficient chemoenzymatic method for the preparation of a variety of optically active *N*,*N*-disubstituted *trans*-cyclohexane-1,2-diamines and their acetamide derivatives from the inexpensive cyclohexene oxide. As a proof of the utility of these diamines, one of them, (1*S*,2*S*)-2-(pyrrolidin-1-yl)cyclohexanamine, has been used in the synthesis of the analgesic U-(−)-50,488.

Experimental Section

General: *Candida antarctica* lipase B (CAL-B, available immobilized on polyacrylamide as Novozyme SP-435, 7300 PLU g^{-1}) was supplied by Novo Nordisk Co. For the enzymatic reactions, ethyl acetate of spectrophotometric grade (stored with 4 Å molecular sieves) was used. Melting points were taken on samples in open capillary tubes and are uncorrected. IR spectra were recorded on an Infrared FT spectrophotometer as KBr pellets (for solids) or neat (for liquids). Flash chromatography was performed by using silica gel 60 (230–400 mesh). Chiral HPLC analyses were performed by using Chiralcel OD and OD-RH columns (Daicel) at 20–35 °C. ^{1}H, ^{13}C NMR, and DEPT spectra were recorded in $CDCl_3$ or CD_3OD by using AC-200 (^{1}H, 200.13 MHz; ^{13}C, 50.3 MHz) and AC-300 or DPX-300 (^{1}H, 300.13 MHz; ^{13}C, 75.5 MHz) spectrometers for routine experiments. An AMX-400 spectrometer (^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz) was used for the acquisition of ^{1}H–^{1}H and ^{1}H–^{13}C correlation experiments. The chemical shift values (δ) are given in ppm and the coupling constants (J) are given in Hertz (Hz). Positive electrospray ionization (ESI^+) was used to record mass spectra. Microanalyses were performed on a Perkin–Elmer model 2400 instrument.

General procedure for the preparation of racemic diamines (±)-*trans*-4a–g: The appropriate secondary amine (49 mmol) was added to a solution of cyclohexene oxide (30 mmol) in EtOH (30 mL), and the resulting mixture was heated under reflux for 18 h. After cooling, the solvent was evaporated and the crude (±)-*trans*-2-aminocyclohexanol (±)-**5a–g**[10b] was purified by flash chromatography (hexane/ethyl acetate or ethyl acetate/methanol mixtures). The purified (±)-*trans*-2-aminocyclohexanol (25 mmol) was dissolved in anhydrous diethyl ether (45 mL), and triethylamine (39 mmol) was added. The solution was cooled to 0 °C, and mesyl chloride (29.7 mmol) was added dropwise. A white precipitate formed and made stirring difficult. After 30 min, triethylamine (49 mmol) was added. After the reaction mixture was allowed to warm to room temperature, concentrated aqueous NH_3 (50 mL) was added and the resulting two-phase reaction mixture was vigorously stirred during 16 h. The layers were separated, and the light-yellow aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried with Na_2SO_4, and evaporated under reduced pressure to give the crude product, which was purified by distillation or flash chromatography.

(±)-*trans*-2-(Pyrrolidin-1-yl)cyclohexanamine ((±)-4a): Yield: 90%; b.p. 55–56 °C (0.5 Torr); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30–1.00 (m, 4H; (H-3, H-4, H-5, H-6)ax), 1.60–1.70 (m, 7H; H-8, H-8′, (H-3, H-4, H-5)eq), 1.94 (br d, $J_{6eq,6ax}$ = 10.6 Hz, 1H; H-6eq,), 2.12 (s, 2H; NH_2), 2.28 (dt, $J_{2,3eq}$ = 3.0, $J_{1,2}$ = $J_{2,3ax}$ = 10.3 Hz, 1H; H-2), 2.45–2.70 ppm (m, 5H; H-1, 2 × CH_2N); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.34 (CH_2), 23.62 (C-8), 24.89 (CH_2), 25.37 (CH_2), 34.84 (CH_2), 46.97 (CH_2N), 52.62 (C-1), 65.07 ppm (C-2); IR (neat): $\tilde{\nu}$ = 3356, 3302 cm^{-1}; MS (ESI^+): *m*/*z* (%): 169.1 (100) $[M+H]^+$, 191.1 (15) $[M+Na]^+$; elemental analysis calcd (%) for $C_{10}H_{20}N_2$: C 71.37, H 11.98, N 16.65; found: C 71.43, H 11.85, N 16.72.

(±)-*trans*-2-(Piperidin-1-yl)cyclohexanamine ((±)-4b): Yield: 86%; b.p. 50–51 °C (0.5 Torr); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78–0.95 (m, 4H), 1.10–1.55 (m, 11H), 1.65–1.76 (m, 2H), 1.95–2.08 (m, 2H), 2.30–2.45 ppm (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.99 (CH_2), 24.53 (CH_2), 25.42 (CH_2), 26.34 (2CH_2), 34.66 (CH_2), 49.15 (2CH_2), 50.12 (CH), 70.68 ppm (CH); IR (neat): $\tilde{\nu}$ = 3358 cm^{-1}; MS (ESI^+): *m*/*z* (%): 183.2

 © 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

(100) $[M+H]^+$, 205.1 (5) $[M+Na]^+$; elemental analysis calcd (%) for $C_{11}H_{22}N_2$: C 72.47, H 12.16, N 15.37; found: C 72.38, H 12.01, N 15.61.

(±)-*trans*-2-(Morpholin-4-yl)cyclohexanamine ((±)-4c): Yield: 85%; b.p. 65–66°C (0.5 Torr); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.70$–1.07 (m, 4H), 1.36–1.67 (m, 5H), 1.70–1.88 (m, 2H), 2.18 (ddd, $J=3.5$, 5.7, 10.7 Hz, 2H), 2.37–2.50 (m, 3H), 3.38–3.54 ppm (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=22.06$ (CH_2), 24.36 (CH_2), 25.23 (CH_2), 34.51 (CH_2), 48.22 (CH_2), 49.84 (CH), 67.10 (CH_2), 70.12 ppm (CH); IR (neat): $\tilde{\nu}=3373$, 3318 cm^{-1}; MS (ESI$^+$): m/z (%): 185.1 (100) $[M+H]^+$, 207.1 (7) $[M+Na]^+$; elemental analysis calcd (%) for $C_{10}H_{20}N_2O$: C 65.18, H 10.94, N 15.20; found: C 65.05, H 10.87, N 15.31.

Methyl (±)-*trans*-1-(2-aminocyclohexyl)piperidine-4-carboxylate ((±)-4d): Yield: 70%; m.p. 168–170°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.92$–1.15 (m, 4H), 1.45–2.05 (m, 12H), 1.70–1.88 (m, 2H), 2.15 (m, 1H), 2.41–2.55 (m, 3H), 2.71 ppm (dt, $J=3.1$ and 11.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=22.47$ (CH_2), 24.77 (CH_2), 25.64 (CH_2), 28.84 (CH_2), 29.00 (CH_2), 34.85 (CH_2), 41.50 (CH), 44.71 (CH_2), 50.45 (CH), 51.33 (CH_2), 51.38 (CH_3), 70.58 (CH), 175.63 ppm (C=O); IR (KBr): $\tilde{\nu}=$ 3360, 3285,1736 cm^{-1}; MS (ESI$^+$): m/z (%): 241.1 (100) $[M+H]^+$, 263.1 (3) $[M+Na]^+$; elemental analysis calcd (%) for $C_{13}H_{24}N_2O_2$: C 64.97, H 10.07, N 11.66; found: C 65.05, H 10.12, N 11.50.

(±)-*trans*-2-(4-Formylpiperazin-1-yl)cyclohexanamine ((±)-4e): Yield: 80%; m.p. 168–170°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=0.90$–1.20 (m, 4H), 1.45–1.70 (m, 3H), 1.85 (m, 1H), 2.05 (dt, $J=3.1$ and 11.0 Hz, 1H), 2.15–2.34 (m, 2H), 2.45–2.63 (m, 3H), 2.90–3.10 (m, 2H), 3.18–3.45 (m, 4H), 7.87 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=22.47$ (CH_2), 24.26 (CH_2), 25.07 (CH_2), 33.86 (CH_2), 40.16 (CH_2), 45.88 (CH_2), 47.41 (CH_2), 48.70 (CH_2), 50.09 (CH), 69.67 (CH), 160.33 ppm (C=O); IR (Nujol): $\tilde{\nu}=3472$, 3344, 1666 cm^{-1}; MS (ESI$^+$): m/z (%): 212.1 (100) $[M+H]^+$, 234.1 (12) $[M+Na]^+$; elemental analysis calcd (%) for $C_{11}H_{21}N_3O$: C 62.52, H 10.02, N 19.89; found: C 62.68, H 10.11, N 19.80.

(±)-*trans*-*N*-Isopropyl-*N*-methylcyclohexane-1,2-diamine ((±)-4f): Yield: 86%; b.p. 48–50°C (0.5 Torr); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=$ 1.00–1.30 (m+2t, $J=6.3$ Hz, 11H), 1.60–1.80 (m, 3H), 1.85–2.00 (m, 2H), 2.10–2.20 (m+s, 4H; CH, CH_3), 2.45–2.60 (m, 1H), 2.84 ppm (heptet, $J=6.3$ Hz, 1H); ^{13}C NMR (75.5 MHz $CDCl_3$): $\delta=20.38$ (CH_3), 20.83 (CH_3), 24.82 (CH_2), 25.47 (CH_2), 25.74 (CH_2), 30.57 (CH_3), 34.72 (CH_2), 51.00 (CH), 51.93 (CH), 66.33 ppm (CH); IR (neat): $\tilde{\nu}=3354$, 3302 cm^{-1}; MS (ESI$^+$): m/z (%): 171.2 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{10}H_{22}N_2$: C 70.53, H 13.02, N 16.45; found: C 70.65, H 12.99, N 16.40.

(±)-*trans*-*N*-Benzyl-*N*-methylcyclohexane-1,2-diamine ((±)-4g): Yield: 84%; b.p. 100–101°C (0.5 Torr); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.00$–1.30 (m, 4H), 1.60–2.00 (m, 6H), 2.10–2.25 (m+s, 4H; CH, CH_3), 2.67 (dt, $J_{1,6eq}=4.3$, $J_{1,2}=J_{1,6ax}=10.3$ Hz, 1H; H-1), 2.37–2.50 (m, 3H), 3.45, 3.67, (AB system, $J_{AB}=13.4$ Hz; CH_2), 7.15–7.35 ppm (m, 5H; Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=21.83$ (CH_2), 24.91 (CH_2), 25.58 (CH_2), 34.99 (CH_2), 36.20 (CH_3), 51.21 (CH), 57.91 (CH_2), 69.36 (CH), 126.55 (CH), 128.00 (CH), 128.42 (CH), 140.15 ppm (C); IR (neat): $\tilde{\nu}=3356$, 3302 cm^{-1}; MS (ESI$^+$): m/z (%): 219.1 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{14}H_{22}N_2$: C 77.01, H 10.16, N 12.83; found: C 76.85, H 10.08, N 13.07.

General procedure for the enzymatic acetylation of (±)-*trans*-4a–g: Ethyl acetate (12 mL) was added to a mixture of the appropriate racemic diamine **4a–g** (2.0 mmol) and CAL-B (200 mg) under a nitrogen atmosphere. The resulting mixture was shaken at 28°C and 200 rpm for 5–8 h. Afterward, the enzyme was filtered and washed with ethyl acetate. For the reactions with **4a–f**, the resulting solution was cooled to 0°C and then treated with benzyl chloroformate (1.6 mmol). After 15 h, the solvent was evaporated, then the acetamide and carbamate present in the residue were separated by flash chromatography (ethyl acetate/methanol mixtures). For the reaction with **4g**, after filtration of the enzyme, the corresponding acetamide and the remaining diamine were separated by flash chromatography with ethyl acetate/methanol (6:1).

(1*R*,2*R*)-*N*-[2-(Pyrrolidin-1-yl)cyclohexyl]acetamide ((1*R*,2*R*)-6a): Yield: 41%; m.p. 88–90°C; $[\alpha]_D^{20}=-63.2$ ($c=1.0$ in $CHCl_3$); 94% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.05$–1.40 (m, 4H), 1.60–1.82 (m, 7H), 1.97 (s, 3H; CH_3), 2.40–2.65 (m, 6H), 3.51 (m ($J_{1,6eq}=3.9$, $J_{1,2}=J_{1,6ax}=10.4$ Hz measured after irradiation of NH signal), 1H; H-1), 6.20 ppm (brs, 1H; NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=21.99$ (CH_2), 23.59 (CH_2), 23.64 (CH_3), 24.23 (CH_2), 24.70 (CH_2), 32.04 (CH_2), 46.95 (CH_2), 52.01 (CH), 61.55 (CH), 170.28 ppm (C=O); IR (KBr): $\tilde{\nu}=3289$, 1634 cm^{-1}; MS (ESI$^+$): m/z (%): 211.1 (80) $[M+H]^+$, 233.1 (25) $[M+Na]^+$; elemental analysis calcd (%) for $C_{12}H_{22}N_2O$: C 68.53, H 10.54, N 13.32; found: C 68.69, H 10.50, N 13.41.

(1*R*,2*R*)-*N*-[2-(Piperidin-1-yl)cyclohexyl]acetamide ((1*R*,2*R*)-6b): Yield: 43%; m.p. 122–124°C; $[\alpha]_D^{20}=-65.4$ ($c=1.0$ in $CHCl_3$); 98% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.95$–1.62 (m, 11H), 1.70–1.88 (m, 2H), 1.92 (s, 3H; CH_3), 2.10–2.32 (m, 3H), 2.40–2.60 (m, 3H), 3.51 (m ($J_{1,6eq}=3.0$, $J_{1,2}=J_{1,6ax}=10.8$ Hz, measured after irradiation of NH signal), 1H; H-1), 6.35 ppm (brs, 1H; NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=22.90$ (CH_2), 23.45 (CH_3), 24.48 (CH_2), 24.70 (CH_2), 25.53 (CH_2), 26.63 (CH_2), 32.61 (CH_2), 48.98 (CH_2), 50.63 (CH), 67.47 (CH), 170.52 ppm (C=O); IR (KBr): $\tilde{\nu}=3286$, 1651 cm^{-1}; MS (ESI$^+$): m/z (%): 225.2 (80) $[M+H]^+$, 247.1 (10) $[M+Na]^+$; elemental analysis calcd (%) for $C_{13}H_{24}N_2O$: C 69.60, H 10.78, N 12.49; found: C 69.50, H 10.64, N 12.61.

(1*R*,2*R*)-*N*-[2-(Morpholin-4-yl)cyclohexyl]acetamide ((1*R*,2*R*)-6c): Yield: 45%; m.p. 115–117°C; $[\alpha]_D^{20}=-66.5$ ($c=1.0$ in $CHCl_3$); 95% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.95$–1.32 (m, 4H), 1.55–1.65 (m, 1H), 1.73–1.86 (m, 2H), 1.93 (s, 3H; CH_3), 2.19 (dt, $J=3.2$, 10.7 Hz, 1H), 2.25–2.38 (m, 3H), 2.56–2.65 (m, 2H), 3.48–3.65 (m, 5H), 6.06 ppm (brs, 1H; NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=22.89$ (CH_2), 23.05 (CH_3), 24.29 (CH_2), 25.00 (CH_2), 32.55 (CH_2), 47.94 (CH_2), 49.52 (CH), 66.88 (CH), 67.18 (CH_2), 169.74 ppm (C=O); IR (KBr): $\tilde{\nu}=3270$, 1652 cm^{-1}; MS (ESI$^+$): m/z (%): 227.1 (20) $[M+H]^+$, 249.1 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{12}H_{22}N_2O_2$: C 63.68, H 9.80, N 12.38; found: C 63.75, H 9.92, N 12.29.

Methyl (1*R*,2*R*)-1-[2-(acetylamino)cyclohexyl]piperidine-4-carboxylate ((1*R*,2*R*)-6d): Yield: 43%; oil; $[\alpha]_D^{20}=+11.25$ ($c=0.93$ in $CHCl_3$); 94% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.89$–1.28 (m, 4H), 1.43 (m, 1H), 1.51–1.85 (m, 6H), 1.88 (s, 3H; CH_3), 2.02 (dt, $J=2.6$, 11.4 Hz, 1H), 2.10–2.25 (m, 2H), 2.32–2.55 (m, 3H), 2.67 (dt, $J=11.1$, 3.7 Hz, 1H), 3.43 (m (dt, $J_{1,6eq}=3.9$, $J_{1,2}=J_{1,6ax}=10.6$ Hz, after amide NH to ND exchange with D_2O), 1H; H-1), 3.59 (s, 3H; CH_3), 6.14 ppm (brs, 1H; NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=22.90$ (CH_2), 23.09 (CH_3), 24.28 (CH_2), 25.15 (CH_2), 28.63 (CH_2), 28.69 (CH_2), 32.49 (CH_2), 41.03 (CH), 44.48 (CH_2), 50.11 (CH), 51.19 (CH_3), 59.84 (CH_2), 66.93 (CH), 169.97 (C=O), 175.26 ppm (C=O); IR (Nujol): $\tilde{\nu}=3296$, 1732, 1651 cm^{-1}; MS (ESI$^+$): m/z (%): 283.1 (100) $[M+H]^+$, 305.1 (5) $[M+Na]^+$; elemental analysis calcd (%) for $C_{15}H_{26}N_2O_3$: C 63.80, H 9.28, N 9.92; found: C 63.95, H 9.35, N 10.01.

(1*R*,2*R*)-*N*-[2-(4-Formylpiperazin-1-yl)cyclohexyl]acetamide ((1*R*,2*R*)-6e): Yield: 38%; m.p. 140–142°C; $[\alpha]_D^{20}=-27.7$ ($c=0.9$ in MeOH); 98% *ee*; ^{1}H NMR (200 MHz, CD_3OD): $\delta=1.15$–1.27 (m, 4H), 1.65–1.97 (m+s, 7H), 2.30–2.48 (m, 3H), 2.64–2.78 (m, 2H), 3.30–3.51 (m, 4H), 3.75 (dt, $J_{1,6eq}=4.3$, $J_{1,2}=J_{1,6ax}=10.3$ Hz, 1H; H-1,), 7.97 ppm (s, 1H); ^{13}C NMR (75.5 MHz, CD_3OD): $\delta=22.79$ (CH_3), 25.41 (CH_2), 26.14 (CH_2), 26.37 (CH_2), 34.14 (CH_2), 41.94 (CH_2), 47.82 (CH_2), 49.15 (CH_2), 50.20 (CH_2), 50.71 (CH), 68.70 (CH), 162.97 (CH), 172.52 ppm (C=O); IR (KBr): $\tilde{\nu}=3325$, 1644 cm^{-1}; MS (ESI$^+$): m/z (%): 254.1 (8) $[M+H]^+$, 276.1 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{13}H_{23}N_3O_3$: C 57.97, H 8.61, N 15.60; found: C 58.04, H 8.50, N 15.88.

(1*R*,2*R*)-*N*-[2-(*N'*-Isopropyl-*N'*-methylamino)cyclohexyl]acetamide ((1*R*,2*R*)-6f): Yield: 43%; oil; $[\alpha]_D^{20}=-64.5$ ($c=1.0$ in $CHCl_3$); 92% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.90$–0.98 (t, $J=6.8$ Hz, 6H), 1.05–1.30 (m, 4H), 1.50–1.80 (m, 3H), 1.86 (s, 3H; CH_3), 2.06 (s, 3H; CH_3), 2.28–2.45 (m, 2H), 2.75 (heptet, $J=6.4$ Hz, 1H), 3.34 (m (dt, $J_{1,6eq}=3.9$, $J_{1,2}=J_{1,6ax}=10.6$ Hz, after amide NH to ND exchange with D_2O), 1H; H-1), 6.20 ppm (brs, 1H; NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=20.33$ (CH_3), 21.45 (CH_3), 23.31 (CH_3), 24.34 (CH_2), 25.35 (CH_2), 25.46 (CH_2), 30.90 (CH_3), 32.42 (CH_2), 50.22 (CH), 50.89 (CH), 63.75 (CH), 170.16 ppm (C=O); IR (KBr): $\tilde{\nu}=3289$, 1650 cm^{-1}; MS (ESI$^+$): m/z (%): 213.2 (100) $[M+H]^+$, 235.1 (8) $[M+Na]^+$; elemental analysis calcd (%) for $C_{12}H_{24}N_2O$: C 67.88, H 11.39, N 13.19; found: C 68.05, H 11.30, N 12.99.

(1*R*,2*R*)-*N*-[2-(*N'*-Benzyl-*N'*-methylamino)cyclohexyl]acetamide ((1*R*,2*R*)-6g): Yield: 45%; m.p. 143–145°C; $[\alpha]_D^{20}=-16.5$ ($c=1.0$ in $CHCl_3$); >99% *ee*; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=0.95$–1.40 (m, 4H), 1.60–2.05 (m+s, 6H), 2.18 (s, 3H; CH_3), 1.86 (s, 3H; CH_3), 2.35 (dt, $J=$ 3.1, 11.0 Hz, 1H), 2.53 (m, 1H), 3.39, 3.69 (AB system, $J_{AB}=13.3$ Hz; CH_2), 3.59 (m, 1H), 6.09 (brs, 1H; NH), 7.15–7.35 ppm (m, 5H; Ph);

© 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.42 (CH_2), 23.57 (CH_3), 24.50 (CH_2), 25.34 (CH_2), 32.67 (CH_2), 36.73 (CH_3), 50.92 (CH), 56.94 (CH_2), 65.27 (CH), 126.87 (CH), 128.22 (CH), 128.39 (CH), 139.77 (C), 170.12 ppm (C=O); IR (KBr): $\tilde{\nu}$ = 3285, 1638 cm^{-1}; MS (ESI$^+$): *m*/*z* (%): 261.1 (100) $[M+H]^+$, 283.1 (20) $[M+Na]^+$; elemental analysis calcd (%) for $C_{16}H_{24}N_2O$: C, 73.81, H 9.29, N 10.76; found: C 74.01, H 9.26, N 10.73.

Benzyl (1*S*,2*S*)-*N*-[2-(pyrrolidin-1-yl)cyclohexyl]carbamate ((1*S*,2*S*)-7a): Yield: 44%; oil; $[\alpha]_D^{20}$ = +49.2 (*c* = 1.05 in $CHCl_3$); 99% *ee*; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.05–1.40 (m, 4H), 1.60–1.85 (m, 7H), 2.35–2.75 (m, 6H), 3.35 (m, 1H), 5.12, 5.09 (AB system, J_{AB} = 12.0 Hz; CH_2), 5.73 (brs, 1H; NH), 7.20–7.35 ppm (m, 5H; Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.06 (CH_2), 23.57 (CH_2), 24.04 (CH_2), 24.51 (CH_2), 31.98 (CH_2), 47.06 (CH_2), 52.89 (CH), 61.78 (CH), 66.11 (CH_2), 127.79 (CH), 127.83 (CH), 128.30 (CH), 136.75 (C), 156.42 ppm (C=O); IR (neat): $\tilde{\nu}$ = 3337, 1715 cm^{-1}; MS (ESI$^+$): *m*/*z* (%): 303.2 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{18}H_{26}N_2O_2$: C 71.49, H 8.67, N 9.26; found: C 71.56, H 8.70, N 9.15.

Benzyl (1*S*,2*S*)-*N*-[2-(piperidin-1-yl)cyclohexyl]carbamate ((1*S*,2*S*)-7b): Yield: 45%; oil; $[\alpha]_D^{20}$ = +49.5 (*c* = 1.0 in $CHCl_3$); 98% *ee*; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.00–1.95 (m, 13H), 2.10–2.30 (m, 3H), 2.45–2.65 (m, 3H), 3.29 (m, 1H), 5.12 (s, 2H; CH_2), 5.72 (brs, 1H; NH), 7.20–7.35 ppm (m, 5H; Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.78 (CH_2), 24.37 (CH_2), 24.70 (CH_2), 25.43 (CH_2), 26.42 (CH_2), 32.74 (CH_2), 49.00 (CH_2), 51.44 (CH), 65.93 (CH_2), 67.66 (CH), 127.64 (CH), 128.22 (CH), 136.85 (C), 156.53 ppm (C=O); IR (neat): $\tilde{\nu}$3348, 1724 cm^{-1}; MS (ESI$^+$): *m*/*z* (%): 317.2 (100) $[M+H]^+$, 339.2 (5) $[M+Na]^+$; elemental analysis calcd (%) for $C_{19}H_{28}N_2O_2$: C 72.12, H 8.92, N 8.85; found: C 72.25, H 8.80, N 8.99.

Benzyl (1*S*,2*S*)-*N*-[2-(morpholin-4-yl)cyclohexyl]carbamate ((1*S*,2*S*)-7c): Yield: 46%; oil; $[\alpha]_D^{20}$ = +45.7 (*c* = 1.0 in $CHCl_3$); 98% *ee*; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.00–1.35 (m, 4H), 1.55–1.92 (m, 3H), 2.16 (dt, *J* = 3.1, 10.6 Hz, 1H), 2.28–2.50 (m, 3H), 2.55–2.70 (m, 2H), 3.33 (m, (dt, $J_{1,6eq}$ = 4.7, $J_{1,2}$ = $J_{1,6ax}$ = 10.2 Hz, after NH to ND exchange with D_2O), 1H; H-1), 3.58–3.75 (m, 4H), 5.09 (s, 2H; CH_2), 5.44 ppm (brd, *J* = 4.7 Hz, 1H; NH); 7.20–7.35 (m, 5H; Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.81 (CH_2), 24.26 (CH_2), 24.98 (CH_2), 32.72 (CH_2), 48.01 (CH_2), 50.78 (CH), 65.81 (CH_2), 67.02 (CH_2), 67.24 (CH), 127.51 (CH), 128.04 (CH), 136.56 (C), 156.11 ppm (C=O); IR (neat): $\tilde{\nu}$ = 3333, 1710 cm^{-1}; MS (ESI$^+$): *m*/*z* (%): 319.2 (100) $[M+H]^+$, 341.1 (15) $[M+Na]^+$; elemental analysis calcd (%) for $C_{18}H_{26}N_2O_3$: C 67.90, H 8.23, N 8.80; found: C 68.07, H 8.26, N 8.63.

Benzyl (1*S*,2*S*)-*N*-{2-[4-(methoxycarbonyl)piperidin-1-yl]cyclohexyl}carbamate ((1*S*,2*S*)-7d): Yield: 50%; oil; $[\alpha]_D^{20}$ = +33.6 (*c* = 0.93 in $CHCl_3$); >99% *ee*; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.95–1.35 (m, 5H), 1.52–1.98 (m, 6H), 2.03–2.30 (m, 3H), 2.45–2.58 (m, 3H), 2.77 (dt, *J* = 3.5, 11.3 Hz, 1H), 3.30 (m, 1H), 3.68 (s, 3H; CH_3), 5.12, 5.09 (AB system, J_{AB} = 12.1 Hz; CH_2), 5.51 (brs, 1H; NH), 7.20–7.35 ppm (m, 5H; Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.99 (CH_2), 24.42 (CH_2), 25.37 (CH_2), 28.61 (CH_2), 28.78 (CH_2), 32.86 (CH_2), 41.29 (CH), 44.78 (CH_2), 50.47 (CH_2), 51.45 (CH_3), 66.12 (CH_2), 67.47 (CH), 127.79 (CH), 127.84 (CH), 128.33 (CH), 136.77 (C), 156.48 (C=O), 175.48 ppm (C=O); IR (neat): $\tilde{\nu}$ = 3352, 1731 cm^{-1}; MS (ESI$^+$): *m*/*z* (%): 375.2 (100) $[M+H]^+$, 397.2 (5) $[M+Na]^+$; elemental analysis calcd (%) for $C_{21}H_{30}N_2O_4$: C 67.35, H 8.07, N 7.48; found: C 67.50, H 8.24, N 7.41.

Benzyl (1*S*,2*S*)-*N*-[2-(4-formylpiperazin-1-yl)cyclohexyl]carbamate ((1*S*,2*S*)-7e): Yield: 40%; m.p. 92–94°C; $[\alpha]_D^{20}$ = +38.9 (*c* = 1.7 in MeOH); 78% *ee*; ^{1}H NMR (200 MHz, CD_3OD): δ = 1.05–1.40 (m, 4H), 1.65–2.07 (m, 5H), 2.30–2.95 (m, 4H), 3.20–3.55 (m, 5H), 4.79–5.18 (overlapping of CH_2 and solvent signals), 7.25–7.36 (m, 5H; Ph), 7.94 ppm (s, 1H); ^{13}C NMR (75.5 MHz, CD_3OD): δ = 25.41 (CH_2), 26.09 (CH_2), 26.16 (CH_2), 34.30 (CH_2), 41.18 (CH_2), 47.00 (CH_2), 49.21 (CH_2), 50.25 (CH_2), 52.17 (CH), 67.17 (CH_2), 69.60 (CH), 128.89 (CH), 129.39 (CH), 138.59 (C), 158.57 (C=O), 162.70 ppm (CH); MS (ESI$^+$): *m*/*z* (%): 375.2 (100) $[M+H]^+$, 397.2 (5) $[M+Na]^+$; elemental analysis calcd (%) for $C_{19}H_{27}N_3O_3$: C 66.06, H 7.88, N 12.16; found: C 65.90, H 8.02, N 12.29.

Benzyl (1*S*,2*S*)-*N*-[2-(*N*′-isopropyl-*N*′-methylamino)cyclohexyl]carbamate ((1*S*,2*S*)-7f): Yield: 38%; oil; $[\alpha]_D^{20}$ = +51.5 (*c* = 0.95 in $CHCl_3$); 93% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, *J* = 7.1 Hz, 6H), 1.18–1.35 (m, 4H), 1.65–1.92 (m, 3H), 2.18 (s, 3H; CH_3), 2.41 (dt, *J* = 3.0, 10.6 Hz, 1H), 2.59 (m, 1H), 2.84 (heptet, *J* = 7.1 Hz, 1H), 3.28 (m, 1H), 5.13 (s, 2H; CH_2), 5.64 (brs, 1H; NH), 7.20–7.35 ppm (m, 5H; Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.42 (CH_3), 21.37 (CH_3), 24.34 (CH_2), 25.33 (CH_2), 25.49 (CH_2), 30.96 (CH_3), 32.67 (CH_2), 50.56 (CH), 51.95 (CH), 63.64 (CH), 65.90 (CH_2), 127.62 (CH), 127.70 (CH), 128.16 (CH), 136.75 (C), 156.50 ppm (C=O); IR (neat): $\tilde{\nu}$ = 3349, 1723 cm^{-1}; MS (ESI$^+$): *m*/*z* (%): 305.1 (100) $[M+H]^+$, 327.1 (15) $[M+Na]^+$; elemental analysis calcd (%) for $C_{18}H_{28}N_2O_2$: C 71.02, H 9.27, N 9.20; found: C 71.28, H 9.40, N 8.99.

(1*S*,2*S*)-*N*-Benzyl-*N*-methylcyclohexane-1,2-diamine ((1*S*,2*S*)-4g): Yield: 49%; $[\alpha]_D^{20}$ = +48.2 (*c* = 1.1 in $CHCl_3$); 86% *ee*. Diamine (1*S*,2*S*)-**4g** with *ee* > 99% ($[\alpha]_D^{20}$ = +48.2 (*c* = 1.1 in $CHCl_3$)) was isolated if the enzymatic reaction was conducted for 9 h.

General procedure for the hydrogenolysis of the benzyl carbamates (1*S*,2*S*)-7a–f: A suspension of (1*S*,2*S*)-**7a–f** (0.75 mmol) and Pd/C (10%, 120 mg) in deoxygenated methanol (15 mL) was stirred for 12 h under a hydrogen atmosphere. The reaction mixture was filtered through Celite, and the filtrate was evaporated to yield pure (1*S*,2*S*)-**4a–f**.

(1*S*,2*S*)-2-(Pyrrolidin-1-yl)cyclohexanamine ((1*S*,2*S*)-4a): Yield: 90%; $[\alpha]_D^{20}$ = +65.2 (*c* = 1.0 in $CHCl_3$); 99% *ee*.

(1*S*,2*S*)-2-(Piperidin-1-yl)cyclohexanamine ((1*S*,2*S*)-4b): Yield: 96%; $[\alpha]_D^{20}$ = +54.0 (*c* = 1.0 in $CHCl_3$); 98% *ee*.

(1*S*,2*S*)-2-(Morpholin-4-yl)cyclohexanamine ((1*S*,2*S*)-4c): Yield: 97%; $[\alpha]_D^{20}$ = +60.1 (*c* = 0.80 in $CHCl_3$); 95% *ee*.

Methyl (1*S*,2*S*)-1-(2-aminocyclohexyl)piperidine-4-carboxylate ((1*S*,2*S*)-4d): Yield: 95%; $[\alpha]_D^{20}$ = +36.4 (*c* = 1.1 in $CHCl_3$); >99% *ee*.

(1*S*,2*S*)-2-(4-Formylpiperazin-1-yl)cyclohexanamine ((1*S*,2*S*)-4e): Yield: 93%; $[\alpha]_D^{20}$ = +47.2 (*c* = 0.75 in CH_3OH); >99% *ee*.

(1*S*,2*S*)-*N*-Isopropyl-*N*-methylcyclohexane-1,2-diamine ((1*S*,2*S*)-4f): Yield: 98%; $[\alpha]_D^{20}$ = +40.7 (*c* = 1.4 in $CHCl_3$); 93% *ee*.

(1*S*,2*S*)-*N*-Methyl-2-(pyrrolidin-1-yl)cyclohexanamine ((1*S*,2*S*)-8): A solution of carbamate (1*S*,2*S*)-**7a** (0.80 mmol) in THF (3 mL) was added to a suspension of $LiAlH_4$ (1.25 mmol) in THF (5 mL) under a nitrogen atmosphere. The mixture was stirred at room temperature for 21 h. After this time, the excess $LiAlH_4$ was destroyed by addition of 3N aqueous Na_2CO_3, the mixture was filtered through Celite, and the solvents were evaporated. Diethyl ether (15 mL) was then added, and the organic solution was extracted with 2N aqueous HCl (3×10 mL). The aqueous phase was washed with diethyl ether (10 mL), and pellets of NaOH were added until a basic pH value was reached. Extraction with diethyl ether (4×15 mL) and evaporation of the organic solvent yielded pure diamine (1*S*,2*S*)-**8**. Yield: 90%; oil; $[\alpha]_D^{20}$ = +90.3 (*c* = 0.95 in $CHCl_3$); 99% *ee* (literature value[15] for (1*S*,2*S*)-(+)-**8**: $[\alpha]_D^{23}$ = +97.6 (*c* = 0.29 in methanol); > 99.5% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80–0.98 (m, 1H), 1.00–1.22 (m, 3H), 1.50–1.75 (m, 7H), 1.95–2.15 (m, 2H), 2.31 (s, 3H; CH_3), 2.32–2.55 (m, 5H), 2.71 ppm (brs, 1H; NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.16 (CH_2), 23.57 (CH_2), 24.39 (CH_2), 25.17 (CH_2), 30.98 (CH_2), 34.00 (CH_3), 46.69 (CH_2), 61.33 (CH), 61.95 ppm (CH); IR (neat): $\tilde{\nu}$ = 3315, 1357 cm^{-1}; MS (ESI$^+$): *m*/*z* (%): 183.1 (100) $[M+H]^+$, 205.1 (5) $[M+Na]^+$, 112.1 (15), 152.1 (10); elemental analysis calcd (%) for $C_{11}H_{22}N_2$: C 72.47, H 12.16, N 15.37; found: C 72.58, H 12.06, N 15.36.

(1*S*,2*S*)-*N*-Methyl-*N*-[2-(pyrrolidin-1-yl)cyclohexyl]-2-(3,4-dichlorophenyl)acetamide ((1*S*,2*S*)-1): Under a nitrogen atmosphere, (1*S*,2*S*)-**8** (0.60 mmol) was dissolved in dichloromethane (5 mL), and 3,4-dichlorophenylacetyl chloride (0.76 mmol) was added at 0°C. After stirring for 5 h, dichloromethane (10 mL) was added, and the organic layer was washed with saturated aqueous $NaHCO_3$ (2×10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated to yield crude (1*S*,2*S*)-**1**, which was purified by flash chromatography (hexane/ethyl acetate 1:2): Yield: 95%; oil. Hydrochloride salt of (1*S*,2*S*)-**1**. $[\alpha]_D^{20}$ = −34.0 (*c* = 0.7 in methanol); 99% *ee*; (literature value[15] for (1*S*,2*S*)-(−)-**1**·HCl: $[\alpha]_D^{20}$ = −36.05 (*c* = 0.73 in methanol); >99% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) corresponding to a 80:20 mixture of rotamers: δ = 0.90–2.00 (m, 12H), 2.40–2.70 (m, 5H), 2.79 (s, 3H for major rotamer, CH_3), 2.80 (s, 3H for minor rotamer, CH_3), 3.46 (dt, $J_{1,6eq}$ = 5.0, $J_{1,2}$ = $J_{1,6ax}$ = 10.6 Hz, 1H for minor rotamer; H-1), 3.60, 3.70 (AB system, J_{AB} = 15.4 Hz; CH_2), 4.49 (dt, $J_{1,6eq}$ = 3.6, $J_{1,2}$ = $J_{1,6ax}$ = 11.4 Hz, 1H for major rotamer; H-1), 7.10 (m, 1H; Ar), 7.33 ppm (m, 2H; Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) corresponding to a 80:20 mixture of rotamers: δ = 22.32, 23.62, 23.71, 24.94, 25.08, 25.11, 25.21, 27.27, 29.57, 29.74, 30.79, 39.45, 40.44, 46.84, 48.09, 54.82, 58.36, 59.58, 60.43,

 © 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

128.07, 128.47, 130.03, 130.51, 130.86, 132.07, 135.66, 135.90, 169.30, 169.59 ppm; IR (neat): $\tilde{\nu}=1634\,cm^{-1}$; MS (ESI$^+$): m/z (%): 369.1 (100) $[M+H]^+$, 371.1 (65) $[M+2+H]^+$, 373.1 (10) $[M+4+H]^+$; elemental analysis calcd (%) for $C_{19}H_{26}Cl_2N_2O_2$: C 61.79, H 7.10, N 7.58; found: C 62.05, H 7.19, N 7.46.

Determination of the enantiomeric excesses: The enantiomeric excess for each optically active compound isolated from the enzymatic reactions was determined by chiral HPLC. The following compounds were directly analyzed: Acetamides **6d**, **6e**, and **6g** were analyzed by using a Chiralcel OD column. The resolution is given by R_s. For (±)-**6d**: $t_R=18.7$ (1*R*,2*R*) and 20.9 min (1*S*,2*S*), $R_s=1.5$ (hexane/propan-2-ol (95:5), 0.8 mL min^{-1}, 20 °C). For (±)-**6e**: $t_R=21.1$ (1*R*,2*R*) and 24.3 min (1*S*,2*S*), $R_s=1.9$ (hexane/propan-2-ol (88:12), 0.8 mL min^{-1}, 35 °C). For (±)-**6g**: $t_R=9.9$ (1*S*,2*S*) and 11.9 min (1*R*,2*R*), $R_s=2.3$ (hexane/propan-2-ol (90:10), 0.8 mL min^{-1}, 20 °C). Carbamates **7a–c** were analyzed by using a Chiralcel OD-RH column. For (±)-**7a**: $t_R=7.5$ (1*R*,2*R*) and 9.1 min (1*S*,2*S*), $R_s=2.4$ (0.5 M aq $NaClO_4$/acetonitrile (50:50), 0.4 mL min^{-1}, 20 °C). For (±)-**7b**: $t_R=9.7$ (1*R*,2*R*) and 13.2 min (1*S*,2*S*), $R_s=2.9$ (0.5 M aq $NaClO_4$/acetonitrile (50:50), 0.4 mL min^{-1}, 20 °C). For (±)-**7c**: $t_R=8.5$ (1*R*,2*R*) and 11.6 min (1*S*,2*S*), $R_s=4.0$ (0.5 M aq $NaClO_4$/acetonitrile (30:70), 0.4 mL min^{-1}, 20 °C). Carbamates **7d** and **7f** were analyzed by using a Chiralcel OD column (hexane/propan-2-ol (90:10), 0.8 mL min^{-1}, 20 °C). For (±)-**7d**: $t_R=8.5$ (1*R*,2*R*) and 14.5 min (1*S*,2*S*), $R_s=7.3$. For (±)-**7f**: $t_R=5.9$ (1*R*,2*R*) and 6.8 min (1*S*,2*S*), $R_s=1.9$.

Amine **4g** was transformed into the acetamide **6g** by conventional treatment with acetyl chloride (1.2 equiv) and 4-dimethylaminopyridine (1.0 equiv) in dichloromethane (>95% yield). Acetamides **6a–c** and **6f** were hydrolyzed (3 N aq NaOH, reflux, 12 h, 93–95% yield), and the resulting amines **4a–c** and **4f** were transformed into the corresponding carbamates. Carbamate **7e** was treated with H_2 and Pd/C in methanol, and the resulting amine **4e** was transformed into the acetamide **6e**.

Acknowledgement

We thank Novo Nordisk Co. for the generous gift of the CAL-B. This work was supported by grants from MCYT (Spain; Project PPQ-2001–2683) and the Principado de Asturias (Spain; Project GE-EXP01–03). J. G.-S. is grateful to the Spanish MEC for a predoctoral fellowship.

[1] For some reviews, see: a) F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159–2231; b) D. Lucet, T. Le Gall, C. Mioskowski, *Angew. Chem.* **1998**, *110*, 2724–2772; *Angew. Chem. Int. Ed.* **1998**, *37*, 2580–2627; c) Y. L. Bennani, S. Hanessian, *Chem. Rev.* **1997**, *97*, 3161–3195. For some recent applications, see: d) T. Olszewska, M. Gdaniec, T. Po-lonski, *J. Org. Chem.* **2004**, *69*, 1248–1255; e) E. M. McGarrigle, D. M. Murphy, D. G. Gilheany, *Tetrahedron: Asymmetry* **2004**, *15*, 1343–1354; f) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 11204–11205.

[2] E. T. Michalson, J. Szmuszkovicz, *Prog. Drug Res.* **1989**, *33*, 135–149.

[3] J. Szmuszkovicz, P. F. Von Voigtlander, *J. Med. Chem.* **1982**, *25*, 1125–1126.

[4] a) J. Szmuszkovicz, EP 126612, **1984**; [*Chem. Abstr.* **1985**, *102*, 184969b]; b) C. R. Clark, P. R. Halfpenny, R. G. Hill, D. C. Horwell, J. Hughes, T. C. Jarvis, D. C. Rees, D. Schofield, *J. Med. Chem.* **1988**, *31*, 831–836; c) G. F. Costello, R. James, J. S. Shaw, A. M. Slater, N. C. J. Stutchbury, *J. Med. Chem.* **1991**, *34*, 181–189; d) J. J. Barlow, T. P. Blackburn, G. F. Costello, R. James, D. J. Le Count, B. G. Main, R. J. Pearce, K. Russell, J. S. Shaw, *J. Med. Chem.* **1991**, *34*, 3149–3158.

[5] a) A. Cowan, D. E. Gmerek, *Trends Pharmacol. Sci.* **1986**, *7*, 69–72; b) M. J. Millan, *Trends Pharmacol. Sci.* **1990**, *11*, 70–76.

[6] a) B. R. De Costa, W. D. Bowen, S. B. Hellewell, C. George, R. B. Rothman, A. A. Reid, J. M. Walker, A. E. Jacobson, K. C. Rice, *J. Med. Chem.* **1989**, *32*, 1996–2002; b) B. R. De Costa, W. D. Bowen, A. Thurkauf, D. T. Finn, S. Vazirani, R. B. Rothman, L. Band, P. C. Contreras, N. M. Gray, *J. Med. Chem.* **1990**, *33*, 3100–3110.

[7] a) S. Hanessian, D. Delorme, S. Beaudoin, Y. Leblanc, *J. Am. Chem. Soc.* **1984**, *106*, 5754–5756; b) A. Alexakis, S. Mutti, P. Mangeney, *J. Org. Chem.* **1992**, *57*, 1224–1237; c) Y. L. Bennani, S. Hanessian, *Tetrahedron* **1996**, *52*, 13837–13866; d) A. Alexakis, A.-S. Chauvin, R. Stouvenel, E. Vrancken, S. Mutti, P. Mangeney, *Tetrahedron: Asymmetry* **2001**, *12*, 1171–1178.

[8] M. Kaik, J. Gawronski, *Tetrahedron: Asymmetry* **2003**, *14*, 1559–1563, and references therein.

[9] a) P. O'Brien, P. Poumellec, *Tetrahedron Lett.* **1996**, *37*, 5619–5622; b) E. Curthbertson, P. O'Brien, T. D. Towers, *Synthesis* **2001**, 693–695.

[10] a) M. Mousseron, J. Jullien, Y. Jolchine, *Bull. Soc. Chim. Fr.* **1952**, *19*, 757–766; b) J. González-Sabín, V. Gotor, F. Rebolledo, *Tetrahedron: Asymmetry* **2004**, *15*, 1335–1341.

[11] For some applications of aziridinium ions in synthesis, see: a) M. Couturier, J. L. Tucker, B. M. Andresen, K. M. DeVries, B. C. Vanderplas, F. Ito, *Tetrahedron: Asymmetry* **2003**, *14*, 3517–3523; b) D. G. Piotrowska, A. E. Wróblewski, *Tetrahedron* **2003**, *59*, 8405–8410; c) D. R. Andrews, V. H. Dahanukar, J. M. Eckert, D. Gala, B. S. Lucas, D. P. Schumacher, I. A. Zavialov, *Tetrahedron Lett.* **2002**, *43*, 6121–6125; d) T.-H. Chuang, K. B. Sharpless, *Org. Lett.* **2000**, *2*, 3555–3557.

[12] For some recent reviews, see: a) F. Van Rantwijk, R. A. Sheldon, *Tetrahedron* **2004**, *60*, 501–519; b) I. Alfonso, V. Gotor, *Chem. Soc. Rev.* **2004**, *33*, 201–209; c) E. M. Anderson, K. M. Larsson, O. Kirk, *Biocatal. Biotransform.* **1998**, *16*, 181–204.

[13] a) I. Alfonso, C. Astorga, F. Rebolledo, V. Gotor, *Chem. Commun.* **1996**, 2471–2472; b) I. Alfonso, F. Rebolledo, V. Gotor, *Chem. Eur. J.* **2000**, *6*, 3331–3338.

[14] C. S. Chen, Y. Fujimoto, G. Girdaukas, C. J. Sih, *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.

[15] B. De Costa, C. George, R. B. Rothman, A. E. Jacobson, K. C. Rice, *FEBS Lett.* **1987**, *223*, 335–339.

[16] R. J. Kazlauskas, A. N. E. Weissfloch, A. T. Rappaport, L. A. Cuccia, *J. Org. Chem.* **1991**, *56*, 2656–2665.

Received: June 16, 2004
Published online: October 7, 2004

 © 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim