Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 481–488

Kinetic resolution of (±)-*trans*- and (±)-*cis*-2-phenylcyclopentanamine by CALB-catalyzed aminolysis of esters: the key role of the leaving group

Javier González-Sabín, Vicente Gotor* and Francisca Rebolledo*

Departamento de Química Orgánica e Inorgánica, Universidad de Oviedo, 33071 Oviedo, Spain

Received 21 October 2003; accepted 14 November 2003

Abstract—Kinetic resolution of (±)-*trans*- and (±)-*cis*-2-phenylcyclopentanamine is effectively performed by lipase B from *Candida antarctica*, (CALB)-catalyzed aminolysis reaction. Whereas reaction between (±)-*trans*-2-phenylcyclopentanamine and ethyl acetate proceeds with a very high *E* value (>200) and conversion (50%), the corresponding acetylation of (±)-*cis*-2-phenylcyclopentanamine happens with low *E* value (16) and conversion (28%). Nevertheless, this problem is overcome using other acyl donors such as (±)-1-phenylethyl and (±)-*cis*-2-phenylcyclopentyl methoxyacetates. The influence of the acyl donor on the CALB-catalyzed aminolysis of (±)-*cis*-2-phenylcyclopentanamine is also studied.

1. Introduction

Amines and their derived amides are important compounds in organic synthesis, because of the presence of these functional groups in many pharmacologically active compounds.[1] Due to the increasing demand for optically active compounds in the pharmaceutical industry, as well as the synthetic applicability of enantiomerically pure amines (as chiral auxiliaries, bases and ligands),[2] the design of efficient methods for the preparation of optically active amines is of special interest. Among the resolution-based procedures, the enzymatic methods are emerging as a useful alternative to the traditional resolutions using an optically active carboxylic acid. Thus, lipase B from *Candida antarctica* (CALB) has proven to be the most effective catalyst for aminolysis reactions in organic solvents, allowing the preparation of a variety of optically active primary amines and amides.[3] The high stereoselectivity and simplicity of these processes make this strategy the most appropriate for the resolution of primary amines bearing the amino group on the stereocentre. These facts, besides the environmentally friendly character of the enzymatic processes, are essential for large-scale industrial applications.[4]

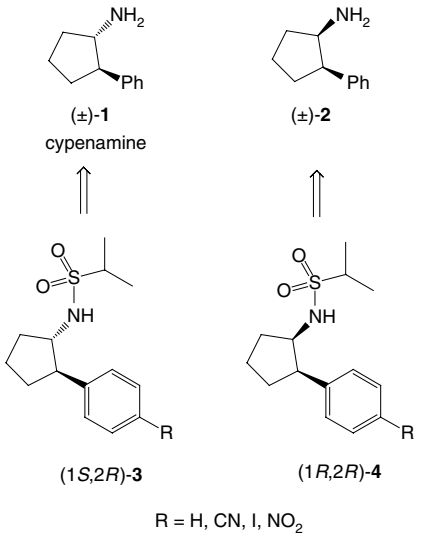
Continuing with our interest in the study of lipase-catalyzed aminolyses, we report herein the resolution of (±)-*trans*- and (±)-*cis*-2-phenylcyclopentanamine [(±)-**1** and (±)-**2**, respectively] by CALB-catalyzed aminolysis of a variety of esters. *trans*-2-Phenylcyclopentanamine **1** (cypenamine) is an antidepressant,[5] and both **1** and **2** are precursors of semicyclic amidines (lactamimides) with potent hypoglycemic activity.[6] Likewise, they have also been used as starting materials in the synthesis of sulfonamides (±)-**3** and (±)-**4**, which were resolved by semipreparative chiral HPLC. These sulfonamides are potentiators of AMPA [2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid] receptors, a subset of ionotropic glutamate receptors whose activity is highly dependent on the stereochemistry at the 2-position of the cyclopentane ring.[7]

To our knowledge, only one approach for the asymmetric synthesis of (1*S*,2*R*)-*trans*-2-phenylcyclopentanamine[8] (1*S*,2*R*)-**1** and another for both enantiomers of *cis*-2-phenylcyclopentanamine[9] **2** have been described, but both approaches imply long reaction times and produce moderate or low yields. The method described here allows the preparation of all stereoisomers of

* Corresponding authors. Tel./fax: +34-985-103448; e-mail addresses: vgs@sauron.quimica.uniovi.es; frv@sauron.quimica.uniovi.es

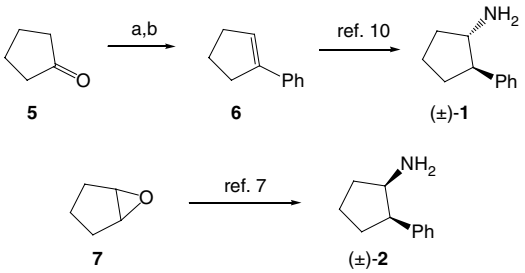
0957-4166/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2003.11.013

2-phenylcyclopentanamine with very high enantiomeric excesses and yields.



2. Results and discussion

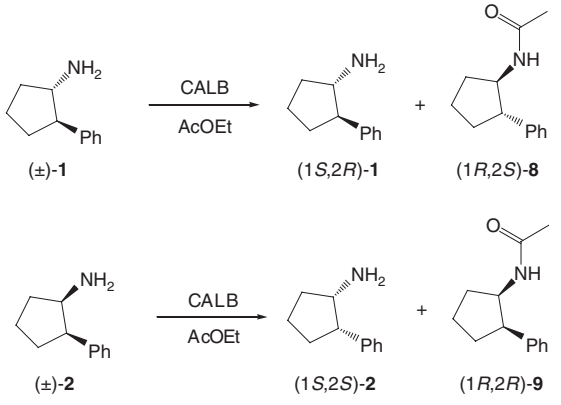
Scheme 1 outlines the synthesis of (±)-**1** and (±)-**2**. Addition of phenylmagnesium bromide to cyclopentanone **5** and subsequent dehydration of the resulting alcohol provided 1-phenylcyclopentene **6**, which was transformed later into (±)-**1**.[10] Preparation of (±)-**2** was easily accomplished from cyclopentene oxide **7** using a known procedure.[7]



Scheme 1. Synthesis of (±)-**1** and (±)-**2**. Reagents and conditions: (a) PhMgBr, Et_2O; (b) *p*-TsOH, THF.

As a first attempt, CALB-catalyzed resolutions of (±)-**1** and (±)-**2** were carried out under the most simple reaction conditions, that is, using ethyl acetate as the acyl donor and solvent. After stopping the reactions, the thus generated amide and the remaining amine were isolated, after selective extraction, with very high yields (Table 1). The stereochemical preference of the CALB was determined by establishing the absolute configuration of the remaining amines to be (1*S*,2*R*)-**1** and (1*S*,2*S*)-**2** after comparison of the specific rotations of their hydrochlorides with those reported.[8,9] In both cases CALB preferentially catalyzed the acetylation of the (1*R*)-amines, following Kazlauskas' rule.[11] However, great differences in reaction rate and enantioselectivity were observed for both diastereomers, which indicates a dramatic influence of the configuration of carbon-2 on the enzyme activity. The process was excellent (enantiomeric ratio,[12] $E > 200$) for the *trans*-diastereomer (±)-**1**, thus allowing both (1*S*,2*R*)-**1** and (1*R*,2*S*)-**8** to be obtained with very high enantiomeric excesses (ee >97%). On the contrary, the reaction with the *cis*-

Table 1. CALB-catalyzed acetylation of (±)-**1** and (±)-**2**



Amine	Time (h)	c (%)[a]	Remaining substrate			Product			E[d]
			Amine	ee_s (%)[b]	Yield (%)[c]	Amide	ee_p (%)[b]	Yield (%)[c]	
(±)-**1**	6.5	50	(1*S*,2*R*)-**1**	98	45	(1*R*,2*S*)-**8**	97	49	>200
(±)-**2**	24	28	(1*S*,2*S*)-**2**	33	65	(1*R*,2*R*)-**9**	85	27	16

[a] Conversion: $c = ee_s/(ee_s + ee_p)$.
[b] Enantiomeric excess determined by chiral HPLC.
[c] Isolated yields.
[d] Enantiomeric ratio calculated according to Ref. 12.

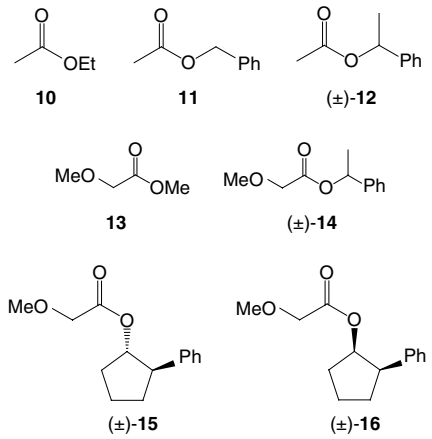


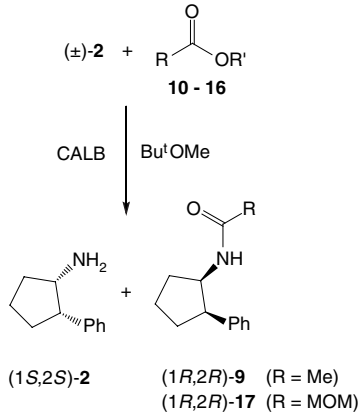
Chart 1.

diastereomer (±)-**2** was markedly slower and happened with low enantioselectivity.

A common approach for improving the lipase catalytic activity lies in changing the acyl donor, the solvent, or both. To achieve satisfactory results in the resolution of (±)-**2**, we decide to test acyl donors **11**–**16** (Chart 1), which incorporate a varied set of leaving groups. The influence of the leaving group of an acyl donor on the resolution of a nucleophile is not clear because, according to the accepted mechanism for lipases,[13] both components are not simultaneously present in the transition state responsible for the enantioselection. Nevertheless, our strategy is based on the following findings: (1) Transesterifications of several racemic alcohols with alkenyl acetates display higher enantioselectivities when the alkenyl group matches the corresponding alcohol.[14] (2) Racemic amines, which behave as good substrates for the enzyme have a beneficial effect on the CALB-catalyzed aminolysis of 1-phenylbutyl acetate.[15] In addition, we thought that aminolysis reactions with acyl donors **11**–**16** could also contribute to an understanding of the role the leaving group plays in lipase catalysis.

CALB-catalyzed reactions of (±)-**2** with esters **10**–**16** were carried out in *tert*-butyl methyl ether as solvent[16] with a 1:3 molar ratio amine/ester (Table 2). A comparison of Table 2 (entry 1) with the second row of Table 1 denotes that the change of solvent does not affect the enantioselectivity. However, the aminolysis of ethyl acetate shown in Table 2 (entry 1) is much slower as a result of the much lower acyl donor concentration. Esters **11** and (±)–**12** (entries 2 and 3) can shed light on the influence of the chiral character of the leaving group. Both reacted at virtually the same rate, but the very high *E* value associated with the chiral (±)-**12** is noteworthy. No efforts were made to determine the enantiomeric ratio for the simultaneous kinetic resolution of (±)-**12**, because the reaction conditions were designed for the

Table 2. Effect of the acyl donors **10**–**16** (Chart 1) on the CALB-catalyzed resolution of (±)-**2**[a]



Entry	Acyl donor	*c* (%)	Remaining substrate (1*S*,2*S*)-**2**		Product (1*R*,2*R*)-**9**,**17**			*E*
			ee_s (%)[b]	Yield (%)[c]	Amide	ee_p (%)[b]	Yield (%)[c]	
1	**10**	7	7	72	**9**	88	7	17
2	**11**	32	42	58	**9**	91	28	32
3	(±)-**12**	31	44	56	**9**	97	24	101
4	**13**	46	77	44	**17**	89	43	40
5	(±)-**14**	42	72	57	**17**	98	41	214
6	(±)-**15**	50	>99	40	**17**	98	45	525[d]
7	(±)-**16**	50	98	43	**17**	>99	49	922[e]

[a] Solvent: Bu^{t}OMe; time: 46 h.
[b] Determined by chiral HPLC.
[c] Isolated yields.
[d] Value obtained from $ee_s = 99\%$.
[e] Value obtained from $ee_p = 99\%$.

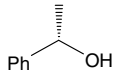
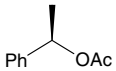
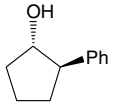
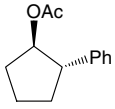
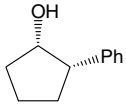
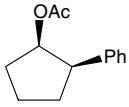
resolution of amine (±)-**2**.[17] Methyl methoxyacetate **13** is more reactive than ethyl acetate and has been efficiently used for the lipase-mediated resolution of amines.[18] Thus, when its aminolysis with (±)-**2** was carried out (entry 4), conversion was very high and the enantioselectivity was slightly higher than that observed with ester **11** (entry 2). Consequently, we decided to prepare ester (±)-**14**, which combines the two structural characteristics that improve the biocatalytic process, namely, the presence of a methoxy group in the acyl moiety and the chirality of the leaving group. As expected, the use of **14** (entry 5) led to a conversion value similar to that obtained with ester **13**, and an excellent enantioselectivity ($E > 200$), allowing us to isolate the methoxyacetamide (1*R*,2*R*)-**17** with high yield and very high ee. Although our goal was already reached, we decided at this point to prepare the racemic acyl donors **15** and **16**, whose leaving groups are structurally related to the amine (±)-**2**. Results obtained with methoxyacetates **15** and **16** were still better (entries 6 and 7), within both cases amide (1*R*,2*R*)-**17** and amine (1*S*,2*S*)-**2** being isolated with very high ee after the optimal 50% conversion.

Whereas esters (±)-**15** and (±)-**16** derive from commercially unavailable alcohols, ester (±)-**14** is easily obtained from the commercial (±)-1-phenylethanol and, moreover, it provides $E > 200$. To extend the applicability of this ester, we performed the CALB-catalyzed aminolysis of (±)-**14** and (±)-*trans*-2-phenylcyclopentanamine (±)-**1**. After 16 h, amine (1*S*,2*R*)-**1** was isolated with 72% ee and the product (1*R*,2*S*)-*N*-(2-phenylcyclopentyl) methoxyacetamide (1*R*,2*S*)-**18** with >99% ee, which gives a $c = 42\%$ and $E = 431$, an enhanced enantioselectivity in comparison with that obtained in the reaction with ethyl acetate (Table 1, entry 1).

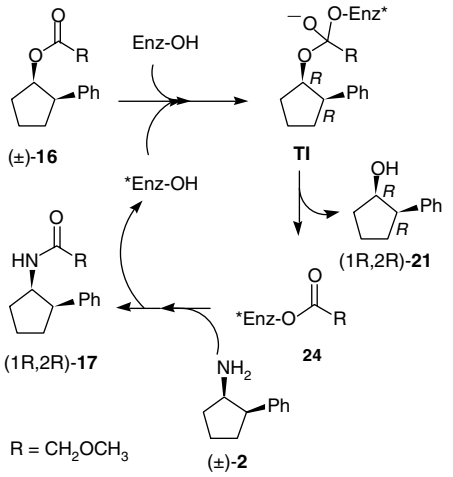
Returning to Table 2, a comparison of the data from entries 5–7 reveals that higher conversions and enantioselectivities are reached the greater the resemblance between the amine and the leaving group is, the best results being observed when the leaving group of the acyl donor matches the amine. On the other hand, esters **14**–**16** derived from alcohols that are also substrates for CALB. Thus, enantioselectivities obtained in their aminolysis reactions (entries 5–7) could also be correlated with the enantioselectivities that CALB shows with these alcohols.

In this context, we carried out the CALB-catalyzed transesterifications of (±)-1-phenylethanol[19] (±)-**19**, (±)-*trans*-2-phenylcyclopentanol[20] (±)-**20** and (±)-*cis*-2-phenylcyclopentanol[21] (±)-**21** with vinyl acetate in Bu^{t}OMe as solvent. The results, summarized in Table 3, clearly show that transesterifications were progressively better in the nucleophile series **21**<**20**<**19**. It is of note that the behaviour of CALB in the transesterification of **20** and **21** suitably correlates with that exhibited in the aminolysis of ethyl acetate with *trans*- and *cis*-2-phenylcyclopentanamine (Table 1), *trans*-alcohol and *trans*-amine being better substrates than their corresponding *cis*-diastereomers. However, if enantioselectivities obtained in the transesterifications of alcohols **19**–**21** (Table 3) are compared with those achieved for the *cis*-amine **2** in the aminolyses of the corresponding *O*-methoxyacetyl derivatives (±)-**14**–**16** (Table 2, entries 5–7), an opposite order is observed. The best enantioselectivity for the amine **2** (Table 2, entry 7) is obtained with the acyl donor (±)-**16**, which derives the alcohol (±)-**21**, this alcohol being transformed by the CALB with the lowest enantioselectivity (Table 3, entry 3). This means that for the aminolysis processes collected in Table 2, the best acyl donor is when the leaving group

Table 3. CALB-catalyzed transesterification of alcohols (±)-**19**-**21** with vinyl acetate[a]

Alcohol	Time (h)	c (%)	Remaining substrate			Product			E
			Alcohol	ee_s (%)[b]	Yield (%)[c]	Ester	ee_p (%)[b]	Yield (%)[c]	
(±)-**19**	9	51	 (*S*)-**19**	97	47	 (*R*)-**12**	99	48	844
(±)-**20**	9	51	 (1*S*,2*R*)-**20**	>99	49	 (1*R*,2*S*)-**22**	97	48	500
(±)-**21**	31	30	 (1*S*,2*S*)-**21**	42	67	 (1*R*,2*R*)-**23**	96	30	74

[a] Solvent: Bu^{t}OMe.
[b] Determined by chiral HPLC.
[c] Isolated yields.



Scheme 2. Description of the CALB-catalyzed aminolysis mechanism.

more closely resembles the amine, rather than when the alcoholic moiety is the better substrate for CALB.

A plausible explanation could lie in the proposed mechanism for the lipase catalysis, exemplified in Scheme 2 for the aminolysis of the ester (±)-**16** with the amine (±)-**2** (Table 2, entry 7). In a first step the enzyme reacts with the acyl donor **16** to give the first tetrahedral intermediate (**TI**), which is mainly formed from the favourable enantiomer (1*R*,2*R*)-**16**. This fact is supported for the high enantiomeric excess (96%) obtained for the leaving (1*R*,2*R*)-2-phenylcyclopentanol (1*R*,2*R*)-**21** in this aminolysis reaction.[22] Despite the known decrease of protein flexibility in organic solvents compared to water,[23] we suggest that in this **TI** the enzyme lightly moulds its active site structure around substrate **16**. This change (Enz*) could be maintained in the acyl-enzyme intermediate **24** and, therefore, it could display a greater enantioselectivity towards substrate **2**. Once completed the catalytic cycle, the enzyme could memorize the form *Enz-OH or could be in equilibrium with Enz-OH, starting the cycle again. These changes, which also take place when other acyl donors are used, could be more favourable when the leaving group is chiral and when the more similar the leaving group and the amine are.

3. Conclusions

The resolution of (±)-*trans*- and (±)-*cis*-2-phenylcyclopentanamine has been efficiently carried out by CALB-catalyzed aminolysis reactions, all stereoisomers being available in very high ees (>97%) and yields. We have developed a practical strategy for enhancing the CALB enantioselectivity based on the utilization of (±)-1-phenylethyl methoxyacetate as the acyl donor. Furthermore, we have demonstrated that the acyl donor bearing the leaving group structurally matching with the amine markedly enhanced the lipase activity, this aspect being more important than the enantioselectivity exhibited for the enzyme towards the alcohol, which acts as the leaving group. This strategy, which does not require pretreatment of the enzyme, could be considered as an alternative to others of proved efficacy such as the use of additives[24] or the molecular imprinting of enzymes.[25]

4. Experimental

4.1. General

Lipase B from *C. antarctica*, Novozym 435, was a gift from Novo Nordisk Co. and was employed without any previous treatment. For the enzymatic reactions, commercial anhydrous *tert*-butyl methyl ether (99.8%) and ethyl acetate of spectrophotometric grade (stored with 4 Å molecular sieves) were used. Acyl donors **11** (benzyl acetate), (±)-**12** [(±)-1-phenylethyl acetate] and **13** (methyl methoxyacetate) are commercially available. IR spectra were recorded on an Infrared FT spectrophotometer using KBr pellets (for solids) or neat (for liquids). Chiral HPLC analyses were performed using Chiralcel OD and OB-H columns (Daicel), at 20 °C. ^{1}H, ^{13}C NMR, and DEPT were recorded using AC-200 (^{1}H, 200.13 MHz and ^{13}C, 50.3 MHz), and AC-300 or DPX-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) spectrometers using $CDCl_3$ as solvent. The chemical shifts are given in delta (δ) values and the coupling constants (J) in hertz (Hz). ESI^{+} was used to record mass spectra (MS). Microanalyses were performed on a Perkin–Elmer model 2400 instrument.

4.2. Enzymatic acetylation of (±)-*trans*- and (±)-*cis*-2-phenylcyclopentanamine (±)-1 and (±)-2. General procedure

To a mixture of racemic amine (1.2 mmol) and CALB (120 mg) under a nitrogen atmosphere, ethyl acetate (6.0 mL) was added. The resulting mixture was shaken at 28 °C and 200 rpm during 6.5 h (for amine **1**) or 24 h (for amine **2**). The enzyme was filtered, successively washed with ethyl acetate and methanol, and the organic solvents were evaporated under reduced pressure. The residue was treated with 3 N aq H_2SO_4 (15 mL) and extracted with dichloromethane (3×15 mL). Aqueous phase was treated with solid NaOH until pH basic, and extracted with diclorometane (4×15 mL). Evaporation of both organic phases yielded the pure amide and the amine, respectively. To avoid the oxidation of the amines, they were transformed into the corresponding hydrochloride (by the addition of concd aq HCl, ethanol and evaporation to dryness).

4.2.1. (1*S*,2*R*)-2-Phenylcyclopentanamine (1*S*,2*R*)-1. Yield: 45%. Hydrochloride salt of (1*S*,2*R*)-**1**: $[\alpha]_D^{20} = +66.0$ (*c* 2.0, CH_3OH) 98% ee. Lit.[8] for (1*S*,2*R*)-(+)-**1**xHCl: $[\alpha]_D^{23} = +68.2$ (*c* 4.0, CH_3OH) 99% ee.

4.2.2. (1*S*,2*S*)-2-Phenylcyclopentanamine (1*S*,2*S*)-2. Yield: 65%. Hydrochloride salt of (1*S*,2*S*)-**2**: $[\alpha]_D^{20} = +30.5$ (*c* 0.88, ethanol) 33% ee. Lit.[9] for (1*S*,2*S*)-(+)-**2**xHCl: $[\alpha]_D^{20} = +97.0$ (*c* 1.5, ethanol) >99% ee.

4.2.3. (1*R*,2*S*)-*N*-(2-Phenylcyclopentyl)acetamide (1*R*,2*S*)-8. Yield: 49%; mp 116–118 °C; $[\alpha]_D^{20} = -39.8$ (*c* 1.0, $CHCl_3$) 97% ee; IR (KBr) 3298, 1639 cm^{-1}; ^1H NMR (200 MHz): δ 1.40–1.98 (m+s, 7H, $2CH_2+CH_3$), 2.06–2.42 (m, 2H), 2.84 (m, 1H, CH), 4.33 (m, 1H, CH), 5.64 (br s, 1H, NH), 7.15–7.38 (m, 5H, Ph); ^{13}C NMR (50.3 MHz): δ 22.04 (CH_2), 23.27 (CH_3), 32.60 (CH_2), 33.10 (CH_2), 51.76 (CH), 56.64 (CH), 126.42 (CH), 127.18 (CH), 128.45 (CH), 142.26 (C), 169.85 (C=O); MS (ESI^+) *m*/*z* (rel intensity): 204.1 [$(M+H)^+$, 55], 226.0 [$(M+Na)^+$, 100]. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 77.03; H, 8.13; N, 6.99.

4.2.4. (1*R*,2*R*)-*N*-(2-Phenylcyclopentyl)acetamide (1*R*,2*R*)-9. Yield: 27%; mp 75–77 °C; $[\alpha]_D^{20} = +88.7$ (*c* 1.0, $CHCl_3$) 85% ee; IR (KBr) 3295, 1641 cm^{-1}; ^1H NMR (200 MHz): δ 1.50–2.3 (m+s, 9H, $3CH_2+CH_3$), 3.38 (q, 1H, $J = 7.0$, CH), 4.52 (quintet, 1H, $J = 7.5$, CH), 4.99 (br s, 1H, NH), 7.08–7.40 (m, 5H, Ph); ^{13}C NMR (50.3 MHz): δ 21.97 (CH_2), 23.14 (CH_3), 29.12 (CH_2), 31.48 (CH_2), 46.87 (CH), 53.53 (CH), 126.40 (CH), 128.24 (CH), 128.30 (CH), 141.04 (C), 169.50 (C=O); MS (ESI^+) *m*/*z* (rel intensity): 204.1 [$(M+H)^+$, 55], 226.0 [$(M+Na)^+$, 100]. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 77.10; H, 8.52; N, 6.93.

4.3. General procedure for the synthesis of methoxyacetates (±)-14–16

Triethylamine (4.0 mmol), methoxyacetyl chloride (4.4 mmol) and a catalytic amount of DMAP (15 mg) were added under nitrogen over a solution of the corresponding alcohol (4.0 mmol) in anhydrous dichloromethane (8.0 mL). The mixture was stirred during 12 h at room temperature. Then, dichloromethane (12 mL) was added and the organic solution was successively washed with 3 N aq HCl (10 mL), H_2O (10 mL), saturated aq $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4) and concentrated to yield the crude ester, which was purified by distillation under reduced pressure.

4.3.1. (±)-1-Phenylethyl methoxyacetate (±)-14. Obtained from (±)-1-phenylethanol. Yield: 98%; bp 70–71 °C (0.5 Torr); IR (neat) 1776, 1194, 1130 cm^{-1}; ^1H NMR (200 MHz): δ 1.59 (d, 2H, $J = 6.3$ Hz, CH_3), 3.40 (s, 3H, CH_3), AB system (δ_A 4.04, δ_B 4.07 $J_{AB} = 16.2$ Hz, CH_2), 6.02 (q, 1H, $J = 6.5$ Hz, CH), 7.20–7.40 (m, 5H, Ph); ^{13}C NMR (75.5 MHz): δ 21.33 (CH_3), 58.31 (OCH_3), 69.02 (CH_2), 71.93 (CH), 125.39 (CH), 127.27 (CH), 127.79 (CH), 140.52 (C), 168.72 (C=O); MS (ESI^+) *m*/*z* (rel intensity): 217.0 [$(M+Na)^+$, 100]. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.15; H, 7.18.

4.3.2. (±)-*trans*-2-Phenylcyclopenthyl methoxyacetate (±)-15. Obtained from (±)-*trans*-2-phenylcyclo-pentanol.[7] Yield: 91%; bp 84–85 °C (0.5 Torr); IR (neat) 1752, 1195, 1129 cm^{-1}; ^1H NMR (200 MHz): δ 1.68–1.97 (m, 4H), 2.12–2.37 (m, 2H), 3.21 (m, 1H, CH), 3.42 (s, 3H, OCH_3), 4.00 (s, 2H, CH_2) 5.25 (m, 1H, CH), 7.17–7.40 (m, 5H, Ph); ^{13}C NMR (75.5): δ 22.58 (CH_2), 31.63 (CH_2), 31.69 (CH_2), 50.72 (CH), 58.95 (OCH_3), 69.58 (CH_2), 82.17 (CH), 126.22 (CH), 126.96 (CH), 128.21 (CH), 142.14 (C), 169.75 (C=O); MS (ESI^+) *m*/*z* (rel intensity): 257.1 [$(M+Na)^+$, 100]. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.62; H, 7.60.

4.3.3. (±)-*cis*-2-Phenylcyclopenthyl methoxyacetate (±)-16. Obtained from (±)-*cis*-2-phenylcyclopentanol (see below). Yield: 90%, bp 84–85 °C (0.5 Torr); IR (neat) 1751, 1195, 1129 cm^{-1}; ^1H NMR (200 MHz): δ 1.65–2.30 (m, 6H), 3.10–3.30 (m, 4H, OCH_3, CH), AB system (δ_A 3.63, δ_B 3.83, $J_{AB} = 16.2$ Hz, CH_2), 5.56 (dt, 1H, $J = 2.0$ and 5.5 Hz, CH), 7.20–7.30 (m, 5H, Ph); ^{13}C NMR (75.5): δ 22.28 (CH_2), 28.97 (CH_2), 32.32 (CH_2), 49.69 (CH), 58.86 (OCH_3), 69.39 (CH_2), 78.08 (CH), 126.25 (CH), 127.80 (CH), 128.38 (CH), 139.21 (C), 169.39 (C=O); MS (ESI^+) *m*/*z* (rel intensity): 257.1 [$(M+Na)^+$, 100]. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.59; H, 7.83.

4.4. Enzymatic acylation of (±)-2 with esters 11–16 and of (±)-1 with 14. Typical procedure

The corresponding ester (3.6 mmol) and *tert*-butyl methyl ether (8.0 mL) were added to a mixture of (±)-**2** or (±)-**1** (1.2 mmol) and CALB (120 mg) under nitrogen atmosphere. The suspension was shaken at 28 °C and 200 rpm during 46 h [for (±)-**2**] and 16 h [for (±)-**1**]. After, the procedure was similar to that for the enzymatic acetylation, but once the remaining amine was extracted with 3 N aq H_2SO_4, combined organic layers were concentrated in vacuo to give a residue containing a mixture of amide, alcohol and ester. Flash chromatography (hexane/AcOEt mixture) of the residue yielded pure amide. Alcohol and ester were also separated except in the case of ester **16** and its corresponding alcohol.

4.4.1. (1*R*,2*R*)-*N*-(2-Phenylcyclopentyl)methoxyacetamide (1*R*,2*R*)-17. Colourless oil; yield: 49%; $[\alpha]_D^{20} = +54.1$ (*c* 0.95, $CHCl_3$) >99% ee; IR (neat) 3312, 1682 cm^{-1}; ^1H NMR (200 MHz): δ 1.60–2.25 (m, 6H), 3.05 (s, 3H, OCH_3), 3.39 (m, 1H, CH), AB system (δ_A 3.53, δ_B 3.79, $J_{AB} = 15.4$, CH_2), 4.56 (quintet, 1H, $J = 7.0$, CH), 6.14 (br s, 1H, NH), 7.15–7.35 (m, 5H, Ph); ^{13}C NMR (75.5 MHz): δ 22.22 (CH_2), 29.16 (CH_2), 31.94 (CH_2), 47.31 (CH), 52.71 (CH), 58.86 (OCH_3), 71.72 (CH_2), 126.34 (CH), 128.15 (CH), 128.22 (CH), 140.66 (C), 168.86 (C=O); MS (ESI^+) *m*/*z* (rel intensity): 234.1 [$(M+H)^+$, 45], 256.1 [$(M+Na)^+$, 100]. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.80; H, 8.03; N, 6.27.

4.4.2. (1*R*,2*S*)-*N*-(2-Phenylcyclopentyl)methoxyacetamide (1*R*,2*S*)-18. Yield: 38%; mp 100–102 °C; $[\alpha]_D^{20} = -44.0$ (*c* 1.0, $CHCl_3$) >99% ee; IR (KBr) 3310, 1651 cm^{-1}; ^1H NMR (200 MHz): δ 1.45–1.95 (m, 4H), 2.10–2.45 (m,

2H), 2.90 (m, 1H, CH), 3.32 (s, 3H, OCH_3), AB system (δ_A 3.75, δ_B 3.84, $J_{AB} = 15.1$, CH_2), 4.38 (quintet, 1H, $J = 8.3$, CH), 6.49 (br s, 1H, NH), 7.15–7.38 (m, 5H, Ph); ^{13}C NMR (75.5 MHz): δ 22.12 (CH_2), 32.58 (CH_2), 32.95 (CH_2), 51.88 (CH), 55.97 (CH), 58.91 (OCH_3), 71.79 (CH_2), 126.39 (CH), 127.17 (CH), 128.41 (CH), 142.19 (C), 169.09 (C=O); MS (ESI^+) m/z (rel intensity): 234.1 [$(M+H)^+$, 52], 256.1 [$(M+Na)^+$, 100]. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.35; H, 8.08; N, 6.08.

4.5. (±)-*cis*-2-Phenylcyclopentyl *p*-nitrobenzoate (±)-25

To a solution of (±)-*trans*-2-phenylcyclopentanol[7] (12.0 mmol) in THF (30 mL) at 0 °C under nitrogen atmosphere, the following solutions were successively added: triphenylphosphine (18 mmol) in THF (20 mL), *p*-nitrobenzoic acid (18 mmol) in THF (25 mL) and diethyl azodicarboxylate (18 mmol) in THF (25 mL). The resulting yellow solution was stirred at room temperature overnight. After, solvent was removed under reduced pressure and the solid residue was extracted with hot hexane (4×30 mL). The hexane solution was concentrated under vacuum and the crude was subjected to flash chromatography (hexane/AcOEt 10:1) yielding (±)-**25** (3.25 g, 87%) as a pale yellow solid: mp 78–80 °C; IR (KBr) 1720, 1525, 1350, 1272 cm^{-1}; ^1H NMR (200 MHz): δ 1.70–2.45 (m, 6H), 3.35 (m, 1H, CH), 5.67 (dt, 1H, $J = 1.8$ and 5.3, CH), 7.10–7.40 (m, 5H, Ph), 7.91 (d, 2H, $J = 9.0$), 8.17 (d, 2H, $J = 9.0$); ^{13}C NMR (75.5 MHz): δ 22.40 (CH_2), 28.85 (CH_2), 32.50 (CH_2), 49.68 (CH), 79.72 (CH), 123.10 (CH), 126.32 (CH), 127.88 (CH), 128.18 (CH), 130.12 (CH), 135.83 (C), 139.10 (C), 150.02 (C), 163.78 (C=O). MS (ESI^+) m/z (rel intensity): 334.0 [$(M+Na)^+$, 100]. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.56; H, 5.43; N, 4.47.

4.6. (±)-*cis*-2-Phenylcyclopentanol (±)-21

(±)-*cis*-2-Phenylcyclopentyl *p*-nitrobenzoate (±)-**25**, (9 mmol) was treated with 1 N NaOH in methanol (18 mL) until disappearance of the starting material (TLC control, hexane/AcOEt 4:1). After, methanol was removed and the residue extracted with H_2O (15 mL) and dichloromethane (3×15 mL). Organic phase was dried and evaporated to yield crude (±)-**21**,[26], which was purified by distillation to reduced pressure: yield, 90%; bp 55–56 °C (0.5 Torr); ^1H NMR (200 MHz): δ 1.33 (br s, 1H, OH), 1.65–2.25 (m, 6H), 3.08 (m, 1H, CH), 4.30 (t, 1H, $J = 4.3$, CH), 7.10–7.40 (m, 5H, Ph); ^{13}C NMR (75.5 MHz): δ 22.31 (CH_2), 27.26 (CH_2), 33.66 (CH_2), 51.88 (CH), 75.64 (CH), 126.54 (CH), 128.42 (CH), 128.50 (CH), 139.79 (C).

4.7. Enzymatic transesterification of alcohols (±)-19–21 with vinyl acetate. General procedure

tert-Butyl methyl ether (10 mL) and vinyl acetate (4.8 mmol) were added to a mixture of the racemic alcohol (1.6 mmol), CALB (160 mg) and 4 Å molecular sieves (40 mg) under nitrogen atmosphere. The suspension was shaken at 28 °C and 200 rpm during 9 h (for **19** and **20**) or 31 h (for **21**). After, the enzyme was filtered, washed with *tert*-butyl methyl ether and the solvent evaporated. Both remaining alcohol and the corresponding acetate present in the residue were separated by flash chromatography (hexane/AcOEt 11:1).

4.7.1. Enzymatic transesterification of (±)-1-phenylethanol (±)-19. Remaining (*S*)-**19**: yield, 47%; $[\alpha]_D^{20} = -42.5$ (*c* 0.67, CH_3OH) 97% ee. Lit.[27] for (*S*)-(−)-**19**: $[\alpha]_D^{20} = -45$ (*c* 5, CH_3OH) >99% ee. Product (*R*)-1-phenylethyl acetate [(*R*)-**12**]: yield, 48%; $[\alpha]_D^{20} = +102$ (*c* 1.2, CH_3OH) 99% ee. Lit.[28] for (R)-(+)-**12**: $[\alpha]_D^{25} = +106$ (*c* 1, ether) >95% ee.

4.7.2. Enzymatic transesterification of (±)-*trans*-2-phenylcyclopentanol (±)-20. Remaining (1*S*,2*R*)-**20**: yield, 49%; $[\alpha]_D^{20} = +84.3$ (*c* 1.0, CH_3OH) >99% ee. Lit.[29] for (1*S*,2*R*)-(+)-**20**: $[\alpha]_D^{20} + 85.2$ (*c* 0.94, CH_3OH) >95% ee. Product (1*R*,2*S*)-2-phenylcyclopentyl acetate [(1*R*,2*S*)-**22**]: yield, 48%; $[\alpha]_D^{20} = -56.5$ (*c* 1.0, CH_3OH) 97% ee. Lit.[29] for (1*R*,2*S*)-(−)-**22**: $[\alpha]_D^{20} = -55.4$ (*c* 0.90, CH_3OH) 94% ee.

4.7.3. Enzymatic transesterification of (±)-*cis*-2-phenylcyclopentanol (±)-21. Remaining (1***S***,2***S***)-**21**: yield, 67%; $[\alpha]_D^{20} = +46.1$ (*c* 2.0 $CHCl_3$) 42% ee. Lit.[30] for (1*R*,2*R*)-(−)-**21**: $[\alpha]_D^{25} = -90.4$ (*c* 2.0 $CHCl_3$) optically pure isomer. Product (1*R*,2*R*)-2-phenylcyclopentyl acetate [(1*R*,2*R*)-**23**]: yield, 30%; $[\alpha]_D^{20} = -48.9$ (*c* 1.9, $CHCl_3$) 96% ee. Lit.[30] for (1*R*,2*R*)-(−)-**23**: $[\alpha]_D^{25} = -47.1$ (*c* 2.0 $CHCl_3$) optically pure isomer. IR (neat) 1737, 1243 cm^{-1}; ^1H NMR (300 MHz): δ 1.70–2.27 (m+s, 9H, $3CH_2+CH_3$), 3.19 (m, 1H, CH), 5.45 (dt, 1H, $J = 2.1$ and 5.3, CH), 7.20–7.35 (m, 5H, Ph); ^{13}C NMR (75.5 MHz): δ 20.88 (CH_3), 22.29 (CH_2), 29.25 (CH_2), 32.43 (CH_2), 49.76 (CH), 77.70 (CH), 126.21 (CH), 127.77 (CH), 128.47 (CH), 139.62 (C), 170.18 (C=O); MS (ESI^+) m/z (rel intensity): 227.1 [$(M+Na)^+$, 100].

4.8. Determination of the enantiomeric excesses and assignment of the absolute configuration

The ee for each optically active compound isolated from the enzymatic reactions was determined by chiral HPLC. Acetamides **8** and **9** were directly analyzed using a Chiralcel OD column; for acetamide (±)-**8**: t_R 10.1 (1*R*,2*S*) and 13.6 (1*S*,2*R*) min, Rs 3.8 (hexane/propan-2-ol 90:10, 0.8 mL/min); for acetamide (±)-**9**: t_R 22.1 (1*R*,2*R*) and 25.3 (1*S*,2*S*) min, Rs 2.0 (hexane/propan-2-ol 96:4, 0.8 mL/min). Amines **1** and **2** were transformed into the corresponding acetamides **8** and **9** by conventional treatment with acetyl chloride (1.2 equiv), DMAP (1.0 equiv) in dichloromethane (>95% yield). Methoxyacetamides **17** and **18** were hydrolyzed (3 N aq NaOH, reflux, 12 h, 93–95% yield) and the resulting amines **2** and **1** were transformed in the acetamides **9**

and **8**, respectively. Alcohol **19** was analyzed using a Chiralcel OB-H column; for (±)-**19**: t_R 12.5 (*S*) and 16.9 (*R*) min, Rs 6.9 (hexane/propan-2-ol 90:10, 0.5 mL/min). Alcohols **20** and **21** were analyzed using a Chiralcel OD column; for (±)-**20**: t_R 14.9 (1*S*,2*R*) and 17.0 (1*R*,2*S*) min, Rs 2.3 (hexane/propan-2-ol 97:3, 0.8 mL/min); for (±)-**21**: t_R 9.8 (1*S*,2*S*) and 11.4 (1*R*,2*R*) min, Rs 2.6 (hexane/propan-2-ol 97:3, 0.8 mL/min). Acetate **12** was analyzed using a Chiralcel OB-H column; for (±)-**12**: t_R 10.9 (*R*) and 11.8 (*S*) min, Rs 1.5 (hexane/propan-2-ol 92:8, 0.5 mL/min). Acetates **22** and **23** were hydrolyzed (1 N NaOH in methanol) to the corresponding alcohols **20** and **21**.

The absolute configuration of the remaining amines and alcohols obtained in the enzymatic processes were determined by comparison of the sign of their optical rotations with those reported. Consequently, absolute configuration for the amides and esters was established.

Acknowledgements

We thank Novo Nordisk Co. for the generous gift of the CALB. This work has been supported by grants from MCYT (Spain; Project PPQ-2001-2683) and the Principado de Asturias (Spain; Project GE-EXP01-03). J.G.-S. thanks the Spanish MEC for a predoctoral fellowship.

References and notes

1. (a) Henkel, T.; Brunne, R. M.; Müller, H.; Reichel, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 643–647; (b) Brown, A. R.; Rees, D. C.; Rankovic, Z.; Morphy, J. R. *J. Am. Chem. Soc.* **1997**, *119*, 3288–3295.
2. (a) Juaristi, E.; León-Romo, J. L.; Reyes, A.; Escalante, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2441–2495; (b) Juaristi, E.; Escalante, J.; León-Romo, J. L.; Reyes, A. *Tetrahedron: Asymmetry* **1998**, *9*, 715–740; (c) Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459–505.
3. (a) Skupinska, K. A.; McEachern, E. J.; Baird, I. R.; Skerlj, R. T.; Bridger, G. J. *J. Org. Chem.* **2003**, *68*, 3546–3551; (b) González-Sabín, J.; Gotor, V.; Rebolledo, F. *Tetrahedron: Asymmetry* **2002**, *13*, 1315–1320; (c) Choi, Y. K.; Kim, M. J.; Ahn, Y.; Kim, M.-J. *Org. Lett.* **2001**, *3*, 4099–4101; (d) López-Serrano, P.; Jongejan, J. A.; Rantwijk, F.; Sheldon, R. A. *Tetrahedron: Asymmetry* **2001**, *12*, 219–228; (e) Sánchez, V. M.; Rebolledo, F.; Gotor, V. *J. Org. Chem.* **1999**, *64*, 1464–1470; (f) Gotor, V. *Bioorg. Med. Chem.* **1999**, *7*, 2189–2197.
4. Schmid, A.; Dordick, J. S.; Hauer, B.; Kieners, A.; Wubbolts, M.; Witholt, B. *Nature* **2001**, *409*, 258–268.
5. McGrath, W. R.; Kuhn, W. L. *Arch. Int. Pharmacodyn Ther.* **1968**, *172*, 405–413.
6. (a) Hartmann, S.; Ullrich, S.; Hupfer, C.; Frahm, A. W. *Eur. J. Med. Chem.* **2000**, *35*, 377–392; (b) Grisar, J. M.; Claxton, G. P.; Carr, A. A.; Wiech, N. L. *J. Med. Chem.* **1973**, *16*, 679–683.
7. Shepherd, T. A.; Aikins, J. A.; Bleakman, D.; Cantrell, B. E.; Rearick, J. P.; Simon, R. L.; Smith, E. C. R.; Stephenson, G. A.; Zimmerman, D. M. *J. Med. Chem.* **2002**, *45*, 2101–2111.
8. Brown, H. C.; Kim, K.-W.; Cole, T. E.; Singaram, B. *J. Am. Chem. Soc.* **1986**, *108*, 6761–6764.
9. Wiehl, W.; Frahm, A. W. *Chem. Ber.* **1986**, *119*, 2668–2677.
10. Brown, H. C.; Kim, K.-W.; Srebnik, M.; Singaram, B. *Tetrahedron* **1987**, *43*, 4071–4078.
11. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.
12. Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
13. Kraut, J. *Ann. Rev. Biochem.* **1977**, *46*, 331–358.
14. Lee, D.; Choi, Y. K.; Kim, M.-J. *Org. Lett.* **2000**, *2*, 2553–2555.
15. García-Urdiales, E.; Rebolledo, F.; Gotor, V. *Adv. Synth. Catal.* **2001**, *343*, 646–654.
16. In a kinetic study, we had demonstrated that *tert*-butylmethyl ether is the solvent in which CALB exhibits a higher catalytic activity: García-Alles, L. F.; Gotor, V. *Biotechnol. Bioeng.* **1998**, *59*, 684–694.
17. For the resolution of (±)-**2**, the use of 4 Å molecular sieves was not necessary. In these conditions, although anhydrous Bu′OMe was used, a side CALB-catalyzed hydrolysis of the acyl donor **12** took place. Thus, the resulting (*R*)-1-phenylethanol arose from aminolysis and hydrolysis of (±)-**12**. For this reason, enantiomeric ratio for the acyl donor was not determined. Nevertheless, the high ee (92%) obtained for the alcohol reveals that the (*S*)-enantiomer of the acyl donor (*S*)-**12** was almost unreacted.
18. Balkenhohl, F.; Ditrich, K.; Hauer, B.; Ladner, W. *J. prakt. Chem.* **1997**, *339*, 381–384.
19. (±)-**1**-Phenylethanol was previously resolved with CALB using *S*-ethyl thiooctanoate ($E > 200$): Frykman, H.; Öhrner, N.; Norin, T.; Hult, K. *Tetrahedron Lett.* **1993**, *34*, 1367–1370.
20. (±)-trans-2-Phenylcyclopentanol was previously resolved ($E > 100$) with a lipase derived from *Pseudomonas* sp (SAM II) under similar reaction conditions: Seemayer, R.; Schneider, M. P. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 171–174.
21. Enzyme-catalyzed kinetic resolution of (±)-**21** has not been reported. Synthesis of (±)-**21** was carried out from (±)-**20** by Mitsunobu reaction with *p*-nitrobenzoic acid and subsequent hydrolysis of the resulting (±)-*cis*-2-phenylcyclopentyl *p*-nitrobenzoate.
22. Similarly, (*R*)-1-phenylethanol was isolated with 92% and 93% ee from reaction of (±)-**2** with (±)-**12** and (±)-**14**, respectively. (1*R*,2*S*)-*trans*-2-Phenylcyclopentanol with 99% ee was obtained from the analogous reaction with (±)-**15**.
23. Affleck, R.; Haynes, C. A.; Clark, D. S. *Proc. Natl. Acad. Sci. U.S.A* **1992**, *89*, 5167–5170.
24. Theil, F. *Tetrahedron* **2000**, *56*, 2905–2919.
25. (a) Rich, J. O.; Mozhaev, V. V.; Dordick, J. S.; Clark, D. S.; Khmelnitsky, Y. L. *J. Am. Chem. Soc.* **2002**, *124*, 5254–5255; (b) Rich, J. O.; Dordick, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 3245–3252; (c) Okahata, Y.; Hatano, A.; Ijiro, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1311–1322; (d) Stahl, M.; Jeppsson-Wistrand, U.; Mansson, M.-O.; Mosbach, K. *J. Am. Chem. Soc.* **1991**, *113*, 9366–9368.
26. Takahashi, K.; Kishi, M. *Tetrahedron* **1988**, *44*, 4737–4746.
27. Fluka catalog, 2002, p 1128.
28. Bianchi, D.; Cesti, P.; Battistel, E. *J. Org. Chem.* **1988**, *53*, 5531–5534.
29. Seemayer, R.; Schneider, M. P. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 171–174.
30. Kim, C. J.; Brown, H. C. *J. Am. Chem. Soc.* **1972**, *94*, 5051–5060.