Tetrahedron: Asymmetry Vol. 3, No. 6, pp. 775-784, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

Lipase-mediated Resolution of 2-Cyclohexen-1-ols as Chiral Building Blocks *en route* to Eburnane Alkaloids

Giacomo CARREA,[a] Bruno DANIELI,[b] Giovanni PALMISANO,[b*] Sergio RIVA,[a*] and Marco SANTAGOSTINO[b]

[a]Istituto di Chimica degli Ormoni, C.N.R., Via Mario Bianco 9, 20131 Milano.

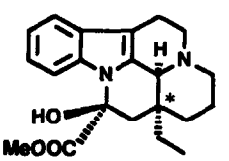
[b]Dipartimento di Chimica Organica e Industriale, Universita' degli Studi di Milano; Centro di Studio per le Sostanze Organiche Naturali del C.N.R., Via Venezian 21, 20133 Milano, Italy.

(*Received* 30 *April* 1992)

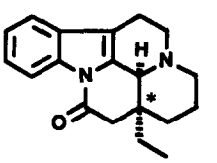
ABSTRACT. Lipase catalyzed esterification of several 2-cyclohexen-1-ols proceeds with excellent enantioselectivity leading to (*S*)-enantiomers as promising chiral building blocks *en route* to eburnane alkaloids

INTRODUCTION

The heteropentacyclic topology of the eburnane alkaloids[1] [*e.g.* (+)-vincamine **1** and (-)-eburnamonine **2**] and their pharmacological profile[2] have stimulated several synthetic studies. Any viable method for preparing **1** and **2** must take into consideration the problem of the quaternary stereogenic center (asterisked C) as well as stereochemical control of the adjacent methine. Previous syntheses of homochiral eburnanes have solved this problem either by using suitable chiral auxiliaries or by classical chemical resolution.[3]



1

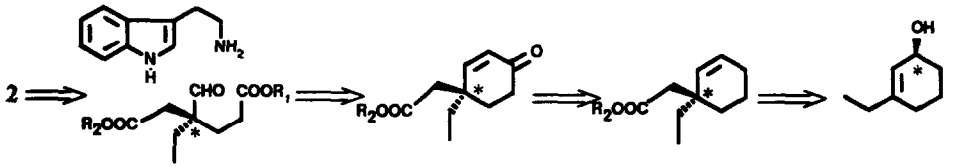


2

Our interest in this area was stimulated by the prospect of designing an enantiocontrolled approach to this class of indole alkaloids, using the strategy outlined in the retrosynthetic format in Scheme I.

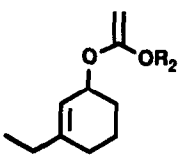
The key feature of our synthetic plan involved generation of the crucial quaternary carbon center

Scheme I

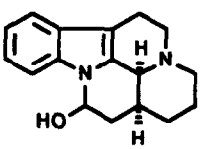


3 4 5 6

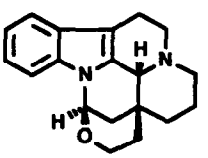
from a secondary allylic carbinol center by a [3,3]-sigmatropic process (Claisen reaction).[4] The concerted, non synchronous suprafacial nature of this process dictates the transfer of stereogenicity (*i.e.*, stereochemical information) and, using enantiomerically enriched allylic alcohol, the rearrangement yields chiral nonracemic adducts. For example, Johnson orthoester modification [$MeC(OR_2)_3$, acid catalyst][5] of the Claisen reaction on **6** would generate **5** *via* the transient cyclohexenyloxyketene acetal **7**. Applied to (*S*)-**6**, this process achieves two goals, namely installation of a quaternary stereocenter[6] with predictable configuration and simultaneous introduction of a C_2-fragment at its correct oxidation level.[7] Furthermore, the endocylic double bond in **5** is strategically located and all the required functions can be built around and through it. Accordingly, the enone **4** is the equivalent of a 1,5-dicarbonyl synthon through a simple oxidative demolition, and the emerging carbonyl functions in **3** provide a convenient handle for the introduction of the basic nitrogen of tryptamine (Pictet- Spengler reaction)



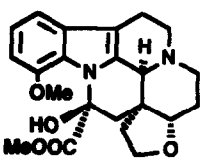
7



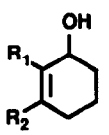
8



9



10



11 R_1,R_2:H

12 R_1:H ; R_2:$(CH_2)_2OMe$ **13** R_1:Br ; R_2:H

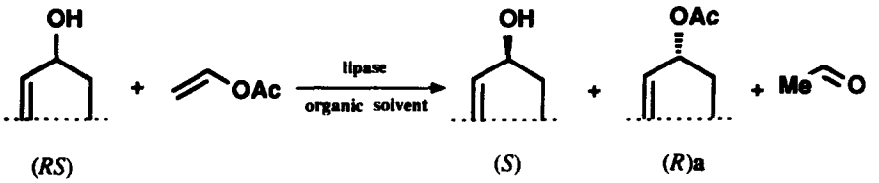
14 R_1:H ; R_2:Br **15** R_1:H ; R_2:Me

Adaptation of Scheme I to other related homochiral targets [*e.g.*, vindeburnol **8**,[8] larutensine **9**[9] and cuanzine **10**[10]] would require fixing the absolute sterochemistry at the carbinol center in (*S*)-**11**, (*R*)-**12** and (*S*)-**12**, respectively, and building up the properly functionalized aldehydo-esters through a judicious choice of protecting groups.[11]

Chiral 2-cyclohexen-1-ols are currently made either by enantioselective reduction of ketones with chiral reducing agents or by enzymatic hydrolysis of the corresponding esters. We anticipated

that these (±)-alcohols would be more conveniently resolved *via* enantioselective esterification, in which an enzyme mediates acyl transfer to the 12 enantiomers of carbinols at different rates (Scheme II). While this manuscript was in preparation, a related report by Mori and Puapoomchareon[12] appeared which has prompted us to communicate our preliminary findings in detail. Thus, we describe in this report the lipase-catalysed transesterification of a variety of substituted (±)-2-cyclohexen-1-ols [*i.e.* **6**, **11-15**], used as initial targets for subsequent evaluation of the potential of our synthetic plan (Scheme I).[13]

Scheme II



RESULTS AND DISCUSSION

We began our investigation with the simplest compound of the series, 2-cyclohexen-1-ol (±)-**11**.[14] However, our attempts to obtain a kinetic resolution of this racemic carbinol, in which we screened more than 20 lipases and proteases, were unsuccessful, probably due to the conformational mobility of this molecule and to the lack of substituents on the cyclohexene ring. Therefore, we turned to 2-bromo-2-cyclohexen-1-ol (±)-**13**,[15] with the hope that the introduction of the halogen on the molecule would result in different anchorage of the two enantiomers at the active site of the enzymes, making it possible to discriminate them. In our preliminary screening, in order to have irreversible esterification,[16] vinyl acetate was both the acylating agent and solvent. As indicated in Table 1, lipase from *Mucor miehei* showed the highest enantioselectivity (E=79)[17] and was used for further investigations. In order to optimize the reaction conditions, analytical-scale acylations were performed in different solvents.

We found[18], as have others[19] that the nature of organic solvents can influence the enantioselectivity of an enzyme toward a given substrate. In this specific case, vinyl acetate was the solvent which gave the highest enantioselecitvity with the fastest reaction rate (Table 2).[20] The preparative scale esterification of (+)-**13** was therefore performed in it and, at 53% conversion, residual (S)-**13** was obtained with 98% e.e. (For details see Experimental Section).

We next turned to the isomeric (±)-3-bromo-cyclohexen-1-ol **14**. This compound has been recently used by Paquette *et al.* to gain enantioselective access to the taxane ring system.[21] The usual preliminary screening indicated that lipase P was the enzyme of choice (Table 3). In a preparative scale resolution of (±)-**14**, after 3 hr of stirring at 45°C, 55% of racemic **14** was acetylated, with the isolation of residual (S)-**14** being 99% e.e..

As the final step of our substrate screening, we used different 3-alkyl-2-cyclohexen-1-ols (*i.e.*, **6**, **12** and **15**). The simplest term of this series 3-methyl-2-cyclohexen-1-ol (seudenol, **15**)[22] is a natural pheromone released by female Douglas-fir beetles (*Dendroctonus pseudotsugae*).[23]

Table 1. Enantioselectivity of Different Lipases with (±)-2-Bromo-2-cyclohexen-1-ol (±)-**13**[a]

Lipase	%conv[b]	e.e.[b] product	E[c]
Pseudomonas cepacia[d]	15	67.7	6
Porcine pancreatic[e]	16	93.3	34
Chromobacterium viscosum[f]	6	68.5	6
Mucor miehei[g]	15	97.0	78
Humicola lanuginosa[d]	19	94.0	40
Penicillium camemberti[d]	17	72.9	7
Candida cylindracea[e]	50	75.0	16

[a]Conditions: To 1 ml of vinyl acetate containing 10 ul of racemic **13**, 50 mg of enzyme and 50 mg of molecular sieves were added and the suspension was shaken at 250 rpm at 45°C
[b]Determined by chiral capillary GLC
[c]E values were calculated from the degree of conversion and e.e. of the product according to Chen et al.[17]
[d]Amano Pharmaceutical Co.; [e]Sigma Chemical Co.; [f]Finnsugar Biochemicals Inc.; [g]Biocatalyst.

One of the enantiomers of **15** [specifically (*S*)-**15**] has been obtained in pure form (> 99% e.e.) from the racemic alcohol in a 46% yield by selective hydrogenation of the double bond of (*R*)-**15** in the presence of BINAP-Ru(II) dicarboxylate complexes.[24] Alcohol (±)-**15** has also been acylated by Wong *et al* with *Pseudomonas* species lipase catalysis to give the (*R*)-acetate **15a** with 67% e.e..

Table 2. Effects of Organic Solvents on the Enantioselectivity of *Mucor miehei* Lipase with (±)-**13**[a]

Solvent	log P[b]	rel. rate	E[c]
dodecane	6.6	7	32
cyclohexane	3.1	13	43
dibutyl ether	2.9	27	37
toluene	2.5	27	56
t-amyl alcohol	1.4	22	29
vinyl acetate	0.3	100	78

[a]Conditions: To 1 ml of solvent containing 10 ul of racemic **13** and 80 ul (ca. 10 equiv) of vinyl acetate, 50 mg of enzyme and 50 mg of molecular sieves were added and the suspension was shaken at 250 rpm at 45°C
[b]Log P values were calculated according to Rekker, R.F.; De Kort, H.M. Eur.J.Med.Chem.Therapeut. **1979**,14,479
[c]Calculated from the degree of conversion and e.e. of the product (determined by chiral capillary GLC) according to Chen et al.[17]

To enhance the optical purity, the optically active **15a** obtained above was subjected to hydrolysis by the same enzyme, to give the final product (*R*)-**15**, in 92% e.e. at 50% conversion. Enzymatic approaches to the resolution of seudenol has also been reported by Mori (hydrolysis of the racemic acetate **15a** by PLE)[25] and by Oehlschlager (acylation by PPL in diethyl ether).[26]

Table 3. Enantioselectivity of Different Lipases with (±)-3-Bromo-2-cyclohexen-1-ol (±)-**14**[a]

Lipase[b]	E[c]	Lipase[b]	E[c]
Pseudomonas cepacia	44	*Humicola lanuginosa*	18
Porcine pancreatic	24	*Penicillium camemberti*	2
Chromobacterium viscosum	26	*Candida cylindracea*	6
Mucor miehei	15		

[a]Conditions: To 1 ml of vinyl acetate containing 10 ul of racemic **14**, 50 mg of enzyme and 50 mg of molecular sieves were added and the suspension was shaken at 250 rpm at 45°C
[b]For lipase sources see footnotes [d-g] of Table 1
[c]Ref. 17

However, both of their methods required sequential enzymatic reactions, and yielded the two pure enantiomers of **15** in 16% and 21% yield (Mori) and (*R*)-**15** in about 2% yield and 95.4% e.e. (Oehlschlager). Enantioselectivities of our lipases were significantly lower for seudenol than for the alcohols previously checked. Nevertheless, lipase from *Mucor miehei* seemed to be significantly better than PPL (Table 4).

Table 4. Enantioselectivity of Different Lipases with (±)-3-Methyl-2-cyclohexen-1-ol (seudenol) (±)-**15**[a]

Lipase[b]	E[c]	Lipase[b]	E[c]
Pseudomonas cepacia	6	*Humicola lanuginosa*	7
Porcine pancreatic	4	*Penicillium camemberti*	2
Chromobacterium viscosum	4	*Candida cylindracea*	2
Mucor miehei	11		

[a]Conditions: See footnote [a] of Table 1, using instead 10 ul of racemic **15**
[b]For lipase sources see footnotes [d-g] of Table 1
[c]Ref. 17

When the organic solvent was changed, enantioselectivity was not significantly affected, but there was a positive effect on the degree of conversion (Table 5). We chose cyclohexane because of its low boiling point and the reaction conditions were further optimized in terms of the concentrations of reagents and of enzyme. Enantiomerically pure residual (*S*)-**15** was in the crude reaction solution after 4 days (at 71% conversion) and was isolated by the usual method. Finally, the last two compounds in our series racemic **6** and **12** were studied. *Pseudomonas cepacia* lipase was the catalyst of choice for (±)-3-ethyl-2-cyclohexen-1-ol (E=69 in vinyl acetate). After 1 hr, residual (*S*)-**6** was enantiomerically pure (at 54% conversion). On the other hand, (±)-3-(2-methoxyethyl)-2-cyclohexen-1-ol **12** was conveniently resolved, again, with *Mucor miehei* lipase (E=58). Residual

(*S*)-**12** was enantiomerically pure at 55% conversion.

Table 5. Effects of Organic Solvents on the Enantioselectivity of *Mucor miehei* lipase with (±)-**15**[a]

Solvent	% conv.[b]	E[c]
THF	40	10
toluene	57	13
benzene	58	11
cyclohexane	63	11
dibutyl ether	66	14
3-pentanone	57	7
t-amyl alcohol	42	7
3-methyl-3-pentanol	41	12
$CHCl_3$	33	9

[a]Conditions: To 1 ml of organic solvent containing 10 ul of racemic **15** and 80 ul (ca. 10 equiv) of vinyl acetate, 50 mg of enzyme and 50 mg of molecular sieves were added and the suspension was shaken at 250 rpm at 45°C
[b]After 24 hr (in neat vinyl acetate the conversion after 24 hr was 59.8%)
[c]Ref.17

In conclusion, we have shown that enzymatic acylation in organic solvents is a suitable method for obtaining enantiomerically pure allylic cyclohexenols. All the lipases tested showed a preference for the (*R*)-enantiomers and, depending on the substrate, enzymes from *Mucor miehei* and *Pseudomonas cepacia* gave the most satisfactory results.[27]

EXPERIMENTAL SECTION

Materials. Lipase sources are reported in the footnotes to Table 1. 2-cyclohexen-1-ol (**11**) and 3-methyl-2-cyclohexen-1-ol (**15**) were purchased from Aldrich. 3-ethyl-2-cyclohexen-1-ol (**6**),[28] 3-(2-methoxyethyl)-2-cyclohexen-1-ol (**12**)[29] and 3-bromo-2-cyclohexen-1-ol (**14**) were prepared according to procedures in the literature. Organic solvents were dried over 3Å molecular sieves before use.

Enzyme immobilization. Lipase from *Pseudomonas cepacia* or Lipase from *Mucor miehei* (3 g) were mixed accurately with Hyflo Supercel (10 g). Then, 10 ml of 0.1M potassium phosphate buffer (pH 7) were added, the mixture was shaken vigorously, and dried by a vacuum pump (24 hr, 0.02 mbar). The water content, determined by the optimized Fischer method, was 2%.

Determination of enantiomeric excess (e.e.) and degree of conversion. Both the percentage conversions of **6**, **11-15** into the corresponding acetates and the e.e. of the ester products or the remaining substrates (or both) were determined by chiral GLC on a CP-cyclodextrin-β-2,3,6-M-19 column (50 m, 0.25 mm id, Chrompack) using H_2 as carrier gas, under the following conditions:

(±)-**6**: oven temperature from 100°C (initial time 5 min) to 135°C, with heating rate of 0.7°C/min [starting (±)-**6** was base-line resolved]

(±)-**11**: oven temperature from 60°C (initial time 20 min) to 70°C, with heating rate of

0.5°C/min [starting (±)-**11** was base-line resolved].

(±)-**12**: oven temperature 105°C for 120 min [acetate (±)-**12a** was base-line resolved]

(±)-**13**: oven temperature from 115°C (initial time 30 min) to 125°C, with heating rate of 1.0°C/min [acetate (±)-**13a** was base-line resolved]

(±)-**14**: oven temperature 105°C for 70 min [both (±)-**14** and the corresponding acetate (±)-**14a** were base-line resolved]

(±)-**15**: oven temperature 95°C for 30 min [starting (±)-**15** was base-line resolved]

*Resolution of (±)-**6** with immobilized* Pseudomonas cepacia *lipase*. Immobilized *Pseudomonas cepacia* lipase (1 g, equivalent to 230 mg of free crude lipase) was added to a solution of (±)-**6** (1 g, 7.94 mmol) in vinyl acetate (67 ml). The suspension was shaken on a plate rotating at 250 rpm, at 45°C, and the reaction progress followed by GLC. After 1 hr (approximately 54% conversion), the enzyme was filtered off and (*S*)-**6** (> 99.5 e.e.) was recovered by flash chromatography (hexane-AcOEt, 6:1).

*Resolution of (±)-**12** with immobilized* Mucor miehei *lipase*. Immobilized *Mucor miehei* lipase (1 g, equivalent to 230 mg of free crude lipase) was added to a solution of (±)-**12** (250 mg, 1.6 mmol) in vinyl acetate (15 ml). The suspension was shaken on a plate rotating at 250 rpm, at 45° C, and the reaction progress followed by GLC. After 3 days (approximately 55% conversion) the enzyme was filtered off and (*S*)-**12** (> 99.5 e.e.)[30] was recovered by flash chromatography (hexane-Et_2O, 3:1).

*Resolution of (±)-**13** with immobilized* Mucor miehei *lipase*.Immobilized *Mucor miehei* lipase (10 g, equivalent to 2.3 g of free crude lipase) was added to a solution of (±)-**13** (1.0 g, 5.65 mmol) in vinyl acetate (75 ml). The suspension was shaken on a plate rotating at 250 rpm, at 45° C, and the reaction progress was followed by GLC. After 10 days (approximately 53% conversion), the enzyme was filtered off and (*S*)-**13** (98% e.e., determined after chemical acetylation) and (*R*)-**13a** (82.6% e.e.) were recovered by flash chromatography (hexane-AcOEt, 9:1).

*Resolution of (±)-**14** with immobilized* Pseudomonas cepacia *lipase*. 330 mg of (±)-**14** were dissolved in 7 ml of vinyl acetate, immobilized lipase P (50 mg, corresponding to 12 mg of free crude lipase) were added and the suspension was shaken at 45° C for 3 hours. The degree of conversion was estimated by GLC to be 55% and the e.e. of the residual alcohol was 99%. The usual work up isolated (*S*)-**14** (99% e.e.) and (*R*)-**14a** (84.3% e.e.)

*Resolution of (±)-**15** with immobilized* Mucor miehei *lipase*. Immobilized *Mucor miehei* lipase (2 g, equivalent to 460 mg of free crude lipase) was added to a solution of (±)-**15** (4 ml, 33.7 mmol) and vinyl acetate (16.5 ml) in cyclohexane (40 ml). The suspension was shaken on a plate rotating at 250 rpm, at 45°C, and the reaction progress followed by GLC. After 4 days (approximately 71% conversion) the enzyme was filtered off and (*S*)-**15** (> 99.5 e.e.) was recovered by flash chromatography (hexane-Et_2O, 3:1).

ACKNOWLEDGMENT

This work was partially supported by C.N.R. Target Project "Biotechnology and Bioinstrumentation". We are also grateful to the C.N.R. for financial support (Progetto Finalizzato "Chimica Fine Secondo")

REFERENCES AND NOTES

1) For a review on the eburnane alkaloids see Döpke,W., 'The Eburnamine-Vincamine Alkaloids' in 'The Alkaloids', (Manske, R.H.F. and Rodrigo, R.G.A., Eds), Vol. XX, pp. 297-332, Academic Press, New York, 1981.

2) Aurrousseau,M., *Chim. Ther.* **1971**, 221; Szporny,L., Szász,K. *Arch. Exp. Pathol. Pharmacol.* **1959**, *236*, 296; Lacroix,P., Quiniou,H.J., Linee,P., Le Poller,J.B. *Arzneim. Forsch.* **1979**,*29*,1094.

3) Takano,S., Yonaga,M., Morimoto,M., Ogasawara,K. *J.Chem.Soc. Perkin Trans. I* **1985**,305; Node,M., Nagasawa,H., Fuji,K. *J.Am.Chem.Soc.* **1987**,*109*,7901 and *J.Org.Chem.* **1990**,*55*,517; Meyers,A.I., Romine,J., Robichaud,A.J. *Heterocycles* **1990**,*55*,3068; Ihara,M., Takahashi,M., Taniguchi,N., Yasui,K., Nitsuma,H., Fukumoto,H. *J.Chem.Soc. Perkin Trans I* **1991**,525.

4) Blechert,S. *Synthesis* **1989**,71 and references cited therein.

5) Johnson,S.W., Werthemann,L., Bartlett,W.R., Brocksom,J.T., Li,T., Faulkner,D.J., Petersen,M.R. *J.Am.Chem.Soc.* **1970**,*92*,741.

6) Asymmetric construction of quaternary carbon centers has been the subject of intense studies, see Martin,S.F. *Tetrahedron* **1980**,*36*,419; Lee,E., Shin,I.-J., Kim,T.-S. *J.Am.Chem.Soc.* **1990**,*112*,260.

7) Since the latent carbonyl residue is attacked to the allylic alcohol, the oxidation level and functionality can be altered by the judicious choice of appropriate carbonyl enol equivalent.

8) Husson,H.P., Imbert,T., Thal,C., Potier,P. *Bull.Soc.Chim. France* **1973**,2013; Farcili,A., Medici,T., Fourneaux,R., Barzaghi,F. **Ger. Offen. 2,807,643** (*Chem. Abstr.* **1979**,*90*,39104).

9) Awang,K., Païs,M., Sévenet,T., Schaller,H., Nasiir,A.M., Hadi,A.H.A. *Phytochemistry* **1991**,*30*,3164.

10) Palmisano,G., Danieli,B., Lesma,G., Passarella,D., Toma,L. *J.Org.Chem.* **1991**,*56*,2380 and references cited therein.

11) R_1 and R_2 represent two orthogonal protective groups for COOH functions (Barany,G., Merrifield,R.B. *J.Am.Chem.Soc.* **1977**,*99*,7363).

12) Mori,K., Puapoomchareon,P. *Liebigs Ann. Chem.* **1991**,1053.

13) To our knowledge, the only systematic investigation of biocatalysed resolution of cyclic allylic alcohols reported so far is the one by Silverton and coworkers. They used the mold *Rhizopus nigricans* for the hydrolysis of approximately 20 racemic acetates. The (*R*) enantiomers were

preferentially hydrolysised but the e.e. of the products were rather low (< 75%) except for two cases (Ito,S., Kasai,M., Ziffer,H., Silverton,J.V. *Can.J.Chem.* **1987**,*65*,574).

14) Optically pure (*R*)-(+)-2-cyclohexen-1-ol has been prepared by reduction of the corresponding ketone with $LiAlH_4$ in the presence of (*S*)-4-anilino-3-methylamino-1-butanol (at -100°C) (Sato,T., Gotoh,Y., Wakabayashi,Y., Fujisawa,T. *Tetrahedron Lett.* **1983**,*24*,4123). See also: Kawasaki,M., Suzuki,Y., Terashima,S. *Chem. Lett.* **1984**,239.

15) (*R*)-**13** has been previously obtained in 90% isolated yield and 97.5% e.e. by enantioselective reduction of the corresponding ketone with diborane in the presence of catalytic amounts of a chiral oxazaborolidine (Corey,E.J., Chen,C.P., Reichard,G.A. *Tetrahedron Lett.* **1989**,*30*,5547 and references therein).

16) Wang,J.F., Lalonde,J.J, Momongan,M., Bergbreiter,D.E., Wong,C.K. *J.Am.Chem.Soc.* **1988**,*110*,7200.

17) Chen,C.S., Fujimoto,Y., Girdaukas,G., Sih,C.J. *J.Am.Chem.Soc.* **1982**,*104*,7294.

18) Secundo,F., Riva,S., Carrea,G. *Tetrahedron: Asymmetry* **1992**,*3*,267.

19) Fitzpatrick,P.A., Klibanov,A.M. *J.Am.Chem.Soc.* **1991**,*113*,3166; Parida,S., Dordick,J.S. *J.Am.Chem.Soc.* **1991**,*113*,2253; Kitaguchi,H., Fitzpatrick,P.A., Huber,J.E., Klibanov,A.M. *J.Am.Chem.Soc.* **1989**,*111*,3084.

20) Similarly to the results obtained with other substrates and lipases (Ref. 18) no correlation was observed between enantiospecificity (E) and solvent hydrophobicity (logP).

21) (*R*)-**14** and (*S*)-**14** have been obtained in 80% yield (but only 55% e.e. by reduction of the corresponding ketone with Darvon alcohol-$LiAlH_4$ and Novrad alcohol-$LiAlH_4$ complexes, respectively (Paquette,L.A., Combrink,K.D., Elmore,S.W., Rogers,R.D. *J.Am.Chem.Soc.* **1991**,*113*,1335 and references therein).

22) Sharpless asymmetric epoxidation of **11** and **15** has been utilized to gain access to chiral nonracemic compounds (Brown,S.M., Davies,S.G., de Sousa,J.A.A. *Tetrahedron: Asymmetry* **1991**,*2*,511.

23) Libbey,L.M., Oehlschlager,A.C., Ryker,L.C. *J.Chem.Ecol.* **1989**,*9*,1383.

24) Kitamura,M., Kasahara,I., Manabe,K., Noyori,R., Takaya,H. *J.Org.Chem.* **1988**,*53*,708.

25) Mori.K., Ogoche,J.I.J. *Liebigs Ann. Chem.* **1988**,903.

26) Johnston,B.D., Morgan,D., Oehlschlager,A.C., Ramaswamy,S. *Tetrahedron: Asymmetry* **1991**,*2*,377.

27) These results were partially disclosed by S.R. at the 'Enzyme Engineering XI' held at Kailua-Kona, Hawaii, Sept 22-27, 1991.

28) Compound (±)-**6** was synthesized by reacting 3-ethoxy-2-cyclohexen-1-one with $EtMgI/Et_2O$. The resulting 3-ethyl-2-cyclohexen-1-one was reduced with $NaBH_4$/Ce(III) chloride in MeOH.

29) Compound (±)-**12** was prepared in a four-step sequence: i) $LiAlH_4$ reduction (THF) of commercially available 3-methoxyphenylacetic acid; ii) etherification (MeI/KOH/DMSO); iii) Birch reduction (Li/liq.NH_3/THF) followed by acidic work-up to give 3-(2-methoxyethyl)-2-cyclohexen-1-one; iv) $NaBH_4/CeCl_3$ reduction.