Enzymatic resolution of (±)-*trans*-2-aminocyclohexanol and (±)-*trans*-2-aminocyclopentanol

Alicia Maestro, Covadonga Astorga and Vicente Gotor *

Laboratorio de Química Bioorgánica, Facultad de Química, Universidad de Oviedo, 33071 Oviedo, Spain

Abstract: *Candida antarctica* lipase (CAL) catalyzes the resolution of (±)-*trans*-2-aminocyclohexanol by alkoxycarbonylation or acylation reactions. Besides, *N*-benzyloxycarbonyl derivatives of (±)-*trans*-2-aminocyclohexanol and (±)-*trans*-2-aminocyclopentanol are efficiently resolved through *O*-acylation by *Pseudomonas cepacia* lipase (PSL). © 1997 Elsevier Science Ltd

Much attention has been paid to the enzymatic resolution of racemic amino alcohols, probably due to their importance both as chiral building blocks and as products of biological and pharmacological interest.[1] Among them we can find cyclic 2-amino alcohols such as (±)-*trans*-2-aminocyclohexanol and (±)-*trans*-2-aminocyclopentanol, which have proven utility in the synthesis of antibiotics,[2] alkaloids[3] and also in the design of suitable ligands in coordination complexes.[4]

Even though there are a number of approaches to the resolution of (±)-*trans*-2-aminocyclohexanol and (±)-*trans*-2-aminocyclopentanol,[5] enzymatic resolution of these amino alcohols remains scarcely reported. There are only a few examples of enzymatic hydrolysis to obtain the desired optically active 2-aminocyclohexanol,[6] but no attention has been paid to the enzymatic resolution of (±)-*trans*-2-aminocyclopentanol. Since biocatalytic approaches to these optically active compounds are gaining more and more importance in organic synthesis and in particular, lipase-catalyzed aminolysis and transesterification reactions have been used in kinetic resolutions of racemic amino alcohols we thought it of interest to try the enzymatic resolution of (±)-*trans*-2- aminocyclohexanol and (±)-*trans*-2-aminocyclopentanol by an aminolysis reaction.

In a first approach to the resolution of (±)-*trans*-2-aminocyclohexanol **1**, dibenzyl carbonate and allyl benzyl carbonate[7] are used as alkoxycarbonylation reagents because the benzyloxycarbonyl group can be easily released under very mild conditions.[8] As *Candida antarctica* lipase (CAL) has proved its utility in the aminolysis of carbonates[9] we chose this enzyme as catalyst. It is noteworthy that the reaction of (±)-*trans*-**1** with carbonates yielded only the aminolysis product, while the *O*-alkoxycarbonylation compound is not detected (Scheme 1).

(±)-*trans*-**1**   CAL / 1,4-dioxane   (1*S*,2*S*)-**3**   +   (1*R*,2*R*)-**1**

R = allyl or benzyl
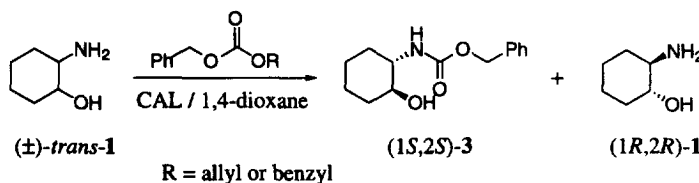
Scheme 1.

When the amino alcohol (±)-*trans*-**1** was reacted with dibenzylcarbonate, carbamate (1*S*,2*S*)-**3** was obtained in low yield (18%) and showed a quite high enantiomeric excess (88%) after six days of reaction (Entry 1, Table 1). This ee was determined by chiral-HPLC analysis of its *O*-benzyloxycarboyl derivative. The unreacted (1*R*,2*R*)-2-aminocyclohexanol was isolated by flash chromatography with a

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* Corresponding author. Email: VGS@dwarf1.quimica.uniovi.es

Table 1.

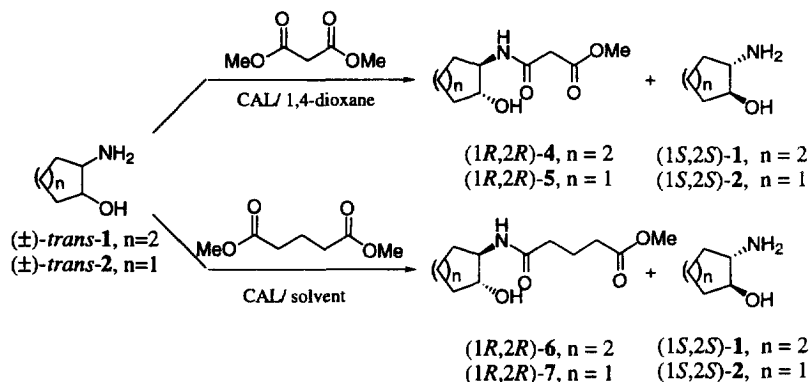| Entry	R	t, h	product (1S,2S)-3		remaining substrate (1R,2R)-1		conv.[c] (%)	E[c]
			yield[a] (%)	ee[b] (%)	yield[a] (%)	ee[b] (%)		
1	benzyl	144	18	88	28	49	36	25
2	allyl	58	24	82	25	29	26	13

[a]After flash chromatography. [b]Determined by HPLC analysis of the Cbz-derivatives on Chiralcel-OD. [c]See ref. 10.

more polar eluent (yield 28%). To determine the enantiomeric excess of (1R,2R)-1 it was necessary to obtain its N,O-bis(benzyloxycarbonyl) derivative. Again, a chiral-HPLC analysis showed a 49% enantiomeric excess for this compound. The calculated conversion (36%) and enantiomeric ratio[10] (E=25) showed that the resolution ability of CAL for this reaction is limited and enantiopure compound (1S,2S)-3 can not be obtained at any significant degree of conversion. Effectively, when the reaction was stopped at lower conversion, one day of reaction, only an 8% yield of (1S,2S)-3 was obtained and its enantiomeric excess was 96%.

Since dibenzylcarbonate does not resolve (±)-trans-1 we tried allyl benzyl carbonate as the alkoxycarbonylation reagent but the results were not successful (Entry 2, Table 1). The configuration of the unreacted amino alcohol 1 was assigned by comparison of its specific rotation with that described in the literature.[5a]

The above results prompted us to try the aminolysis of (±)-trans-1 with an acylating agent. Based on the good results obtained by our group for the resolution of (±)-trans-cyclohexane-1,2-diamine[11] in which CAL showed a high enantioselectivity when dimethyl malonate was used in 1,4-dioxane, we decided to employ dimethyl esters such as dimethyl malonate or dimethyl glutarate as acylating agents.

When (±)-trans-1 reacted with dimethyl malonate using 1,4-dioxane as solvent, CAL catalyzed the formation of the 2-hydroxyamidoester (1R,2R)-4. The same chemoselectivity was observed in the reaction of (±)-trans-1 with dimethyl glutarate. We completed this investigation by extending the study to the (±)-trans-2-aminocyclopentanol 2 (Scheme 2).

(1R,2R)-4, n = 2   (1S,2S)-1, n = 2
(1R,2R)-5, n = 1   (1S,2S)-2, n = 1

(±)-trans-1, n=2
(±)-trans-2, n=1

(1R,2R)-6, n = 2   (1S,2S)-1, n = 2
(1R,2R)-7, n = 1   (1S,2S)-2, n = 1

Scheme 2.

From the data shown in Table 2, we can see that it was possible to obtain the aminolysis product (1R,2R)-4 with dimethyl malonate in high enantiomeric excess only at low conversion[12] (c=6 and 7%) because CAL showed a poor enantioselectivity in this reaction (Entries 1 and 2). However, the enantiomerically enriched aminoalcohol (1S,2S)-1 could be obtained if the reaction was extended beyond 50% conversion. In fact, (1S,2S)-1 was obtained in 87% ee after 14 hours of reaction (c=58%) (Entry 3).

When dimethyl glutarate was used as the acylating agent, CAL gave better results for the enzymatic aminolysis of (±)-trans-1 (Table 3, entries 1 and 2). Moreover, the assays carried out in other solvents

Table 2.

Entry	solvent	t, h	product (1R,2R)-4		remaining substrate (1S,2S)-1		conv.[c] (%)	E[c]
			yield[a] (%)	ee[b] (%)	yield[a] (%)	ee[b] (%)		
1	1,4-dioxane	1.5	10	88	60	6	6	16
2	1,4-dioxane	2	18	89	48	7	7	18
3	1,4-dioxane	14	64	63	48	87	58	12

[a]After flash chromatography. [b]Determined by HPLC analysis of the Cbz-derivatives on Chiralcel-OD. [c]See ref. 10.

Table 3.

| Entry	solvent	t, h	product (1R,2R)-6		remaining substrate (1S,2S)-1		conv.[c] (%)	E[c]
			yield[a] (%)	ee[b] (%)	yield[a] (%)	ee[b] (%)		
1	1,4-dioxane	96	50	90	71	51	36	31
2	1,4-dioxane	144	66	84	79	79	48	27
3	toluene	96	31	59	65	24	29	5
4	t-amyl alcohol	96	48	84	62	45	35	18

[a]After flash chromatography. [b]Determined by HPLC analysis of the Cbz-derivatives on Chiralcel-OD. [c]See ref. 10.

such as toluene or tert-amyl alcohol drive, in equal reaction times, to lower yields and enantiomeric excesses. Therefore 1,4-dioxane is the best solvent for this aminolysis reaction.

When the same reaction scheme was applied to (±)-trans-2-aminocyclopentanol 2 worse results than in the preceding example were obtained. Thus, if dimethyl malonate was used, 2-hydroxyamidoester 5 is obtained with low ee (30%). The 2-hydroxyamidoester 7 obtained by reaction of (±)-trans-2 with dimethyl glutarate showed 48% ee and 44% yield.

The absolute configurations of compounds 4–7 were assigned as (1R,2R) by comparison of the specific rotation of the remaining unreacted aminoalcohol with the described values in the literature.[5a,6a] In this case CAL showed the same preference as in previous reports about aminolysis reaction[11,13] and the opposite to that found for the compound 3 in the reaction with carbonates.

Since the results obtained in the aminolysis reaction were not completely satisfactory we decided to use another biocatalyst in order to improve the enantioselectivity for this reaction. We tried the reaction of (±)-trans-1 with vinyl acetate as acyl donor and Pseudomonas cepacia lipase (PSL) in 1,4-dioxane but the results were again unsuccessful (very low yields for the N-acetylated and also for the N,O-diacetylated). At this point we thought of a change in strategy. As we already knew that N-protected 2-aminoalkan-2-ols could be well resolved through transesterification reaction,[1c] the resolution was carried out using the same previously described experimental conditions but with N-benzyloxycarbonyl derivative as starting material (Scheme 3).

(±)-trans-3, n = 2
(±)-trans-9, n = 1

(1R,2R)-8, n = 2
(1R,2R)-10, n = 1

(1S,2S)-3, n = 2
(1S,2S)-9, n = 1
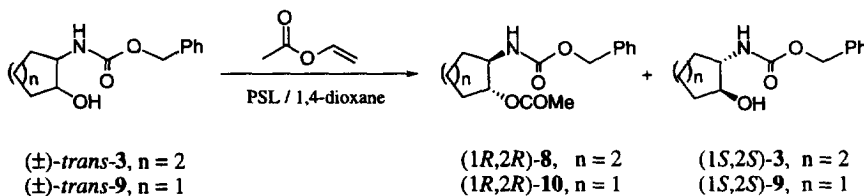
Scheme 3.

Under these reaction conditions lipase PS showed a high enantioselectivity towards the substrate and yielded the O-acetylcarbamate (1R,2R)-8 with an enantiomeric excess >99% ([α]_D=+7.7, c=1.05, CHCl₃) while the unreacted 2-hydroxycarbamate (1S,2S)-3 was recovered with 49% ee ([α]_D=+1.8, c=1.01, CHCl₃). These data gave c=33% and E>100 (Table 4, Entry 1). To assign the absolute configuration to compound (1S,2S)-3, its specific rotation was compared with that obtained for the same

Table 4.

Entry	t, d	product (1R,2R)	yield[a] (%)	ee[b] (%)	remaining substrate (1S,2S)	yield[a] (%)	ee[b] (%)	conv.[c] (%)	E[c]
1, n=2	6	8	31	>99	3	63	49	33	>100
2, n=1	5	10	47	98	9	57	>99	51	>100

[a]After flash chromatography. [b]Determined by HPLC analysis of the Cbz-derivatives on Chiralcel-OD. [c]See ref. 10.

compound in the reaction of (±)-*trans*-1 with dibenzylcarbamate (Scheme 1). The same methodology was extended to (±)-*trans*-2-aminocyclopentanol 2 and again highly satisfactory results were obtained (98% ee for the product and >99% ee for the unreacted substrate) (Table 4, Entry 2).

On this occasion absolute configurations have been assigned by comparison with the signs of specific rotation of the compounds previously synthesized by us in Schemes 1 and 2.

In summary, we have reported a very simple and efficient method for the enzymatic resolution of (±)-*trans*-2-aminocyclohexanol 1 through an aminolysis reaction catalyzed by CAL. We have also found that PSL efficiently catalyzes the acetylation of *N*-Cbz derivatives of (±)-*trans*-2-aminocyclohexanol 1 and (±)-*trans*-2-aminocyclopentanol 2. It is of note that this is the first enzymatic resolution of (±)-*trans*-2-aminocyclopentanol 2.

Experimental section

General

Candida antarctica lipase (CAL), SP 435, was a gift from Novo Nordisk Co. *Pseudomonas cepacia* lipase (PS lipase) was purchased from Amano Pharmaceutical Co. All reagents were of commercial quality and were purchased from Aldrich Chemie. Solvents were distilled over an adequate desiccant and stored under nitrogen. Precoated TLC plates silica gel 60 F254 from Merck were used, and for column chromatography, Merck silica gel 60/230–400 mesh was used. Mps were taken using a Gallenkamp apparatus and are uncorrected. Optical rotations were measured using a Perkin–Elmer 241 polarimeter. IR spectra were recorded on a Perkin–Elmer Mattson 3000 Infrared Fourier transform spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained using a Bruker AC-300 (^{1}H- 300 MHz and ^{13}C- 75 MHz) spectrometer. Mass spectra were recorded on a Hewlett–Packard 5897 A spectrometer. Microanalyses were performed on a Perkin–Elmer 240B elemental analyser. HPLC analyses were performed in a Shimadzu LC liquid chromatograph.

Ammonolysis of cyclohexane or cyclopentane oxide

In a sealed tube the cycloalkane oxides (20 mL) were dissolved in a 10% solution of ammonia in methanol (75 mL). The reaction proceeded in nearly quantitative yield at 60°C. The amino alcohols (±)-*trans*-1 and (±)-*trans*-2 were purified by flash chromatography using methanol–dichloromethane–aqueous ammonia 2:2:0.1 as eluent.

General procedure for the synthesis of benzyl (1S,2S)-N-(2-hydroxycyclohexyl)carbamate 3

6 mmol of carbonate[7] and 2 mmol of amino alcohol (±)-*trans*-1 were added to a suspension of CAL (120 mg) in 1,4-dioxane (8 mL) under nitrogen atmosphere. The mixture was shaken at 30°C and 250 rpm for the time indicated in Table 1. Then, the enzyme was filtered off, washed with dichloromethane (2×10 mL) and the organic solvents evaporated. The crude was subjected to column chromatography using ethyl acetate–hexane 1:1 as eluent to isolate the carbamate and then methanol–dichloromethane–aqueous ammonia 2:2:0.1 for the remaining unreacted amino alcohol (1R,2R)-1.

The compound (1S,2S)-3 is a white solid, mp 102–103°C (from ethyl acetate–hexane). ^{1}H-NMR (300 MHz, CDCl$_3$) δ 1.11–1.39 (m, 4H), 1.68–1.82 (m, 2H), 1.96–2.06 (m, 2H), 3.03 (br. s, O*H*), 3.30–3.41 (m, 2H, C*H*-NH and C*H*-OH), 4.87 (br. s, 1H, N*H*), 5.09–5.12 (ABq, 2H, *J*=12.4 Hz, O-C*H$_2$*-Ph), 7.30–7.39 (m, 5Harm); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 24.0 (*C*H$_2$), 24.6 (*C*H$_2$), 31.7

(CH_2), 34.1 (CH_2), 57.0 (CH-NH), 74.8 (CH-OH), 67.0 (O-CH_2-Ph), 128.1 (CHarm), 128.5 (CHarm), 136.2 (Carm), 157.3 (CO); IR (KBr) 3313, 1691 cm^{-1}. MS (EI) *m/z*: 249 ($C_{14}H_{19}NO_3$+2%), 91 (C_7H_7+100%). $C_{14}H_{19}NO_3$ calc. 67.45% C, 7.68% H, 5.62% N; found 67.75% C, 7.44% H, 5.44% N. The determination of ee for benzyl carbamate **3** was made by chiral-HPLC, determined from its *O*-Cbz derivative using hexane:propan-2-ol 90:10 as eluent, 0.8 mL/min. 96% ee, two peaks t_R 12.2 and 13.9 min; Rs, 2; $[\alpha]_D^{23}$=+1.8 (c 0.5 in CHCl$_3$). The unreacted enantiomer was obtained in nearly racemic form and its ee was determined from its *N,O*-bis-Cbz derivative, 6% ee, two peaks t_R 12.1 and 14.4 min.

General procedure for the syntheses of 2-hydroxyamidoesters 4–7

1.5 mmol of diester and 3 mmol of amino alcohol (±)-*trans*-**1** or (±)-*trans*-**2** were added to a suspension of CAL (180 mg) in 1,4-dioxane (12 mL) under nitrogen atmosphere. The mixture was shaken at 30°C and 250 rpm during the time indicated in Tables 2 and 3. Then, the enzyme was filtered off, washed with dichloromethane (2×10 mL) and the organic solvents were evaporated. The crude was subjected to column chromatography using acetone–diethyl ether–propan-2-ol 2:4:0.1 as eluent to isolate the 2-hydroxyamidoesters and then methanol–dichloromethane–aqueous ammonia 2:2:0.1 for the remaining unreacted amino alcohols (1*S*,2*S*)-**1** or (1*S*,2*S*)-**2**.

Methyl (1R,2R)-N-[(2-hydroxycyclohexyl)carbamoyl]acetate 4

The previously described procedure gave (1*R*,2*R*)-**4** as a white solid, mp 112–114°C (from ethyl acetate–hexane). ^{1}H-NMR (300 MHz, CDCl$_3$) δ 1.19–1.40 (m, 4H), 1.69–1.75 (m, 2H), 1.96–2.06 (m, 2H), 3.30–3.43 (m, 1H, CH-OH), 3.36 (s, 2H, CO-CH_2-CO), 3.63–3.75 (m, 1H, CH-NH), 3.75 (s, 3H, OCH_3), 7.35 (d, 1H, NH); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 23.9 (CH_2), 24.4 (CH_2), 31.1 (CH_2), 34.1 (CH_2), 41.0 (CO-CH_2-CO), 52.4 (OCH_3), 55.6 (CH-NH), 74.2 (CH-OH), 166.4 (CO), 169.8 (CO); IR (KBr) 3283, 1745, 1643 cm^{-1}. MS (EI) *m/z*: 215 ($C_{10}H_{17}NO_4$+5%), 118 (+100%). $C_{10}H_{17}NO_4$ calc. 55.80% C, 7.96% H, 6.51% N; found 56.15% C, 7.75% H, 6.17% N. The determination of ee for 2-hydroxyamidoester (1*R*,2*R*)-**4** was made by chiral-HPLC, determined from its *O*-Cbz derivative using hexane:ethanol 95:5 as eluent, 0.8 mL/min. 89% ee, two peaks t_R 21.9 and 27.6 min; $[\alpha]_D^{23}$=+7.5 (c 0.89 in CHCl$_3$). For *rac*-2-hydroxyamidoester, two peaks t_R 21.2 and 26.4 min; Rs, 3.7. For the unreacted enantiomer 7% ee was obtained, determined from its *N,O*-bis-Cbz derivative (see conditions for compound **3**).

Methyl (1R,2R)-N-[(2-hydroxycyclopentyl)carbamoyl]acetate 5

The 2-hydroxyamidoester (1*R*,2*R*)-**5** was obtained as a yellow oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 1.43–1.55 (m, 1H), 1.59–1.86 (m, 3H), 1.96–2.12 (m, 1H), 2.13–2.22 (m, 1H), 3.35 (s, 2H, CO-CH_2-CO), 3.76 (s, 3H, OCH_3), 3.83–3.92 (m, 1H, CH-OH), 3.96–4.03 (m, 1H, CH-NH), 7.50 (br. s, 1H, NH); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 21.0 (CH_2), 29.8 (CH_2), 32.2 (CH_2), 40.6 (CO-CH_2-CO), 52.4 (OCH_3), 60.1 (CH-NH), 78.7 (CH-OH), 166.7 (CO), 169.7 (CO); IR 3269, 1736, 1655 cm^{-1}. MS (EI) *m/z*: 202 ($C_9H_{15}NO_4$.H+8%), 56 (+100%).

Methyl 4-{(1R,2R)-N-[(2-hydroxycyclohexyl)carbamoyl]}butyrate 6

The 2-hydroxyamidoester (1*R*,2*R*)-**6** was obtained as a white solid, mp 80–81°C (from ethyl acetate–hexane). ^{1}H-NMR (300 MHz, CDCl$_3$) δ 1.11–1.31 (m, 4H), 1.63–1.70 (m, 2H), 1.89–1.96 (m, 4H), 2.23 (t, 2H, *J*=7.3 Hz, CH_2-CONH), 2.35 (t, 2H, *J*=7.0 Hz, CH_2-COO), 3.23–3.29 (m, 1H, CH-OH), 3.53–3.65 (m, 1H, CH-NH), 3.63 (s, 3H, OCH_3), 3.93 (br. s, 1H, OH), 6.20 (d, 1H, NH); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 20.8 (CH_2), 23.9 (CH_2), 24.4 (CH_2), 31.3 (CH_2), 32.8 (CH_2), 34.2 (CO-CH_2-CO), 35.2 (CO-CH_2-CO), 51.5 (OCH_3), 55.5 (CH-NH), 74.5 (CH-OH), 173.7 (CO), 173.8 (CO); IR (KBr) 3369, 3288, 1732, 1639 cm^{-1}. MS (EI) *m/z*: 244 ($C_{12}H_{21}NO_4$.H+5%), 129 ($C_6H_9O_3$+100%). $C_{12}H_{21}NO_4$ calc. 59.24% C, 8.70% H, 5.76% N; found 59.26% C, 8.92% H, 5.78% N. The determination of ee for 2-hydroxyamidoester (1*R*,2*R*)-**6** was made by chiral-HPLC, determined from its *O*-Cbz derivative using hexane:ethanol 95:5 as eluent, 0.8 mL/min. 84% ee, two peaks t_R 17.6

and 23.1 min; $[\alpha]_D^{23}$=+15.5 (c 1.0 in CHCl$_3$). For *rac*-2-hydroxyamidoester, two peaks t$_R$ 18.1 and 23.9 min; Rs, 4. For the unreacted enantiomer 78% ee was obtained, determined from its *N,O*-bis-Cbz derivative (see conditions for compound **3**).

Methyl 4-{(1R,2R)-N-[(2-hydroxycyclopentyl)carbamoyl]}butyrate 7

The 2-hydroxyamidoester (1*R*,2*R*)-**7** was obtained as a yellow oil. ^{1}H-NMR (200 MHz, CDCl$_3$) δ 1.38–2.18 (m, 8H), 2.28 (t, 2H, C*H$_2$*-CONH), 2.40 (t, 2H, C*H$_2$*-COO), 3.68 (s, 3H, C*H$_3$*), 3.76–3.87 (m, 1H, C*H*-OH), 3.89–4.00 (m, 1H, C*H*-NH), 6.15 (br. s, 1H, N*H*); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 20.7 (*CH$_2$*), 21.1 (*CH$_2$*), 30.1 (*CH$_2$*), 32.3 (*CH$_2$*), 32.9 (CO-*CH$_2$*-CO), 34.9 (CO-*CH$_2$*-CO), 51.6 (O*CH$_3$*), 60.4 (*CH*-NH), 79.3 (*CH*-OH), 173.7 (*CO*), 174.2 (*CO*); IR 3295, 1736, 1640 cm^{-1}. MS (EI) *m/z*: 211 (C$_{11}$H$_{19}$NO$_4$–H$_2$O+20%), 91 (+100%).

Preparation of racemic benzyl N-(2-hydroxycycloalkane)carbamates 3 and 9

To a solution in water (5 mL) of amino alcohol (2 mmol) and sodium carbonate (0.42 g, 4 mmol) was added benzyl chloroformate (4.3 mmol) dropwise over 0.5 h period at 0–5 °C. The reaction mixture was stirred an additional 2 h at room temperature and extracted with dichloromethane. The organic layer was dried and evaporated to dryness to give the desired product in 85–100% yield.

Benzyl (1R,2R)-N-(2-hydroxycyclopentyl)carbamate 9

The racemic 2-hydroxycarbamate **9** was purified by recrystallization in ethyl acetate–hexane, mp 57–59°C. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 1.31–1.44 (m, 1H), 1.61–1.81 (m, 3H), 1.97–2.17 (m, 2H), 3.66–3.75 (m, 1H, C*H*-OH), 3.83 (s, 1H, O*H*), 4.01–4.13 (m, 1H, C*H*-NH), 4.96 (br. s, 1H, N*H*), 5.10 (s, 2H, O-C*H$_2$*-Ph), 7.30–7.40 (m, 5Harm); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 20.7 (*CH$_2$*), 30.1 (*CH$_2$*), 32.1 (*CH$_2$*), 60.4 (*CH*-NH), 66.9 (O-*CH$_2$*-Ph), 79.0 (*CH*-OH), 128.1 (*CH*arm), 128.2 (*CH*arm), 128.5 (*CH*arm), 136.1 (*C*arm), 157.3 (*CO*); IR (KBr) 3304, 1692 cm^{-1}. MS (EI) *m/z*: 235 (C$_{13}$H$_{17}$NO$_3$+2%), 91 (C$_7$H$_7$+100%).

General procedure for the syntheses of benzyl carbamates 8 and 10

10 mmol of vinyl acetate and 1 mmol of carbamates (±)-*trans*-**3** or (±)-*trans*-**9** were added to a suspension of PS lipase (320 mg) in 1,4-dioxane (9 mL) under nitrogen atmosphere. The mixture was shaken at 30°C and 250 rpm for 6 days and 5 days respectively. Then, the enzyme was filtered off, washed with dichloromethane (2×10 mL) and the organic solvents were evaporated. The crude was subjected to column chromatography using ethyl acetate–hexane 1:3 as eluent.

Benzyl (1R,2R)-N-(2-acetoxycyclohexyl)carbamate 8

The previously described procedure gave (31%) of (1*R*,2*R*)-**8** as a white solid, mp 61–63°C. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 1.16–1.48 (m, 4H), 1.63–1.73 (m, 2H), 1.91–2.18 (m, 2H), 1.95 (s, 3H, C*H$_3$*), 3.54–3.68 (m, 1H, C*H*-NH), 4.55–4.67 (m, 1H, C*H*-OCOMe), 4.79 (d, 1H, N*H*), 5.06–5.12 (ABq, 2H, *J*=12.1 Hz, O-C*H$_2$*-Ph), 7.34 (s, 5Harm); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 21.0 (*CH$_3$*), 23.9 (*CH$_2$*), 24.2 (*CH$_2$*), 30.9 (*CH$_2$*), 32.2 (*CH$_2$*), 54.2 (*CH*-NH), 66.4 (O-*CH$_2$*-Ph), 74.7 (*CH*-OCOMe), 128.0 (*CH*arm), 128.1 (*CH*arm), 136.6 (*C*arm), 155.9 (*CO*), 171.4 (*CO*); IR (KBr) 3358, 1728, 1696 cm^{-1}. MS (EI) *m/z*: 291 (C$_{16}$H$_{21}$NO$_4$+7%), 91 (C$_7$H$_7$+100%). Determination of ee for (1*R*,2*R*)-**8**, >99%, was made by chiral-HPLC using hexane:propan-2-ol 90:10 as eluent, 0.8 mL/min; t$_R$ 6.3 min; $[\alpha]_D^{23}$=+7.7 (c 1.05 in CHCl$_3$). For *rac*-benzyl carbamate, two peaks t$_R$ 6.5 and 8.9 min; Rs, 3.5. For the unreacted enantiomer (63%) 49% ee was obtained, determined from its methyl ester derivative by chiral-HPLC using the same above described conditions.

Benzyl (1R,2R)-N-(2-acetoxycyclopentyl)carbamate 10

The previously described procedure gave (47%) of (1*R*,2*R*)-**10** as a white solid, mp 55–56°C. ^{1}H-NMR (200 MHz, CDCl$_3$) δ 1.40–1.81 (m, 4H), 2.03 (s, 3H, C*H$_3$*), 2.06–2.21 (m, 2H), 3.93–3.99 (m, 1H, C*H*-NH), 4.90–5.00 (m, 1H, C*H*COMe), 5.09 (s, 2H, O-C*H$_2$*-Ph), 7.30–7.36 (m, 5Harm); ^{13}C-NMR (50 MHz, CDCl$_3$) δ 20.6 (*CH$_2$*), 21.0 (*CH$_3$*), 29.6 (*CH$_2$*), 30.4 (*CH$_2$*), 57.4 (*CH*-NH), 66.6

(O-CH_2-Ph), 79.2 (*C*H-OH), 127.9 (*C*Harm), 128.4 (*C*Harm), 136.3 (*C*arm), 155.9 (*C*O), 171.0 (*C*O); IR (KBr) 3340, 1726, 1691 cm^{-1}. MS (EI) *m/z*: 277 ($C_{15}H_{19}NO_4$+4%), 91 (C_7H_7+100%). Ee for (1*R*,2*R*)-**10** 98% determined by chiral-HPLC using hexane:propan-2-ol 90:10 as eluent, 0.8 mL/min; two peaks t_R 10.8 and 12.2 min. For *rac*-benzyl carbamate, two peaks t_R 10.9 and 12.2 min; Rs, 1.5; $[\alpha]_D^{23}$=−18.5 (c 0.9 in CHCl$_3$). The unreacted enantiomer (57%) was obtained in enantiomerically pure form, determined from its methyl ester derivative, >99% ee; t_R 12.7 min; $[\alpha]_D^{23}$=−9.8 (c 0.9 in CHCl$_3$).

Acknowledgements

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