Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 1990–1994

Highly enantioselective enzymatic resolution of *cis*-fused octalols mediated by *Candida antarctica* lipase (Novozym 435)

Tiago O. Vieira, Helena M. C. Ferraz, Leandro H. Andrade and André L. M. Porto*

Instituto de Química, Universidade de São Paulo, Av. Prof. Lineu Prestes, 748, CEP 05508-900, São Paulo, SP, Brazil

Received 5 June 2006; accepted 12 July 2006

Abstract—Optically active *cis*-fused octalin acetates have been prepared by esterification of *cis*-fused octalols using *Candida antarctica* lipase (CALB—Novozym 435). The enzyme efficiently resolved the racemic octalols by kinetic resolution, to afford *cis*-fused octalols and *cis*-fused octalin acetates with high enantiomeric excesses (up to >99%) and good yields (>40%).

1. Introduction

The *cis*-fused decalinic and octalinic moieties occur in a number of natural terpenoid products, such as *cis*-clerodanes, eremophilanes, cadinanes, and others.[1] These systems are important key intermediates for the synthesis of bakkane sesquiterpenes.[2] The asymmetric synthesis of *cis*-fused decalins and/or octalins has not really been explored, and only a few articles concerning this subject have been published. A very elegant and straightforward approach to this kind of skeleton is a Diels–Alder reaction mediated by chiral Lewis acids.[3,4] Biocatalysis has also proven to be an alternative tool to reach this system, through lipase catalyzed desymmetrization or kinetic resolution of decalins. Some examples are the enantioselective synthesis of decalin skeletons, mediated by the acylase from *Aspergillus melleus*,[5] and the synthesis of *meso*-decalins by the lipase from *Candida antarctica*.[6] Several lipase catalyzed-desymmetrizations of oxygenated decalins[7] and the kinetic resolution of naphthalenol by *Candida antarctica* have been described.[8]

We have recently reported an efficient kinetic resolution of propargylic and allylic alcohols by *Candida antarctica* lipase (CALB—Novozym 435) with high enantioselectivity.[9,10] Herein, we report the stereoselective enzymatic resolution of the *cis*-fused octalols **4**–**6**, using the immobilized enzyme CALB.

2. Results and discussion

2.1. Preparation of the substrates

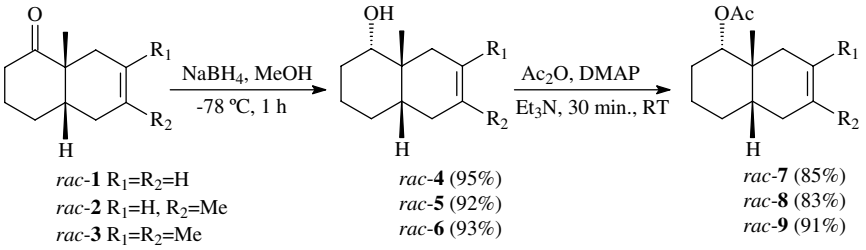
The racemic *cis*-fused octalols **4**–**6** were obtained in excellent yields by a stereoselective reduction of the corresponding *cis*-octalones **1**–**3**, using sodium borohydride in methanol. Classical acetylation of these alcohols led to the racemic acetates **7**–**9** (Scheme 1). The starting octalones **1**–**3** were prepared by the reaction of 2-methylcyclohexenone with butadiene, isoprene or 2,3-dimethyl-1,3-butadiene, respectively, after some improvement[11] of the previously described procedures.[12,13]

2.2. Enzymatic resolution

The (±)-*cis*-fused octalol **5** was arbitrarily chosen for evaluation of the enzymatic resolution, which was performed using hexane as a solvent and vinyl acetate as an acyl donor, as previously reported by us.[9,10] Nine lipases, namely CALB (Novozym 435—immobilized from *Candida antarctica* lipase type B—10,000PLU/g), CALA (Novozym 735, liquid), CALB L (Novozym, liquid), Lipozyme TL 100L (Novozym, liquid), Lipozyme 1M (Novo Nordisk—immobilized by *Mucor miehei*), Lipolase 100T (immobilized), Lipase E.C. 3.1.1.3 (Sigma-lyophilized from *Candida rugosa*), Lipase E.C. 3.1.1.3 (Sigma-lyophilized from *Mucor javanicus*) and Lipase E.C. 3.1.1.3 (Sigma-Type II from porcine pancreas), were chosen as the candidate enzymes. The conditions and results obtained so far are shown in Table 1. In this screening, (*S*)-alcohol **5** and (*R*)-acetate **8** were obtained with good enantioselectivity at 32 °C, using CALB

* Corresponding author. Tel.: +16 3373 8102; fax: +16 3773 9952; e-mail addresses: almporto@iqsc.usp.br; almporto@iq.usp.br

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.07.014



rac-**1** R_1=R_2=H
rac-**2** R_1=H, R_2=Me
rac-**3** R_1=R_2=Me

rac-**4** (95%)
rac-**5** (92%)
rac-**6** (93%)

rac-**7** (85%)
rac-**8** (83%)
rac-**9** (91%)

Scheme 1.

Table 1. Enzymatic resolution of *cis*-octalol **5** with several enzymes (analytical scale)

Entry	Enzymes (lipases)	*c* **8**	ee **8**	ee **5**	*E*
1	Novozym 435 CAL-B	45	>98	82	>200
2	Novozym 735 CAL-A	14	>98	16	>200
3	CAL-B L	—	—	—	—
4	Lipozyme TL 100L	—	—	—	—
5	Lipozyme IM	2	>98	4	Nc
6	Lipolase	—	—	—	—
7	Lipase E.C. 3.1.1.3 (*Candida rugosa*)	9	>98	10	Nc
8	Lipase E.C. 3.1.1.3 (*Mucor javanicus*)	—	—	—	—
9	Lipase E.C. 3.1.1.3 (Porcine pancreas)	—	—	—	—

c (%): Conversion calculated from the substrate (ee_S) and the product (ee_P).
$c = (ee_S)/(ee_P + ee_S)$.
ee (%) enantiomeric excess.
E: enantiomeric ratio.
Nc = Not calculated.

(Table 1, entry 1). The other enzymes employed did not efficiently resolve substrate **5**.

The control of the reactions is very important in enzymatic processes, since it is necessary to adjust time and conversion. In this work, we selected for analysis varying the reaction times, ranging from 20 min to 48 h, at two different temperatures (Table 2). As can be observed from the data in Table 2, the conversion at 40 °C in 48 h was very efficient for the three studied (±)-*cis*-octalols **4**–**6**. Thus, the chemoenzymatic resolution of (±)-*cis*-octalol **4** by CALB led to (1*S*,4a*S*,8a*R*)-alcohol **4** and (1*R*,4a*R*,8a*S*)-acetate **7** with high enantiomeric excess (>99%), in good isolated yield (Table 3). Similar results were observed for *cis*-octalols **5** and **6** (Table 3). The enzymatic resolution of *cis*-octalols **4**–**6** is summarized in Scheme 2.

It should be noted that the preparation of chiral alcohol (−)-**6**, through an asymmetric Diels–Alder reaction, followed by reduction of the adduct with $NaBH_4$, has already been described.[3] The enantiomer thus produced was (1*S*,4a*S*,8a*R*)-octalol **6**, which has the same configuration of our octalol **6**, not esterified by CALB.

2.3. Determination of the enantiomeric excess and absolute configuration

The enantiomeric excesses of octalols **4**–**6** and octalin acetates **7**–**9** were calculated from the chiral GC chromatograms, by comparison with the racemic samples (Fig. 1). The absolute configuration of (−)-**6** was determined by the comparison of the specific rotation with the literature data.[3] By analogy, we assigned the (1*S*,4a*S*,8a*R*)-configuration

Table 2. Enzymatic resolution of *cis*-octalols **4**–**6** with Novozym 435 (small scale)

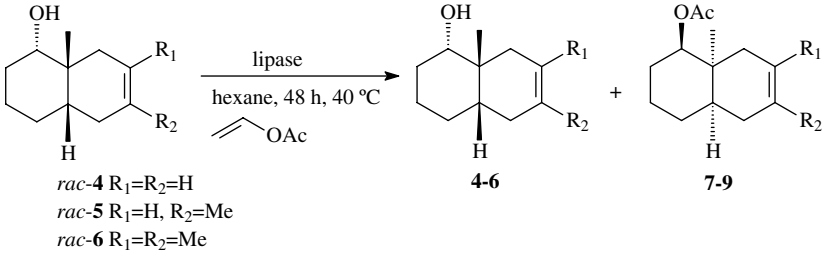
Entry	*t*	(±)-*cis*-Octalols	Temperature 32 °C				Temperature 40 °C			
			c	ee Acetates	ee Octalols	*E*	*c*	ee Acetates	ee Octalols	*E*
1	24	**4**	45	>98	80	—	50	>98	>98	—
2	48		50	>98	>98	>200	50	>98	>98	>200
3	24	**5**	44	>98	78	—	50	>98	97	—
4	48		50	>98	97	>200	50	96	97	>200
5	24	**6**	10	>98	11	—	32	>98	46	—
6	48		19	>98	23	123	32	>98	46	156

t: Time (h).
c (%): Conversion calculated from the substrate (ee_S) and the product (ee_P), $c = (ee_S)/(ee_P + ee_S)$.
ee (%) enantiomeric excess.
E: enantiomeric ratio.

Table 3. Enzymatic resolution of *cis*-octalols **4–6** with Novozym 435 at 40 °C (semi-preparative scale)

Entry	(±)-*cis*-Octalols	*c*	ee Acetates	ee Octalols	*E*	Yield (%) octalols	Yield (%) acetates
1	**4** (195 mg)	50	>99	>99	>200	41	44
2	**5** (280 mg)	48	>98	92	>200	41	41
3	**6** (280 mg)	50	>99	>99	>200	41	47

c (%): Conversion calculated from the substrate (ee_S) and the product (ee_P), $c = (ee_S)/(ee_P + ee_S)$.
ee (%) enantiomeric excess.
E: enantiomeric ratio.



Scheme 2.

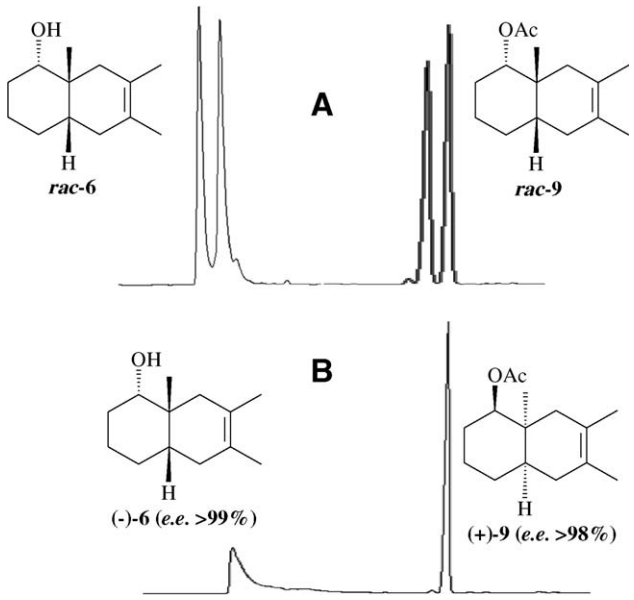


Figure 1. Chromatograms: A. (±)-octalol **6** and (±)-octalin acetate **9**; B. enzymatic resolution of (±)-octalol **6** (280 mg) by Novozym 435 in hexane (48 h).

for alcohols **4** and **5**. The suggested stereochemical preference of CALB was based on Kazlauskas rule.[14]

3. Conclusion

The enzymatic resolution of *cis*-octalols **4–6** with lipase from *Candida antarctica* (CALB—Novozym 435) was very efficient. The resolved products—octalols **4–6** and octalin acetates **7–9**—were obtained in very good yields and excellent enantiomeric excesses (up to 99%). Therefore, we believe that this chemoenzymatic resolution could be successfully applied to substrates containing *cis*-fused skeletons with three stereogenic centers.

4. Experimental

4.1. General

All solvents and chemicals used were previously purified according to the usual methods. Column chromatography was carried out with Merck silica gel (230–400 mesh). Thin layer chromatography (TLC) was performed with silica gel F-254 on aluminum. ^1H and ^{13}C NMR spectra were recorded on either a Bruker DPX-300 spectrometer or a Bruker AC-200 spectrometer, using as an internal standard tetramethylsilane and the central peak of $CDCl_3$ (77 ppm). Near infrared spectra were recorded on a Bomem MB-100 spectrophotometer. Low resolution mass spectrometry was performed in a Shimadzu CGMS-17A/QP5050A instrument equipped with capillary column HP-1 (J&W Scientific 25 m × 0.32 mm × 1.05 μm). The carrier gas was helium. Compound names were obtained using the software ChemDraw Ultra®, version 8.0. Conversions and enantiomeric excesses of the enzyme-catalyzed reactions were determined using a Shimadzu GC-17A gas chromatograph equipped with a chiral capillary column GAMA DEX™ 120 (packed β-cyclodextrin (30 m × 0.25 mm × 0.25 μm)—Supelco or Chirasil-Dex CB β-cyclodextrin (25 m × 0.25 mm)—Varian). The carrier gas was hydrogen with a pressure of 100 kPa. Optical rotation values were measured in a Jasco DIP-378 polarimeter and the reported data refer to the Na-line value using a 1 dm cuvette. Novozym 435—immobilized lipase from *Candida antarctica* was obtained as a gift from Novo Nordisk (Paraná—Brazil).

4.1.1. 1,2,3,4,4a,5,8-Heptahydro-8a-methylnaphthalen-1-ol (±)-4. To a solution of octalone **1** (1.00 g, 6.11 mmol) in MeOH (30 mL), at −78 °C, $NaBH_4$ was added. The resulting suspension was stirred at this temperature for 1 h and then H_2O was added. The aqueous phase was extracted with AcOEt (30 mL, 3 times) and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvent, (±)-**4** was obtained as a colorless oil (0.962 g, 95% yield) and was used without further purification. IR

(film): 3379 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 1.05 (s, 3H), 1.22–1.77 (m, 10H), 2.13–2.39 (m, 2H), 3.31 (dd, *J* 10.7 and 4.6 Hz, 1H); 5.50–5.63 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 23.3, 23.9, 25.9, 28.6, 29.0, 30.6, 37.1, 39.3, 78.1, 123.8, 124.0; MS (EI) *m*/*z* (%) 166 (M^+, 2), 148 ($[M-H_2O]^+$, 57), 92 (100).

4.1.2. 1,2,3,4,4a,5,8-Heptahydro-6,8a-dimethylnaphthalen-1-ol (±)-5. Obtained from octalone **2**, as a colorless oil, in 92% yield, using the same procedure described for (±)-**4**. This product was used without further purification. IR (film): 3388 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.01 (s, 3H), 1.2–1.7 (m, 10H); 1.64 (bs, 3H); 2.13–2.33 (m, 2H), 3.32 (dd, *J* 11.1 and 4.4 Hz, 1H), 5.27 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 23.4, 23.7, 24.0, 26.1, 28.9, 30.6, 34.0, 36.5, 39.9, 78.2, 117.7, 130.7; MS (EI) *m*/*z* (%) 180 (M^+, 5), 162 ($[M-H_2O]^+$, 55), 105 (100).

4.1.3. 1,2,3,4,4a,5,8-Heptahydro-6,7,8a-trimethylnaphthalen-1-ol (±)-6. Obtained from octalone **3**, as a colorless oil, in 93% yield, using the same procedure described for (±)-**4**. NMR data are in agreement with those of the literature.[3]

4.1.4. Typical procedure[15] for the acetylation of the alcohols. Preparation of 1,2,3,4,4a,5,8-heptahydro-8a-methylnaphthalen-1-yl acetate (±)-7. To a solution of alcohol (±)-**4** (0.332 g, 2.02 mmol) and DMAP (0.049 g, 0.404 mmol) in Et_3N (2 mL), Ac_2O (0.57 mL, 0.62 g, 6.02 mmol) was added. The resulting solution was stirred for 30 min under an N_2 atmosphere at room temperature, when MeOH (2 mL) was added. The solvent was concentrated in vacuum and the residue partitioned between H_2O and AcOEt. The aqueous phase was extracted with AcOEt and the combined organic layers were successively washed with H_2O and brine and then dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude product was purified by column flash chromatography on silica (200–400 mesh) using AcOEt/hexanes (15%) to give (±)-**7** (0.353 g, 85%) as a colorless oil. IR (film): 1737 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 0.93 (s, 3H), 1.24–1.82 (m, 9H), 2.04 (s, 3H), 2.27–2.39 (m, 2H), 4.56 (dd, *J* 10.5 and 4.8 Hz, 1H), 5.50–5.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 21.2, 23.3, 23.7, 26.8, 27.1, 28.4, 28.9, 36.1, 39.3, 80.1, 123.6, 123.9, 171.0; MS (EI) *m*/*z* (%) 208 (M^+, 0.04), 148 ($[M-AcOH]^+$, 71), 43 (100).

Acetates (±)-**8** [IR (film): 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.89 (s, 3H), 1.2–1.8 (m, 12H), 2.04 (s, 3H), 2.25–2.32 (m, 2H), 4.58 (dd, *J* 11.2 and 4.6 Hz, 1H), 5.26–5.27 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 21.2, 23.3, 23.6, 23.7, 26.9, 27.0, 28.6, 33.9, 35.8, 39.9, 80.1, 117.5, 130.5, 170.9; MS (EI) *m*/*z* (%) 222 (M^+, 0.6), 162 ($[M-AcOH]^+$, 73), 43 (100)] and (±)-**9** [IR (film): 1734 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$): 19.4, 19.8, 21.2, 23.0, 24.1, 27.9, 29.7, 33.2, 35.2, 37.6, 41.7, 79.7, 125.2, 125.7, 170.7; MS (EI) *m*/*z* (%) 176 ($[M-AcOH]^+$, 7), 43 (100)] were obtained as colorless oils, in 83% and 91% yields, respectively, using the same procedure described above.

4.1.5. Enzymatic reactions. *Analytical-scale* (Table 1): To a 10 mL test tube containing 600 μL of hexane (HPLC grade), 60 μL of vinyl acetate and 6 mg of Novozym was added *cis*-octalol **5** (3 μL). The reaction mixture was stirred for 48 h at 32 °C and then analyzed by CG/FID in a chiral capillary column.

Small scale (Table 2): To a 50 mL Erlenmeyer flask containing 10 mL of hexane (HPLC grade), 1 mL of vinyl acetate and 100 mg of Novozym were added *cis*-octalols **4**–**6**. The reaction mixture was stirred on a rotatory shaker (32 and 40 °C, 160 rpm) and analyzed from 20 min to 48 h by CG/FID in a chiral capillary column.

Semi-preparative scale (Table 3): To a 50 mL Erlenmeyer flask containing 20 mL of hexane (HPLC grade), 1 mL of vinyl acetate and 200 mg of Novozym were added the *cis*-octalols (**4**: 195 mg; **5**: 280 mg; **6**: 280 mg). The reaction mixture was stirred on a rotatory shaker (32 and 40 °C, 160 rpm) and analyzed at 24 h and 48 h by CG/FID in a chiral capillary column. The mixture was then filtered and the solvent evaporated. The residue was purified by silica gel column chromatography, using hexane/ethyl acetate as an eluent.

4.1.6. Control of the chemoenzymatic resolution of *cis*-octalols. The reaction progress was monitored by collecting samples of 0.1 mL from 20 min to 48 h (Tables 2 and 3). These samples were previously analyzed by CG/FID in a chiral capillary column. Alcohols **4**–**6** and acetates **7**–**9** were compared with the racemic mixtures previously analyzed. General GC conditions: Injector: 200 °C; Detector: 220 °C; Pressure: 100 kPa.

(a) Oven 100–180 °C; rate 1 °C (40 min); retention time for **4** (1*S*,4a*S*,8a*R* isomer = 25.5 min; 1*R*,4a*R*,8a*S* isomer = 26.3 min). Chiral column CHIRASIL DEX CB.
(b) Oven 100–180 °C; rate 1 °C (40 min); retention time for **5** [(1*S*,4a*S*,8a*R*)-isomer = 27.0 min; (1*R*,4a*R*,8a*S*)-isomer = 28.8 min]. Chiral column CHIRASIL DEX CB.
(c) Oven 100 °C (60 min); rate 10 °C (180 °C); retention time for **6** [(1*S*,4a*S*,8a*R*)-isomer = 64.4 min; (1*R*,4*RS*,8a*S*)-isomer = 64.8 min]. Chiral column GAMA DEX™ (Supelco).
(d) Oven 100–180 °C; rate 1 °C (40 min); retention time for **7** [(1*S*,4a*S*,8a*R*)-isomer = 20.9 min; (1*R*,4a*R*,8a*S*)-isomer = 22.8 min]. Chiral column CHIRASIL DEX CB.
(e) Oven 150 °C; rate 2 °C (30 min); retention time for **8** [(1*S*,4a*S*,8a*R*)-isomer = 23.8 min; (1*R*,4a*R*,8a*S*)-isomer = 25.1 min]. Chiral column CHIRASIL DEX CB.
(f) Oven 100 °C (60 min); rate 10 °C (180 °C); retention time for **9** [(1*S*,4a*S*,8a*R*)-isomer = 66.8 min; (1*R*,4a*R*,8a*S*)-isomer = 67.0 min]. Chiral column GAMA DEX™ (Supelco).

4.1.7. Assignment of the absolute configuration. The absolute configuration of alcohol **6** was determined by the comparison of the sign of the measured specific rotation with that of the literature.[3] The absolute configurations of alcohols **4**–**5** and acetates **7**–**9** were determined by correlation with the data of **6**. The observed stereochemical preference of the enzyme is in accordance with the rule of Kazlauskas.[13]

(a) (1*S*,4a*S*,8a*R*)-1,2,3,4,4a,5,8-heptahydro-8a-methylnaphthalen-1-ol **4**: $[\alpha]_D^{25} = +6.6$ (*c* 8.6, $CHCl_3$), ee 99%.
(b) (1*S*,4a*S*,8a*R*)-1,2,3,4,4a,5,8-heptahydro-6-8a-dimethylnaphthalen-1-ol **5**: $[\alpha]_D^{25} = -1.6$ (*c* 3.02, $CHCl_3$), ee 99%.
(c) (1*S*,4a*S*,8a*R*)-1,2,3,4,4a,5,8-heptahydro-6,7,8a-trimethylnaphthalen-1-ol **6**: $[\alpha]_D^{25} = -8.0$ (*c* 1.35, $CHCl_3$), ee 99%.
(d) (1*R*,4a*R*,8a*S*)-1,2,3,4,4a,5,8-heptahydro-8a-methylnaphthalen-1-yl acetate **7**: $[\alpha]_D^{25} = -24.0$ (*c* 3.25 $CHCl_3$), ee 99%.
(e) (1*R*,4a*R*,8a*S*)-1,2,3,4,4a,5,8-heptahydro-6,8a-dimethylnaphthalen-1-yl acetate **8**: $[\alpha]_D^{25} = -8.5$ (*c* 2.95, $CHCl_3$), ee 92%.
(f) (1*R*,4a*R*,8a*S*)-1,2,3,4,4a,5,8-heptahydro-6,7,8a-trimethylnaphthalen-1-yl acetate **9**: $[\alpha]_D^{25} = +13.5$ (*c* 2.73, $CHCl_3$), ee 99%.
(g) (1*R*,4a*R*,8a*S*)-1,2,3,4,4a,5,8-heptahydro-6,7,8a-trimethylnaphthalen-1-ol **6** after hydrolysis of **9**: $[\alpha]_D^{25} = +7.8$ (*c* 1.78, $CHCl_3$), ee 99%.

Acknowledgements

The authors express their gratitude to Novo Nordisk (Curitiba-Paraná-Brazil) for a gift of CALB (Novozym 435). We are also indebted to FAPESP, CAPES, and CNPq for their continuous financial support.

References

1. Singh, V.; Iyer, S. R.; Pal, S. *Tetrahedron* **2005**, *61*, 9197–9231.
2. Silva, L. F., Jr. *Synthesis* **2001**, 671–689.
3. Anderson, J. C.; Blake, A. J.; Graham, J. P.; Wilson, C. *Org. Biomol. Chem.* **2003**, *1*, 2877–2885.
4. Nozawa, M.; Murakami, Y.; Noda, K.; Tamatsukuri, R.; Kato, K.; Akita, H. *Chem. Pharm. Bull.* **2000**, *48*, 1176–1186.
5. Akita, H.; Nozawa, M.; Shimizu, H. *Tetrahedron: Asymmetry* **1998**, *9*, 1789–1799.
6. Chênevert, R.; Courchesne, G.; Jacques, F. *Tetrahedron: Asymmetry* **2004**, *15*, 3587–3590.
7. Toyooka, N.; Nishino, A.; Momose, T. *Tetrahedron* **1997**, *53*, 6313–6326.
8. Franssen, M. C. R.; Jongejan, H.; Kooijman, H.; Spek, A. L.; Bell, R. P. L.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron: Asymmetry* **1999**, *10*, 2729–2738.
9. Raminelli, C.; Comasseto, J. V.; Andrade, L. H.; Porto, A. L. M. *Tetrahedron: Asymmetry* **2004**, *15*, 3117–3122.
10. Raminelli, C.; da Silva, N. C.; dos Santos, A. A.; Porto, A. L. M.; Andrade, L. H.; Comasseto, J. V. *Tetrahedron* **2004**, *61*, 409–415.
11. Ferraz, H. M. C.; Vieira, T. O.; Silva, L. F., Jr. *Synthesis*, in press.
12. Nagakura, I.; Ogata, H.; Ueno, M.; Kitahara, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2995–2996.
13. Fringuelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 5056–5065.
14. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.
15. Murry, J. E. M.; Musser, J. H.; Ahmad, M. S.; Blaszczak, L. C. *J. Org. Chem.* **1975**, *40*, 1829–1832.