Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 3507–3514

TETRAHEDRON: *ASYMMETRY*

Resolution of 3-α-naphthoxy-1,2-propanediol using *Candida antarctica* lipase

Loreto Salazar, Jose L. Bermudez, Cesar Ramírez, Emilio F. Llama and Jose V. Sinisterra *

Dpto. Química Orgánica y Farmacéutica, Facultad de Farmacia, U.C.M. 28040 Madrid, Spain

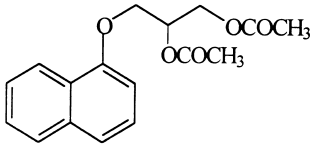
Received 12 July 1999; accepted 16 August 1999

Abstract

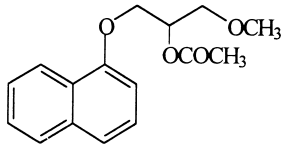
The stereochemistry of the *Candida antarctica* lipase B (CALB) catalyzed resolution of diacetate **1** or diol **4** was analyzed. The primary and secondary acetate hydrolyses were studied separately using monoacetates **2** and **3**. The enantioselectivity of CALB was found to be lower towards primary rather than secondary acetates/alcohols. The steric course of the process is discussed. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

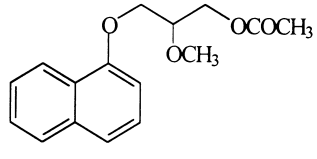
Optically active 1,2-diols are known to be synthetic building blocks for numerous natural products, pharmaceuticals and fine chemicals.[1] The synthesis of homochiral alcohols has been successfully afforded in many cases by enzymatic transformations of racemic or prochiral compounds.[2] The ability of *Candida antarctica* lipase B (CALB) in the resolution of a wide structural range of racemic primary or secondary alcohols has been reported.[3,4] Desymmetrization of prochiral 1,3-propanodiols has also been described with this enzyme.[5]



1



2



3

In a previous paper, we have reported the resolution of 1-aryloxy-3-chloro-propan-2-ols with lipase B from *C. antarctica* (CALB) in organic medium with good results.[6] Now, we have carried out the hydrolysis of diacetate of 3-naphthyloxypropane-1,2-diol **1** and the secondary and primary acetates **2** and **3** and the acylation of the diol **4**, in order to study the regioselectivity and stereoselectivity of immobilized

* Corresponding author. E-mail: jvsgago@eucmax.sim.ucm.es

PII: S0957-4166(99)00366-3

Table 1
Reaction of acylation of **4**

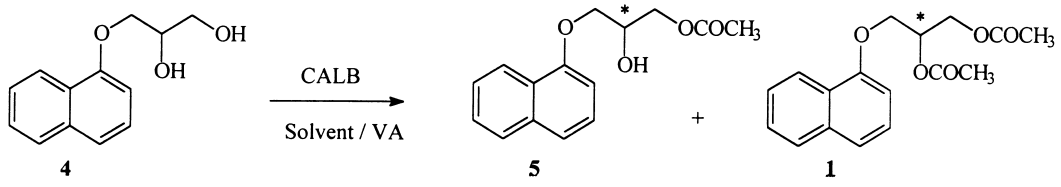
Solvent	time (h)	yield **1** (%)	ee (%)	yield **5** (%)	ee (%)	E[10]
diethyl ether	192	74	7	26	17	1.3
isooctane	72	58	64	41	17	5.4
t-BuOMe	72	39	34	61	23	2.5
toluene	72	36	44	63	20	3.1

- Reaction was carried out with 0.23 mmol of **4**, 1.2 mmol of VA, 1.5 g of molecular sieves in 10 ml of solvent and 10 mg of lipase CALB Novozym 435 ® at 4° C. Ee % were measured by HPLC using a Chiracel OD column. Absolute configuration was not determined.

lipase B on polymeric resin (Novozym 435®, Novo Nordisk). This topic has been extensively studied with lipases from *Pseudomonas cepacia*, *Chromobacterium viscosum*, and pancreatic lipase etc.,[7,8] but not as far as we know with this isoenzyme.

2. Results and discussion

In a first attempt, acylation of 3-naphthyloxy-propane-1,2-diol **4**[9] with vinyl acetate, using several solvents, was performed (Table 1, Scheme 1). The reaction was left until starting diol **4** disappeared as detected by TLC.



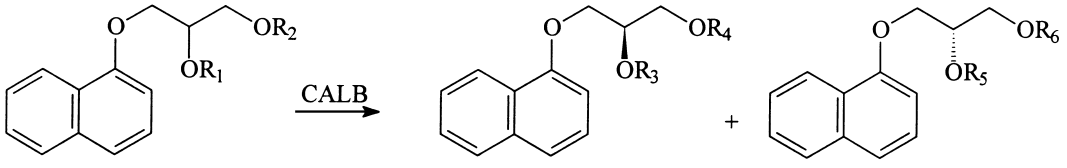
Scheme 1.

Despite the high regioselectivity afforded towards the primary alcohol,[11] low or moderate enantioselectivity was observed in the acylation to obtain the diacetate **1**. A similar behavior has been described for the lipase of *P. cepacia* and analogous substrates.[8]

Hydrophobic solvents gave better yields compared to more hydrophilic solvents such as diethyl ether. A similar behavior of CALB has been found by our research team, for several reactions in organic media.[12] Longer reaction times when the solvent was diethyl ether (192 h) were necessary to achieve the total conversion of **4**, compared to when it was isooctane (72 h). The low ee (7%) in diethyl ether could be due to a chemical migration of the acyl group from the primary to the secondary alcohol (compound **6**), that is acylated to give diacetate **1**, being more important in this solvent than in the others.

After that, we focused our interest towards the resolution via hydrolysis of the corresponding diacetate **1**. The different regioselectivity and stereoselectivity of lipases for the resolution of 1,2-diols via acylation or hydrolysis has been previously reported.[13] Generally, very high regioselectivity towards the primary hydroxyl group but usually low enantioselectivity has been observed for the lipase-catalyzed acylations of 1,2-diols, whereas hydrolysis of 1,2-diol diacetates with the same enzyme proceeded with moderate regioselectivity but higher enantioselectivity.

In order to study separately the hydrolytic processes of primary and secondary acetates, we synthesized the analogous compounds of **1**, **2** and **3**, whose primary and secondary acetates have been substituted by a methoxy function (Scheme 2).



2 $R_1 = R_5 = Ac$; $R_2 = R_6 = CH_3$
3 $R_1 = R_5 = CH_3$; $R_2 = R_6 = Ac$

7 $R_3 = H$; $R_4 = CH_3$
8 $R_3 = CH_3$; $R_4 = H$

Scheme 2.

Higher enantioselective hydrolysis of secondary acetate **2** was expected compared to primary acetate **3** (Table 2). The *R* enantiomer is preferred in agreement with the empirical rule described for enantiopreference of lipases in hydrolysis of secondary alcohols.[15,16] Lower enantioselectivity was found in the hydrolysis of primary acetate **3**. These results agree with the rule reported by Weissfloch et al.[17] that predicted the opposite enantiopreference of lipases in the hydrolysis of the primary and secondary alcohols. This rule was useful for monoacetates **2** and **3**. However, Weissfloch et al. postulated the inapplicability of this rule for substrates bearing an oxygen atom attached to the stereocenter.

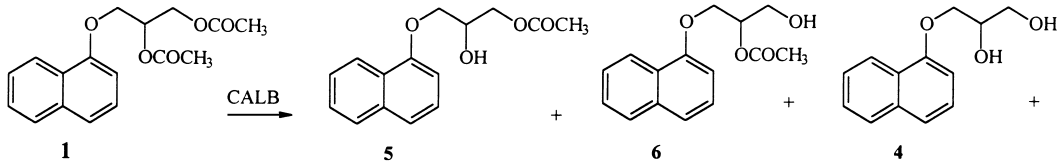
Then, hydrolysis of diacetate **1** was carried out for 3 h and 72 h to compare these results with those obtained in the hydrolysis of compounds **2** and **3** (Scheme 3, Table 3).

Compounds **4** and **6** were obtained in high enantiomeric excess in both reactions; therefore, overall enantioselectivity is moderate at 3 h and good at 72 h. Only a small yield of monoacetate **5** was obtained at 3 and 72 h, whose enantiomeric excess decreased with longer reaction times. This could be attributed to the different enantiopreference in the hydrolysis of primary acetate of diacetate **1** (enantiomer *R*) than in the monoacetate **5** (enantiomer *S*). A similar behavior has been reported by Egri et al.[13] in the

Table 2
Reaction of hydrolysis of **2** and **3**

nº	Comp.	time (h)	ester (%) **2** and **3**	$[\alpha]_D^{25}$ (*c*, 0.5-1) * (Cl_2CH_2) # (EtOH)	ee (%)	config.	alcohol (%) **7** and **8**	$[\alpha]_D^{25}$ (*c*, 0.5-1) * (Cl_2CH_2) # (EtOH)	ee (%)	config.	E
1	**2**	72	38	* - 19.4 # - 14.4	90	S	47	* + 2.5 # + 5.2	82	R[a]	30.8
2	**3**	3	49	* + 5.8 # + 5.5	38	R[b]	42	* - 8.7 # + 0.7	45	R[b]	3.8

a) Absolute configuration was assigned by comparison of the sign of the specific rotation reported for the compound (*R*)-3-methoxy-1-phenoxy-2-propanol $[\alpha]_D^{20} = +2.6$ (*c* 0.76 EtOH) 90.1 % ee[14]. b) We assigned R to the configuration of alcohol and remaining acetate tentatively, because of the sign of the specific rotations.



1 **5** **6** **4**

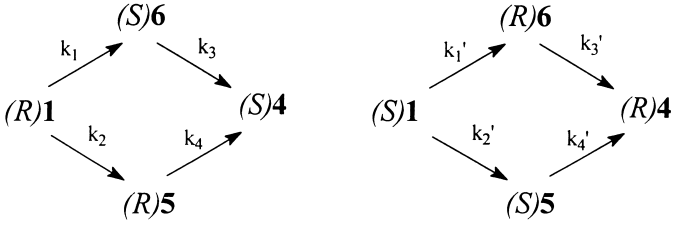
Scheme 3.

Table 3
Reaction of hydrolysis of compound **1**

	3 h			72 h		
Comp.	Yield (%)	ee (%)	Config.*	Yield (%)	ee (%)	Config.*
1	57	9	S	5	90	S
5	3	70	S	7	46	S
6	18	75	S	40	85	S
4	12	90	R	40	90	R

*Absolute configuration was assigned by comparison of the sign of the specific rotations with that reported for compound **4**[9] after hydrolysis of compounds **1**, **5** and **6** to give the corresponding diol.

hydrolysis/acylation of several diacetates and their corresponding monoacetates, using *Pseudomonas fluorescens* lipase, the preferred enantiomer in the hydrolysis of the diacetate being the opposite to that chosen for both monoacetates. The high ee of compounds **1** and **6** at 72 h suggested that acyl migration is negligible in the hydrolytic conditions used. According to our data, we postulate a classic double step kinetic mechanism[18] in an irreversible reaction (Scheme 4), were $k_1 > k_{1'}$, $k_{2'} > k_2$, $k_{3'} > k_3$ and $k_{4'} > k_4$, with k_1, $k_{1'} > k_2$, $k_{2'}$ and k_4, $k_{4'} > k_3$, $k_{3'}$.

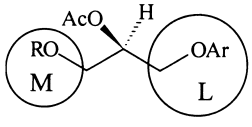


Scheme 4.

In the first step, the primary acetate hydrolysis of diacetate **1** afforded **6**, which is hydrolyzed to give major (*R*)-**4**, with the ee of **6** slightly increasing from 3 h to 72 h. On the other hand, slow hydrolysis of secondary acetate of **1** gave (*S*)-**5**>(*R*)-**5**. The faster hydrolysis of (*S*)-**5** to (*R*)-**4** is responsible for the ee of **5** decreasing with the reaction time.

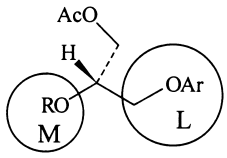
3. Conclusion

The hydrolysis of acetate **2** afforded the (*R*)-alcohol. Also, the hydrolysis of diacetate **1** afforded a mixture of monoacetate (*S*)-**6** and diol (*R*)-**4** as major products. These results are in agreement with the rule reported by Kazlauskas et al.[15] (Fig. 1), to predict the more reactive enantiomer of secondary alcohols.



R = H, CH_3, Ac

Figure 1.



R = H, CH_3

Figure 2.

On the other hand, the hydrolysis of the primary acetate of diacetate **1** is biased towards the (*R*)-enantiomer with low enantioselectivity, whereas the hydrolysis of the secondary acetate is more enantioselective, with the (*S*)-enantiomer being preferentially hydrolyzed. This fact does not agree with the rule reported by Weissfloch et al.,[17] that predicts the enantiopreference of lipases towards primary acetates with moderate or high ee (Fig. 2). However, that rule could be applied to the hydrolysis of primary monoacetate **3** (R=CH_3) and to the monoacetate **5** (R=H). The acyl group present on the oxygen of the stereogenic center seems to be the one responsible for the different behavior in this enzymatic resolution.

4. Experimental

The ^{1}H (250 MHz) and ^{13}C (63 MHz) NMR spectra were measured on a Bruker AC-250 in $CDCl_3$ solution, using TMS as internal reference. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Flash chromatography was performed with SDS silica gel 60 (0.063–0.040), and TLC using SDS silica gel 60 F254 aluminum sheets. Enantiomeric excesses (%) were determined by HPLC using a Waters 1590 system with UV–vis detector, on a Chiracel OD column. GC was performed on a Shimadzu GC-14A using an SPB™-1 column.

*4.1. Synthesis of 3-methoxy-1-(α-naphthyloxy)-2-propyl acetate **2***

Glycidyl-α-naphthyl-ether[19] (4.0 g, 20 mmol) was refluxed for 1 h in a solution of NaOMe in MeOH (1.45 g, 63 mmol of Na in 40 mL of MeOH). The solvent was evaporated, the residue disolved wih CH_2Cl_2 and acidified with concentrated HCl. The organic phase was washed with H_2O, dried with Na_2SO_4 and concentrated. Purification of the crude compound by chromatography on a column of SiO_2 with ethyl acetate–CH_2Cl_2 (1:1) as eluent afforded 2.6 g (11 mmol, 56% yield) of 3-methoxy-1-(α-naphthyloxy)-propan-2-ol. ^{1}H NMR (δ ppm): 8.29–6.82 (m, 7H, Ar); 4.33 (q, 1H, CH); 4.21 (d, 2H, C*H*$_2$-OAr); 3.69 (m, 2H, C*H*$_2$OMe); 3.45 (s, 3H, -OMe); 2.88 (d, 1H, OH). ^{13}C NMR (δ ppm): 154.1 (C_1); 134.4 (C_{10}); 127.5 (C_5); 126.4 (C_6); 125.8 (C_3); 125.4 (C_9); 125.2 (C_7); 121.7 (C_8); 120.6 (C_4); 104.9 (C_2); 73.7 (*C*H_2-OAr); 69.0 (CH); 68.9 (*C*H_2-OMe); 59.2 (CH_3-O).

Compound **7** (1 g, 4.3 mmol) was stirred at room temperature with acetic anhydride (6.3 g, 61 mmol) and dry pyridine (5 mL) for 4 h. The mixture was evaporated at reduced pressure, CH_2Cl_2 was added and the organic solution was washed with H_2O. The organic phase then was dried and evaporated. The residue was purified by chromatography on a column of SiO_2 with Cl_2CH_2 as eluent, yielding 0.84 g (3 mmol, 71%) of **2**. ^{1}H NMR (δ ppm): 8.22–6.79 (m, 7H, Ar); 5.50 (q, 1H, CH); 4.29 (m, 2H, C*H*$_2$-OAr); 3.75 (m, 2H, C*H*$_2$-OMe); 3.40 (s, 3H, -OMe); 2.12 (s, 3H, CH_3-CO). ^{13}C NMR (δ ppm): 171.0 (CO); 154.6 (C_1); 134.9 (C_{10}); 127.9 (C_5); 126.9 (C_6); 126.2 (C_9); 125.9 (C_3); 125.7 (C_7); 122.3 (C_8); 121.1 (C_4); 105.2 (C_2); 71.6 (*C*H_2-OAr); 71.3 (CH); 67.0 (*C*H_2-OMe); 59.8 (CH_3O); 21.6 (*C*H_3-CO).

4.2. Synthesis of 2-methoxy-3-(α-naphthyloxy)-1-propyl acetate **3**

A solution of 1-chloro-3-(α-naphthyloxy)-propan-2-ol[19] (0.95 g, 4 mmol) in 20 mL of dry CH_2Cl_2 was stirred under a nitrogen atmosphere and methoxy tetrafluoroborate (0.71 g, 4.8 mmol) was added. The mixture was stirred at room temperature in an inert atmosphere for 4 days. The reaction was then quenched with ice, the organic phase was washed with a solution of $NaHCO_3$, and after that washed with H_2O, dried and concentrated. The residue was purified by chromatography on a column of SiO_2 with hexane:CH_2Cl_2 (1:1) as eluent, yielding 0.44 g (1.76 mmol, 44%) of 3-chloro-2-methoxy-1-(α-naphthyloxy)-propane. ^{1}H NMR (δ ppm): 8.23–6.81 (m, 7H, Ar); 4.28 (d, 2H, C*H*$_2$-OAr); 3.95 (m, 1H, CH); 3.84 (m, 2H, C*H*$_2$-Cl); 3.59 (s, 3H, -OMe). ^{13}C NMR (δ ppm): 154.2 (C_1); 134.4 (C_{10}); 127.4 (C_5); 126.4 (C_6); 125.7 (C_3); 125.4 (C_9); 125.3 (C_7); 121.7 (C_8); 120.7 (C_4); 104.8 (C_2); 79.0 (CH); 67.0 (*C*H_2OAr); 58.3 (CH_3O); 43.3 (CH_2-Cl).

A mixture of 3-chloro-2-methoxy-1-(α-naphthyloxy)-propane (0.44 g, 1.75 mmol), 10 mL of dry DMF and potassium acetate (0.86 g, 8.7 mmol) was stirred for 24 h at 100°C. After that time, toluene was added and organic phase was washed with a saturated solution of NaCl, dried with Na_2SO_4 and concentrated. The residue was purified by chromatography on a column of SiO_2 with hexane:CH_2Cl_2 (1:2) as eluent, yielding 0.36 g (1.31 mmol, 75%) of **3**. ^{1}H NMR (δ ppm): 8.26–6.80 (m, 7H, Ar); 4.40 (m, 2H, C*H*$_2$-OAc); 4.24 (m, 2H, C*H*$_2$-OAr); 3.95 (m, 1H, CH); 3.59 (s, 3H, -OMe); 2.11 (s, 3H, CH_3-CO). ^{13}C NMR (δ ppm): 170.9 (CO); 154.2 (C_1); 134.4 (C_{10}); 127.4 (C_5); 126.5 (C_6); 125.7 (C_3); 125.5 (C_9); 125.3 (C_7); 121.9 (C_8); 120.8 (C_4); 104.7 (C_2); 77.4 (CH); 66.9 (*C*H_2-OAr); 63.3 (*C*H_2-OAc); 58.4 (CH_3O); 20.8 (*C*H_3-CO).

4.3. Synthesis of 2-methoxy-3-(α-naphthyloxy)-propan-1-ol **8**

A mixture of **3** (0.43 g, 1.57 mmol) and K_2CO_3 (1.1 g, 7.9 mmol) in 25 mL of MeOH was stirred overnight at room temperature. The solvent was evaporated and CH_2Cl_2 was added to the residue, the organic solution was washed with H_2O, dried with Na_2SO_4 and concentrated, yielding 0.32 g (1.38 mmol, 88%) of 2-methoxy-3-(1-naphthyloxy)-propan-1-ol. ^{1}H NMR (δ ppm): 8.25–6.81 (m, 7H, Ar); 4.25 (m, 2H, C*H*$_2$-OAr); 3.97–3.84 (m, 3H, CH and C*H*$_2$-OH); 3.62 (s, 3H, -OMe); 2.04 (broad s, 1H, OH). ^{13}C NMR (δ ppm): 154.2 (C_1); 134.4 (C_{10}); 127.5 (C_5); 126.4 (C_6); 125.7 (C_3); 125.5 (C_9); 125.3 (C_7); 121.8 (C_8); 120.6 (C_4); 104.6 (C_2); 79.9 (CH); 67.1 (*C*H_2-OAr); 62.3 (*C*H_2-OH); 58.4 (CH_3-O).

4.4. General procedure of enzymatic hydrolysis of acetates **1**, **2** and **3**

The reaction was carried out with 0.18 mmol of substrate (**1**, **2** or **3**), 0.9 mmol of H_2O, 10 mL of dry *t*-BuOMe and 10 mg of C.A.L. Novozym 435® and stirred at 25°C, and the resolution was followed by TLC. The mixture of compounds was separated in every case by column chromatography with SiO_2, using as eluent a mixture of Cl_2CH_2:ethyl acetate (10:1): Acetates **2** and **3**: Table 2. Diacetate **1**: Table 3 (72 h).

4.4.1. 1,2-Diacetoxy-3-(α-naphthyloxy)-propane **1**

^{1}H NMR (δ ppm): 8.20–6.77 (m, 7H, Ar); 5.55 (q, 1H, CH); 4.46 (m, 2H, C*H*$_2$-OAr); 4.28 (d, 2H, C*H*$_2$-OAc); 2.11 and 2.08 (2 s, 6H, CH_3-CO). ^{13}C NMR (δ ppm): 170.8 and 170.5 (CO); 154.1 (C_1); 134.6 (C_{10}); 127.6 (C_5); 126.7 (C_6); 125.8 (C_3); 125.6 (C_7); 125.5 (C_9); 121.9 (C_8); 121.1 (C_4); 104.9 (C_2); 69.8 (CH); 66.5 (*C*H_2-OAr); 62.8 (*C*H_2-OAc); 21.1 and 20.9 (*C*H_3-CO). $[\alpha]_D^{25}$ −10.9 (*c* 0.28,

Cl_2CH_2), 90% ee. The hydrolysis of diacetate with K_2CO_3 in MeOH gave the diol **4** (*R*) $[\alpha]_D^{25}$ −5.7 (*c* 0.7, EtOH) [lit. **4** (*R*) $[\alpha]_D^{20}$ −7.4 (*c* 1, EtOH)].[7]

*4.4.2. 2-Hydroxy-3-(α-naphthyloxy)-1-propyl acetate **5***

^{1}H NMR (δ ppm): 8.22–6.80 (m, 7H, Ar); 4.34 (m, 3H, CH and C*H*$_2$-OAr); 4.22 (m, 2H, C*H*$_2$-OAc); 2.60 (s, 1H, OH); 2.11 (s, 3H, CH_3-CO). ^{13}C NMR (δ ppm): 171.4 (CO); 153.9 (C_1); 134.4 (C_{10}); 127.6 (C_5); 126.6 (C_6); 125.7 (C_3); 125.5 (C_7); 125.4 (C_9); 121.6 (C_8); 121.0 (C_4); 105.0 (C_2); 68.9 (*C*H_2-OAr); 68.8 (CH); 65.7 (*C*H_2-OAc); 21.0 (*C*H_3-CO). $[\alpha]_D^{25}$ +3.2 (*c* 0.2, Cl_2CH_2), 46% ee. The hydrolysis of monoacetate with K_2CO_3 in MeOH gave the diol **4** (*R*) $[\alpha]_D^{25}$ −2.3 (*c* 0.4, EtOH).

*4.4.3. 1-Hydroxy-3-(α-naphthyloxy)-2-propyl acetate **6***

^{1}H NMR (δ ppm): 8.20–6.79 (m, 7H, Ar); 5.38 (m, 1H, CH); 4.31 (d, 2H, C*H*$_2$-OAr); 4.00 (d, 2H, C*H*$_2$-OH); 2.13 (s, 3H, CH_3-CO); 1.98 (broad s, 1H, OH). ^{13}C NMR (δ ppm): 170.9 (CO); 154.0 (C_1); 134.4 (C_{10}); 127.5 (C_5); 126.5 (C_6); 125.7 (C_3); 125.4 (C_7, C_9); 121.8 (C_8); 120.9 (C_4); 104.9 (C_2); 73.0 (CH); 66.5 (*C*H_2-OAr); 62.3 (*C*H_2-OH); 21.2 (*C*H_3-CO). $[\alpha]_D^{25}$ −23.3 (*c* 0.65, Cl_2CH_2), 85% ee. The hydrolysis of monoacetate with K_2CO_3 in MeOH gave the diol **4** (*S*) $[\alpha]_D^{25}$ +4.3 (*c* 1, EtOH).

*4.4.4. 3-(α-Naphthyloxy)-1,2-propanediol **4***

^{1}H NMR (δ ppm): 8.21–6.80 (m, 7H, Ar); 4.23 (m, 3H, CH and C*H*$_2$-OAr); 3.87 (m, 2H, C*H*$_2$-OH); 2.69 and 2.11 (2 broad s, 2H, OH). ^{13}C NMR (δ ppm): 154.0 (C_1); 134.5 (C_{10}); 127.6 (C_5); 126.5 (C_6); 125.8 (C_3); 125.4 (C_7 and C_9); 121.5 (C_8); 120.9 (C_4); 105.0 (C_2); 70.5 (*C*H_2-OAr); 69.2 (CH); 63.8 (*C*H_2-OH). $[\alpha]_D^{25}$ −6.8 (*c* 0.7, Cl_2CH_2); −4.9 (*c* 0.7, EtOH), 90% ee.

Acknowledgements

This work was supported by a grant from C.I.C.Y.T. (Mº de Educación y Ciencia, Spain) Project BIO 97-0514. We thank Novo Nordisk Bioindustries for a gift of *Candida antarctica* lipase.

References

1. Klunder, J. M.; Ko, S. Y.; Sharpless, K. B. *J. Org. Chem*. **1986**, *51*, 3710.
2. Dranz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis: A Comprehensive Handbook;* VCH: Weinheim, 1995.
3. (a) Ohtani, T.; Nakatsuma, H.; Kamezawa, M.; Tachibana, H.; Naoshima, Y. *J. Mol. Catal*. *B* **1998**, *4*, 53. (b) Andersson, E. M.; Larsson, K. M.; Kirk, O. *Biocatal. Biotransform*. **1998**, *16*, 181.
4. Gais, H.-J.; von der Weiden, I. *Tetrahedron: Asymmetry* **1996**, *7*, 1253.
5. (a) Saksena, A. K.; Girijavallabhan, V. M.; Lovey, R. G.; Pike, R. E.; Wang, H.; Ganguly, A. K.; Morgan, B.; Zaks, A.; Puar, M. S. *Tetrahedron Lett.* **1995**, *36*, 1787. (b) Fadel, A.; Arzel, Ph. *Tetrahedron: Asymmetry* **1997**, *8*, 283.
6. Bermudez, J. L.; Campo, C.; Salazar, L.; Llama, E. F.; Sinisterra, J. V. *Tetrahedron: Asymmetry* **1996**, *7*, 2485.
7. Theil, F. *Catalysis Today* **1994**, *22*, 517.
8. Theil, F.; Lemke, K.; Ballschuh, S.; Kunath, A.; Schick, H. *Tetrahedron: Asymmetry* **1995**, *6*, 1323.
9. Theil, F.; Weidner, J.; Ballschuh, S.; Kunath, A.; Schick, H. *J. Org. Chem*. **1994**, *59*, 388.
10. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc*. **1982**, *104*, 7294.
11. Traces of the secondary acetate **6** were observed by TLC. Chemical monoacylation of diol **4** (compound **5**) has also been afforded in a blank assay (toluene at 25°C) without enzyme.
12. Arroyo, M.; Sinisterra, J. V. *J. Org. Chem*. **1994**, *59*, 4410.
13. Egri, G.; Baitz-Gács, E.; Poppe, L. *Tetrahedron: Asymmetry* **1996**, *7*, 1437.
14. Waagen, V.; Hollingsaeter, I.; Partali, V.; Thorstad, O.; Anthonsen, T. *Tetrahedron: Asymmetry* **1993**, *4*, 2265.

15. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656.
16. (a) Xie, Z.-F.; Suemune, H.; Sakai, K. *Tetrahedron: Asymmetry* **1990**, *1*, 395. (b) Xie, Z.-F. *Tetrahedron: Asymmetry* **1991**, *2*, 733.
17. Weissfloch, A. N. E.; Kazlauskas, R. J. *J. Org. Chem*. **1995**, *60*, 6959.
18. Faber, K. In *Biotransformations in Organic Chemistry*; Springer Verlag: Berlin, 1997; 3rd ed., p. 29.
19. Bevinakatti, H. S.; Banerji, A. A. *J. Org. Chem.* **1991**, *56*, 5372.