Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: *Asymmetry* 16 (2005) 2475–2485
Tetrahedron: *Asymmetry*

Enzymatic desymmetrization of 3-arylglutaric acid anhydrides

Anna Fryszkowska,[a] Marta Komar,[a] Dominik Koszelewski[a] and Ryszard Ostaszewski[a,b,*]

[a]*Faculty of Chemistry, Warsaw University of Technology, Noakowskiego 3, 00-664 Warsaw, Poland*
[b]*Institute of Organic Chemistry PAS, Kasprzaka 44/52, 01-224 Warsaw, Poland*

Received 25 May 2005; accepted 13 June 2005

Abstract—Optically active (*R*)- and (*S*)-3-arylglutaric acid monoesters **3** were synthesized in quantitative yields and good stereoselectivities by lipase-catalyzed desymmetrization of the corresponding 3-arylglutaric anhydrides **2** with alcohols. It was observed that the stereochemical outcome of the reaction was influenced by the substituents present on the aromatic ring. The influence of the enzyme, alcohol, and solvent was systematically examined. Absolute configurations of the monoesters **3** were assigned by chemical correlation to corresponding lactones **4**.

1. Introduction

Chiral 3-arylglutaric acid derivatives are important building blocks for the synthesis of a number of biologically active compounds (Fig. 1). Two of the most important are: (−)-paroxetine hydrochloride **I**[1,2]—a selective serotonine receptor antagonist and (*R*)-Baclofen **II**—a selective $GABA_B$ receptor agonist, which is used clinically in the treatment of spasticity.[3] Three other biologically active compounds: compound **III**[4]—antiasthmatic drug; compound **IV**[5]—antagonist of receptor CCR5 involved in HIV-1 transmission to cells; compound **V**, 2-azaspiro[3.5]nonan-1-one, SCH 54016—a potent cholesterol inhibitor[6]—all possess a chiral glutaric fragment in their structures, which is essential for their activity.

The lipase catalysis is a well-established method for the preparation of enantiomerically pure building blocks for the synthesis of structurally complex molecules with controlled stereochemistry.[7–9] Chiral glutaric derivatives can be obtained via an enzymatic route as well. A commonly applied path to access the enantiomerically pure 3-arylglutaric acid monoesters is the lipase-catalyzed hydrolysis of respective prochiral glutarate diesters.[2,10–13] Optically active products were obtained in good yields with good to excellent enantioselectivities in hydrolyses catalyzed by PLE,[2,6,10–12] PPL,[13] α-chymotrypsin,[10,11] or *Candida antarctica* lipase, type B.[13] Despite its high efficiency, this methodology requires the use of aqueous reaction media, which complicates the overall process and product purification.

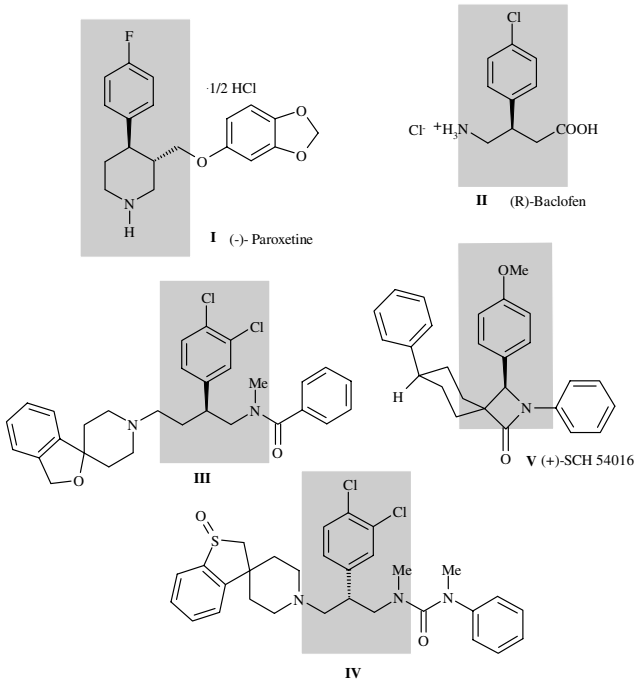
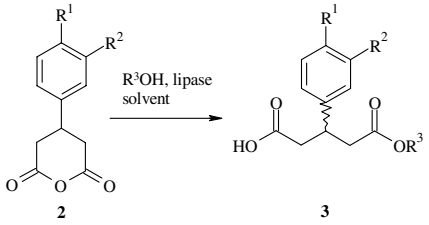


Figure 1. Biologically active compounds containing a 3-arylglutaric building block.

* Corresponding author. Tel.: +48 22 343-2120; fax: +48 22 632 66 81; e-mail: rysza@icho.edu.pl

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.06.025



Scheme 1. Enzymatic desymmetrization of 3-arylglutaric anhydrides **2**.

Enzymatic desymmetrization of the corresponding *meso*-anhydride with an alcohol is a complementary/parallel approach to the diester hydrolysis.[14] This synthetic path leads to the same monoester products, but working with aqueous media is avoided. As the reaction is conducted in organic solvents, tedious product isolation is eliminated.

In the literature, only desymmetrizations of 3-alkyl- and 3-hydroxyglutaric anhydride derivatives have been described.[15–19] Recently, we announced the lipase-catalyzed desymmetrization of the 3-arylglutaric anhydrides **2a–c** in the synthesis of chiral peptidomimetics.[20,21] Encouraged by our preliminary results and the importance of monoesters **3** for the pharmaceutical industry,[1–5,22] we herein report on the enzymatic desymmetrization of 3-arylglutaric anhydrides **2** (Scheme 1). The influence of the aromatic ring substituent, enzyme, alcohol, and solvent on the stereochemical outcome of the reaction was investigated in detail.

2. Results and discussion

The substrates, that is, anhydrides **2**, were obtained by a three-step methodology from the respective aryl aldehydes according to literature procedures (Scheme 2).[23,24] 3-Arylglutaric acids were obtained by the condensation of 2 equiv of ethyl acetylacetate with respective benzaldehydes **1**, followed by hydrolysis and decarboxylation catalyzed by potassium hydroxide.[23] These products were dehydrated to give anhydrides **2**[24] in 19–80% overall yield. Model racemic 3-arylglutaric acid monoesters **3** were obtained in reaction with the appropriate alcohol in pyridine, according to the published procedure.[24]

2.1. Preliminary screening of biocatalysts for the desymmetrization reaction of anhydride 2a

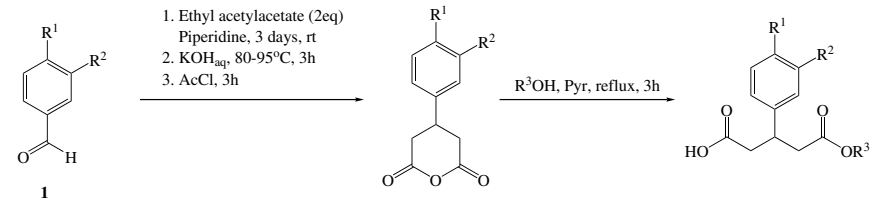
In a preliminary study, 16 commercially available enzymes were screened as biocatalysts for the desymmetrization of 3-phenylglutaric anhydride **2a** with ethanol. These reactions were conducted in *iso*-propyl ether, based on the literature data on the desymmetrization of 3-alkylglutaric anhydrides.[15–19] We tested 2 esterases [rabbit liver esterase (RLE) and porcine liver esterase (PLE)], 8 native lipases [*Candida lypolytica*, *Candida rugosa*, *Mucor javanicus*, *Rhisophus niveus*, *Pseudomonas cepacia* (Amano PS), wheat germ, porcine kidney, and porcine pancreas lipase], and 6 immobilized lipases (Amano PS-C, Amano PS-D, Chirazyme L-1, c.-f., lyso (lipases from *Ps. cepacia*) and Novozym 435, Chirazyme L-2, c.-f., C3, lyo., Chirazyme L-2, c.-f., C2, lyo. (lipases from *C. antarctica* type B)].

We found that only immobilized lipases showed high activity in the desymmetrization of **2a**. Generally, the reactions reached full conversion within 1–3 days. In the case of the native, non-immobilized enzymes, either no product formation was observed, or the reaction proceeded sluggishly.

2.2. Comparison of various solvents

In the next step, the objective was to find the most advantageous solvent for the desymmetrization reaction. Anhydride **2a** and ethanol were used as substrates, and Novozym 435 was chosen as the biocatalyst. Enantiomeric excesses of the products were determined by chiral HPLC analysis. The results are summarized in Table 1. These experiments demonstrated that the reaction proceeds efficiently in ethers (entries 1–5, Table 1). The enantioselectivities obtained in various ethers are comparable (76–78% ee). The reaction times ranged from 43 h (TBME and *iso*-propyl ether, entries 1 and 2 in Table 1) to 3–7 days for the other ethers.

Although the reaction in cyclohexane reached full conversion within 20 h, the enantioselectivity obtained was lower (62% ee, entry 6 in Table 1). In other organic solvents, for example, toluene, xylene, and chloroform, the reactions proceed sluggishly, and the monoesters **3a** were obtained in either low enantiomeric excess or with no optical activity at all. These results are consistent



Scheme 2. Synthesis of 3-arylglutaric anhydrides **2** and model racemic monoacids **3**.

Table 1. Influence of the solvents on desymmetrization of 3-phenylglutaric acid anhydride **2a** with ethanol by Novozym 435[a]

Entry	Solvent	Time	% ee of **3a**
1	*tert*-Butyl-methyl ether	43 h	76
2	*iso*-Propyl ether	43 h	78
3	*n*-Propyl ether	7 days	78
4	*n*-Butyl ether	3 days	75
5	Ethyl ether	5 days	76
6	Cyclohexane	20 h	62
7	Dioxane	6 days	26
8	Benzene	8 days	7
9	Toluene	5 weeks[b]	34
10	Xylene	5 weeks[b]	31
11	Chloroform	5 weeks[b]	0
12	Methylene chloride	5 weeks[b]	0
13	Acetone	4 weeks[b]	45
14	Acetonitrile	5 weeks[b]	31

[a] Reaction conditions: substrate **2a** (0.05 mmol, 10.0 mg) in the respective solvent (1 mL), ethanol (0.075 mmol), Novozym 435 (7.5 mg), rt.
[b] Conversion <100%.

with literature observations that the use of ether solvents is advantageous for the reaction course.[15–19] *iso*-Propyl ether was the most appropriate, not only from the viewpoint of solubility and reactivity of the substrates, but also because of the highest resulting enantiomeric excess of monoesters **3a**.

2.3. The influence of the biocatalyst on the desymmetrization reaction of anhydrides 2a–d

As it was stated above, the initial lipase screening demonstrated that the use of immobilized enzymes is beneficial for the reaction course. Therefore, the influence of several immobilized lipases on the desymmetrization of anhydrides **2a**–**d** was investigated. The results are summarized in Table 2. The majority of the tested immobilized enzymes catalyzed quantitatively the reaction of 3-arylglutaric anhydrides **2** with ethanol in *i*-Pr_2O within a few days. The reaction time and enantioselectivity were strongly dependent on the enzyme carrier.

We observed that all the lipases immobilized in Sol–Gel–AK were much less reactive than other immobilized enzymes (entries 4, 6, 9, and 10 in Table 2). In the presence of these enzymes, the reactions proceeded slowly and monoacid **3a** was obtained in low enantiomeric excess.

All immobilized lipases from *Candida antarctica* type B (CALB) showed pro-(*S*)-stereoselectivity in reaction with all anhydrides **2**, catalyzing the formation of (*S*)-monoesters **3a**–**d**. Novozym 435, Chirazyme L-2, C3, and Chirazyme L-2, C2 (Table 2, entries 1–3) catalyzed the desymmetrization reaction ranging from several hours to a few days leading to the monoester formation in good enantiomeric excess. Among lipases used in this study, Chirazyme L-2, C3 (Table 2, entry 2) appeared to catalyze the formation of monoesters (*S*)-**3** with highest enantiomeric excess. Another lipase from the *Candida* species—*Candida cylindracea* immobilized in Sol–Gel–AK showed the same enantioselectivity [pro-(*S*)] but the reaction was slow and the enantioselectivity poor.

Upon change of the enzyme for *Pseudomonas sp.* lipases (Table 2, entries 5–8), we observed a different lipase enantioselectivity. The (*R*)-**3a** was obtained by desymmetrization of anhydride **2a** with the use of this enzyme. The highest enantiomeric excess for (*R*)-**3a** (77% ee) and the shortest reaction time (19 h) were obtained for desymmetrization catalyzed by Amano PS-C. Native lipase Amano PS catalyzed the reaction as well, but the reaction time was more than 20 times longer in comparison to the reaction time using the immobilized enzyme (Table 2, entries 7 vs 8).

Surprisingly, the application of Amano PS-C lipase for hydrolysis of three other anhydrides resulted in a change of its enantioselectivity to pro-(*S*), since (*S*)-enantiomers

Table 2. Desymmetrization of 3-arylglutaric acid anhydrides **2a**–**d** by various lipases with ethanol in *iso*-propyl ether[a]

Entry	Lipase	**3a**		**3b**		**3c**		**3d**	
		Time (h/days)	% ee (Conf.)	Time (days)	% ee (Conf.)	Time (days)	% ee (Conf.)	Time (days)	% ee (Conf.)
1	Novozym 435 (CALB)	61/—	78 (*S*)	5	68 (*S*)	13	68 (*S*)	4	60 (*S*)
2	Chirazyme L-2, c.-f., C3, lyo. (CALB)	19/—	83 (*S*)	4	71 (*S*)	7	68 (*S*)	2	77 (*S*)
3	Chirazyme L-2, c.-f., C2, lyo. (CALB)	—/18	68 (*S*)	—	—	45	62 (*S*)	21	45 (*S*)
4	*Candida cylindracea* immob. in Sol–Gel–AK	—/46[b]	24 (*S*)	—	—	—	—	—	—
5	Chirazyme L-1, c.-f., lyso. (*Ps. cepacia*)	—/9	11 (*R*)	4	16 (*S*)	—	—	7	24 (*S*)
6	*Ps. cepacia* immob. on Sol–Gel–AK	—/46[b]	55 (*R*)	—	—	—	—	9	30 (*S*)
7	Amano PS (*Ps. cepacia*)	—/16	77 (*R*)	—	—	—	—	—	—
8	Amano PS-C immob. (*Ps. cepacia*)	19/—	77 (*R*)	4	16 (*S*)	8	52 (66[c]) (*S*)	2	44 (*S*)
9	Hog pancreas immob. in Sol–Gel–AK	—/18	6 (*R*)	—	—	—	—	—	—
10	*Mucor miehei* immob. in Sol–Gel–AK	—/46[b]	48 (*R*)	—	—	—	—	—	—

[a] To a solution of anhydride **2** (0.05 mmol) in *iso*-propyl ether (1 mL), ethanol (0.075 mmol) was added, followed by respective lipase: Novozym 435: 7.6 mg; Chirazyme L-2, c.-f., C3, lyo.: 5.7 mg; Chirazyme L-2, c.-f., C2, lyo.: 2.8 mg; *C. cylindracea* immob.: 5.4 mg; SP 430: 6.2 mg; Chirazyme L-1, c.-f., lyso.: 5.7 mg; *Ps. cepacia* immob. on Sol–Gel–AK: 9.1 mg; Amano PS: 6.2 mg; Amano PS-C: 6.0 mg; Hog pancreas immob.: 3.5 mg; *Mucor miehei* immob.: 5.1 mg. For anhydride **2e**, the enzyme quantities were as follows: Novozym 435: 5.3 mg; Chirazyme L-2, c.-f., C3, lyo.: 5.4 mg; Chirazyme L-2, c.-f., C2, lyo.: 5.1 mg; Chirazyme L-1, c.-f., lyso.: 5.2 mg; Amano PS-D: 2.0 mg; Amano PS-C: 7.0 mg; *Ps. cepacia* immob. on Sol–Gel–AK: 5.6 mg.
[b] Conversion <100%.
[c] After crystallization.

of monoesters **3b–d**, R^3 = Et were obtained (Table 2, entry 8). The same phenomenon was observed in case of Chirazyme L-1, however products were characterized by low ee (Table 2, entry 5).

Applying various enzymes, we obtained various stereoselectivities and the change of reaction kinetics. The way of lipase immobilization is crucial for both catalytic activity and selectivity.

2.4. Effect of substituent of the phenyl ring

As a general trend, the reaction with 3-phenylglutaric anhydride **2a** is the fastest, while the anhydrides bearing the substituents on aromatic ring **2b**, **2c**, and **2e** require longer reaction times. Also, the enantiomeric excesses of monoesters **3a** were generally the highest. The substituents on the phenyl ring influenced the enantioselectivity of the enzyme and the enantiomeric excesses were lower for compounds **3b–e**.

2.5. The influence of the nucleophile

Five different alcohols were used as nucleophiles in the desymmetrization reaction of anhydrides **2a–e** catalyzed by Novozym 435. Herein we tested methanol, ethanol, butanol, allyl, and benzyl alcohol. The results are summarized in Table 3. Novozym 435 shows pro-(*S*) selectivity for all the alcohols, regardless of the nucleophile used. Although the nucleophile does not change the enzyme selectivity, it can influence the enantiomeric excess of the products and reaction kinetics.

As a general trend, the enzymatic synthesis of monoesters proceeds most efficiently for small aliphatic alcohols: ethanol and methanol. Also, the enantiomeric excesses obtained using these alcohols were the highest. The use of longer-chain alcohols did not improve the enantioselectivity. The monoesters of allyl alcohol were obtained in lower stereoselectivities and the reaction times were much longer. The desymmetrization with butanol and benzyl alcohol was sluggish and, in most cases, the enantiomeric excess was poor.

We observed that the monoesters of the same configuration may have different signs of optical rotary power. Therefore, the sign of the rotation could not be used for assigning the configuration of the product, and transformation of the monoesters to lactones was a requirement.

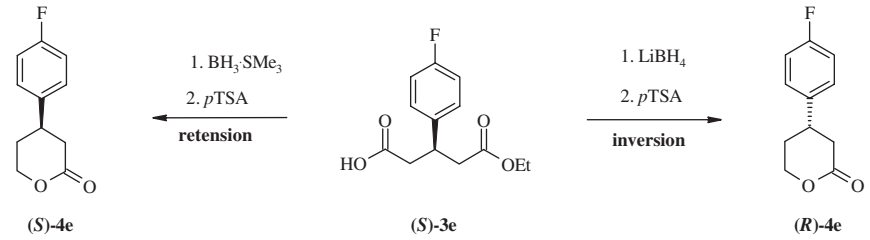
2.6. Absolute configuration assignment

The absolute configurations of the respective monoesters **3a–e** were assigned by selective reduction of the ester moiety and lactonization to lactones **4**. The sign

Table 3. Influence of the alcohol on the desymmetrization reaction (the absolute configuration assignment of the chiral monoesters **3**[a] by transformation to lactone **4**)

Ester **3**	R^3	Yield of chemical reaction (%[a])	Yield of enzymatic reaction (%) (config.)[b]	Time (days)	$[\alpha]_D$ ($CHCl_3$)	Lactone **4** yield (%) (config.)[c]	$[\alpha]_D^{20}$ ($CHCl_3$)
3a	R^3 = Me	66	99 (80[d]) (*S*)	5	−3.6 (*c* 1.10)	52 (*R*)	−5.7 (*c* 2.10)
	R^3 = Et	91	99 (72[d]) (*S*)	4	−4.0 (*c* 1.10)	34 (*R*)	−5.2 (*c* 1.40)
	R^3 = Bu	51	99 (93[d]) (*S*)	17	−2.1 (*c* 1.50)	46 (*R*)	−7.1 (*c* 2.00)
	R^3 = Bn	64	99 (61[d]) (*S*)	32	+0.6 (*c* 0.90)	27 (*R*)	−2.1 (*c* 1.00)
	R^3 = Allyl	—	99 (85[d]) (*S*)	9	−4.9 (*c* 0.88)	47 (*R*)	−4.1 (*c* 1.95)
3b	R^3 = Me	75	99 (34[d]) (*S*)	5	−9.6 (*c* 0.88)	—	—
	R^3 = Et	89	99 (61[d]) (*S*)	4	−3.8 (*c* 0.90)	36 (*R*)	−8.7 (*c* 1.38)
	R^3 = Bu	72	99 (53[d]) (*S*)	23	−2.2 (*c* 0.90)	62 (*R*)	−4.5 (*c* 1.43)
	R^3 = Bn	29	99 (47[d]) (*S*)	33	+0.4 (*c* 0.90)	16 (*R*)	−3.0 (*c* 0.70)
	R^3 = Allyl	—	99 (64[d]) (*S*)	17	−6.3 (*c* 0.40)	41 (*R*)	−6.3 (*c* 2.15)
3c	R^3 = Me	87	99 (95[d]) (*S*)	8	+7.6 (*c* 0.60, EtOH)	71 (*R*)	−7.7 (*c* 3.20)
	R^3 = Et	63	99 (93[d]) (*S*)	19	+8.3 (*c* 0.95, EtOH)	28 (*R*)	−6.7 (*c* 1.90)
	R^3 = Bu	87	28 (*S*)	25	+2.3 (*c* 0.50, EtOH)	69 (*R*)	−3.4 (*c* 2.00)
	R^3 = Bn	44	36 (*S*)	33	−0.4 (*c* 0.50, EtOH)	15 (*R*)	−6.7 (*c* 0.45)
	R^3 = Allyl	—	67 (*S*)	25	+7.3 (*c* 0.65, EtOH)	65 (*R*)	−5.4 (*c* 2.60)
3d	R^3 = Me	97	99 (80[d]) (*S*)	5	+5.0 (*c* 1.00, EtOH)	35 (*R*)	−8.1 (*c* 1.60)
	R^3 = Et	88	38 (*S*)	5	+3.8 (*c* 1.00, EtOH)	37 (*R*)	−7.1 (*c* 2.00)
	R^3 = Bu	99	16 (*S*)	5	+1.3 (*c* 0.50, EtOH)	60 (*R*)	−3.5 (*c* 1.70)
	R^3 = Bn	49	39 (*S*)	5	−1.5 (*c* 1.00, EtOH)	37 (*R*)	−1.8 (*c* 1.60)
	R^3 = Allyl	75	18 (*S*)	5	+1.7 (*c* 1.00, EtOH)	62 (*R*)	−5.0 (*c* 1.80)
3e	R^3 = Me	85	99 (90[d]) (*S*)	1	−4.3 (*c* 1.00)	49 (*R*)	−3.2 (*c* 1.90)
	R^3 = Et	91	99 (89[d]) (*S*)	1	−4.7 (*c* 1.00)	67 (*R*)	−1.7 (*c* 1.34)
	R^3 = Bu	86	99 (*S*)	25	−2.2 (*c* 0.50)	15 (*R*)	−3.1 (*c* 0.50)
	R^3 = Bn	86	99 (40[d]) (*S*)	7	−1.7 (*c* 0.80)	67 (*R*)	−1.8 (*c* 2.15)
	R^3 = Allyl	89	99 (76[d]) (*S*)	7	−2.5 (*c* 0.90)	41 (*R*)	−4.9 (*c* 1.69)

[a] Reaction conditions: anhydride **2** (2.4 mmol) in pyridine (3 mL) and absolute alcohol (14.8 mmol), reflux, 2 h.
[b] Reaction conditions for enzymatic desymmetrization: anhydride **2** (0.5 mmol), *iso*-propyl ether (10 mL), the respective absolute alcohol R^3OH (7.50 mmol), Novozym 435 (75.0 mg), rt.
[c] Reduction of ester group catalyzed by $LiBH_4$ followed by dehydration in toluene with *p*-TsOH.
[d] Yield after crystallization.



Scheme 3. The absolute configuration assignment of 3-(4-fluorophenyl)glutaric monoethyl ester **3e**.

of the specific rotation was compared to the literature data. The results are summarized in Table 3.

Selective reduction of the ester or acid group can provide a product with either an (*R*)- or (*S*)-configuration, according to Scheme 3. Reduction of the ester group of monoester lactone (*S*)-**3e** by lithium borohydride, followed by lactonization catalyzed by *p*-toluenesulfonic acid (Scheme 3) always led to lactone (*R*)-**4e**. Reduction of the acid group of ester **3e** with BMS, followed by lactonization led to formation of the lactone (*S*)-**4e** with retention of the configuration. That the two compounds are enantiomeric is evident from their CD spectra presented in Figure 2. Moreover, independent of the result of the enzymatic reaction, the lactone required for the synthesis of Paroxetine is available.

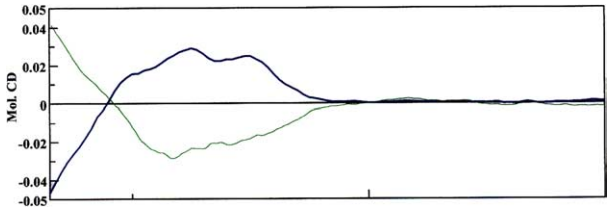


Figure 2. Circular dichroism spectra for lactones (*S*)-**4e** (green) and (*R*)-**4e** (blue).

3. Conclusions

A new enzymatic method for the synthesis of chiral 3-arylglutaric monoesters **3** by the enantioselective desymmetrization of anhydride **2** has been proposed. The use of immobilized enzymes is favorable for the reaction kinetics. Among several aprotic solvents tested, the ethers, especially *iso*-propyl ether, gave the best results. The use of various lipases for the transformation of 3-phenylglutaric anhydride **2a** led to different enantiomers of monoester **3a**, $R^3 = Et$. Monoester (*S*)-**3a**, $R^3 = Et$ was obtained in desymmetrization reaction catalyzed by Novozym 435 with 78% ee and monoester (*R*)-**3a**, $R^3 = Et$ with 77% ee in the reaction catalyzed by Amano PS-C. The highest enantiomeric excess was obtained for the desymmetrization of unsubstituted phenylglutaric anhydride.

We also transformed chiral monoesters **3** into lactones **4** with either retention or inversion of configuration.

Our approach undoubtedly provided a new methodology for the synthesis of optically active 3-arylglutaric derivatives. Non-aqueous reaction medium simplifies the work-up procedure making this process attractive for industrial purposes. Therefore these results can be attractive alternative in the synthesis of important compounds with biological activity, such as Paroxetine **I** or Baclofen **II**.

4. Experimental

4.1. General

NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard using a 200 MHz Varian Gemini 200 spectrometer. Chemical shifts are reported in parts per million and coupling constants (*J*) given in hertz (Hz). MS spectra were recorded on an API-365 (SCIEX) apparatus. IR spectra were recorded in $CHCl_3$ on a Perkin–Elmer FT-IR Spectrum 2000 apparatus. Optical rotations were measured in 1-dm cell of 1 mL capacity using Jasco DIP-360 polarimeter operating at 589 nm. CD spectra were measured using a JASCO J-715 spectropolarimeter in 1-cm and 1-mm cells in acetonitrile at the concentrations of approximately 2×10^{-4} M. HPLC analyses were performed on a Chiracel OD-H column (4.6 mm $\phi \times 250$ mm, from Diacel Chemical Ind., Ltd.) equipped with a pre-column (4 mm $\phi \times 10$ mm, 5 μ) using LC-6A Shimadzu apparatus with UV SPD-6A detector and Chromatopac C-R6A analyzer. Elemental analyses were performed on CHN Perkin–Elmer 240 apparatus. Melting points are uncorrected. All reactions were monitored by TLC on Merck silica gel plates 60 F_{254}. Column chromatography was performed on Merck silica gel 60/230–400 mesh.

Lipases Amano PS-D, Amano PS-C immobilized, and Amano PS-D were purchased from Amano. Lipases from *Candida lipolytica*, *C. rugosa*, *C. cylindracea* immobilized in Sol–Gel–AK, *Mucor javanicus*, *M. miehei* immobilized in Sol–Gel–AK, porcine pancreas lipase immobilized in Sol–Gel–AK, *Ps. cepacia*, *Ps. cepacia* immobilized in Sol–Gel–AK, and *Rhisopus niveus*, *C. cylindracea* were purchased from Fluka. Lipases from porcine pancreas, wheat germ, acylase from porcine kidney, and esterases from porcine liver and from rabbit liver were purchased from Sigma. Chirazyme L-2, c.-f., C3, lyo. (*C. antarctica* lipase type B), and Chirazyme L-2, c.-f., C2, lyo. (*C. antarctica* lipase type B), Chirazyme L-1, c.-f., lyso. (*Ps. cepacia* lipase) were purchased from Roche. Novozym 435 was purchased from Novo Nordisk.

All the chemicals were obtained from common chemical sources. The solvents were of analytical grade. Absolute THF was obtained by drying over KOH, followed by distillation from sodium benzophenone ketyl.

4.2. General procedure for the synthesis of 3-arylglutaric acid anhydrides 2

4.2.1. 3-Phenylglutaric acid anhydride 2a. Anhydride **2a** was obtained according to literature procedures[23,24] in 40% yield as white crystals (EtOAc/hexane): mp 104–105 °C (lit. 104–105[25]); ^{1}H NMR δ 2.86 (dd, $J = 11.3$ Hz, $J = 17.2$ Hz, 2H), 3.08 (dd, $J = 4.5$ Hz, $J = 17.2$ Hz, 2H), 3.30–3.50 (m, 1H), 6.90–7.40 (m, 5H); ^{13}C NMR δ 33.5, 37.8, 126.2, 127.6, 128.8, 139.0, 165.9.

4.2.2. 3-(4-Chlorophenyl)-glutaric acid anhydride 2b. Anhydride **2b** was prepared in 80% overall yield as white crystals (EtOAc/hexane): mp 126 °C (lit. 131–133[26]), $R_f = 0.36$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^{1}H NMR δ 2.82 (dd, $J = 11.4$ Hz, $J = 17.2$ Hz, 2H), 3.08 (dd, $J = 4.5$ Hz, $J = 17.2$ Hz, 2H), 3.34–3.50 (m, 1H), 6.91 (d, $J = 8.4$ Hz, 2H), 7.12 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR δ 35.5, 37.0, 127.6, 129.2, 134.0, 137.5, 165.5. Anal. Calcd for $C_{11}H_9ClO_3$: C, 58.81; H, 4.04. Found: C, 58.19; H, 4.05.

4.2.3. 3-(4-Methoxyphenyl)-glutaric acid anhydride 2c. Anhydride **2c** was prepared in 19% overall yield as white crystals (EtOAc/hexane): mp 155–156 °C (lit. 155–157[27]), $R_f = 0.60$ (hexane/EtOAc, 6:4); ^{1}H NMR δ 2.82 (dd, $J = 11.2$ Hz, $J = 17.0$ Hz, 2H), 3.08 (dd, $J = 4.5$ Hz, $J = 17.0$ Hz, 2H), 3.31–3.44 (m, 1H), 3.81 (s, 1H), 6.91 (d, $J = 8.4$ Hz, 2H), 7.12 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR δ 33.3, 37.3, 55.3, 114.7, 127.3, 131.0, 159.1, 166.0. Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.90; H, 5.44.

4.2.4. 3-(3,4-Dichlorophenyl)-glutaric acid anhydride 2d. Anhydride **2d** was prepared in 39% overall yield as white crystals (EtOAc/hexane): mp 132–135 °C (lit. 198[28]), $R_f = 0.74$ (hexane/EtOAc, 6:4); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.79–2.94 (dd, $J = 11.8$ Hz, $J = 17.4$ Hz, 2H), 3.10 (dd, $J = 4.5$ Hz, $J = 17.4$ Hz, 2H), 3.35–3.60 (m, 1H), 7.10 (dd, $J = 2.1$ Hz, $J = 8.2$ Hz, 1H), 7.35 (d, $J = 2.1$ Hz, 1H), 7.52 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.3, 35.5, 125.6, 127.9, 130.0, 130.4, 121.7, 139.5, 165.2. Anal. Calcd for $C_{11}H_8Cl_2O_3$: C, 50.99; H, 3.11. Found: C, 50.70; H, 3.19.

4.2.5. 3-(4-Fluorophenyl)-glutaric acid anhydride 2e. Anhydride **2e** was prepared in 28% overall yield as white crystals (EtOAc/hexane): mp 98 °C (lit. 98.5–99[1]); $R_f = 0.60$ (hexane/EtOAc, 6:4); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.80–2.92 (dd, $J = 11.2$ Hz, $J = 17.0$ Hz, 2H), 3.14 (dd, $J = 4.5$, $J = 17.4$ Hz, 2H), 3.37 (m, 1H), 7.02–7.14 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 37.0, 40.1, 114.6 (d, $J = 21.3$ Hz), 128.5 (d, $J = 8.0$ Hz), 138.3 (d, $J = 2.9$ Hz), 160.9 (d, $J = 243.9$ Hz), 166.0. Anal. Calcd for $C_{11}H_9O_3F$: C, 63.46; H, 4.36. Found: C, 62.09; H, 4.46.

4.3. General procedure for the chemical synthesis of 3-arylglutaric acid monoesters 3

Racemic monoesters **3** were synthesized by refluxing the corresponding anhydride and alcohol in pyridine, as described previously by Burger and Hoffstetter,[24] and then recrystallized from ethyl ether/hexane. Yields and melting points are summarized in Table 3. The spectroscopic data and analyses are described for the respective chiral monoesters **3**.

4.4. Enzymatic desymmetrization of 3-arylglutaric anhydrides

4.4.1. General procedure for the synthesis of chiral monoesters of 3-arylglutaric acids 3 with Novozym 435 in *iso*-propyl ether. To a solution of anhydride **2** (0.50 mmol) dissolved in *iso*-propyl ether (10 mL), lipase (75.0 mg), and absolute ethanol (0.80 mmol) were added. The reaction was carried out at room temperature and its progress monitored with TLC ($CHCl_3$/MeOH/HCOOH, 100:2:0.05, v:v:v). The enzyme was filtered off and residue concentrated in vacuo to give monoester **3** as a colorless oil. The product was recrystallized from Et_2O/hexane (or EtOAc/hexane).

4.4.2. (*S*)-3-Phenylglutaric acid monomethyl ester (*S*)-3a, R^3 = Me. The reaction reached its full conversion after 5 days to give (*S*)-**3a**, R^3 = Me as a colorless oil. After crystallization from Et_2O/hexane, the ester was obtained in 80% yield as white crystals: mp 54–55 °C; $[\alpha]_D^{20} = -3.6$ (*c* 1.10, $CHCl_3$); ^{1}H NMR δ 2.73–2.79 (m, 4H), 3.61 (s, 3H), 3.62–3.80 (m, 1H), 7.20–7.33 (m, 5H); ^{13}C NMR δ 37.9, 40.2, 40.4, 51.6, 127.0, 137.1, 138.6, 142.2, 172.0, 177.6; LSIMS ((+), NBA) (*m*/*z*): 245 ([M+Na]$^+$, 64%); 223 ([M+H]$^+$, 100%); LSIMS ((+), NBA+NaOAc) (*m*/*z*): 281 ([M+2Na]$^+$, 100%), 245 ([M+Na]$^+$, 72%). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.83; H, 6.22. The spectroscopic data are in agreement with those obtained for the monoester synthesized chemically in 66% yield as white crystals: mp 93–95 °C (lit. 93–95[25]).

4.4.3. (*S*)-3-Phenylglutaric acid monoethyl ester (*S*)-3a, R^3 = Et. The reaction reached its full conversion after 43 h to give (*S*)-**3a**, R^3 = Et as a colorless oil. After crystallization from Et_2O/hexane, the ester was obtained in 66% yield as white crystals: mp 58–59 °C (lit. 59–60[24]); $[\alpha]_D^{20} = -9.5$ (*c* 1.10, benzene) {lit. $[\alpha]_D^{25} = +9.5$ (*c* 1.1, benzene), for (*R*)-enantiomer},[29] $R_f = 0.24$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); HPLC analysis [hexane/*i*-PrOH/CH_3COOH 185:14:1; $\lambda = 226$ nm; 1.0 mL/min; t_R (*S*) = 8.26 min, t_R (*R*) = 8.95 min] 78% ee; ^{1}H NMR δ 1.85 (t, $J = 7.1$ Hz, 3H), 2.68–2.81 (m, 4H), 3.10–3.25 (m, 1H), 4.08 (q, $J = 7.1$ Hz, 2H), 7.28 (m, 5H); ^{13}C NMR δ 14.0, 38.0, 40.2, 40.7, 60.5, 127.0, 127.2, 128.6, 128.7, 142.2, 171.6, 177.5; LSIMS (+), NBA (*m*/*z*), 259 ([M+Na]$^+$, 56%), 237 ([M+H]$^+$, 100%); LSIMS (+), NBA+NaOAc (*m*/*z*), 281 ([M+2Na]$^+$, 100%), 259 ([M+Na]$^+$, 41%); IR ($CHCl_3$) ν_{max}: 3513 (OH), 1727 (CO) cm^{-1}. The spectroscopic and physical data are in agreement with those obtained for the monoester synthesized chemically in 91% yield as white crystals.

4.4.4. (*S*)-3-Phenylglutaric acid monobutyl ester (*S*)-3a, R^3 = Bu. The reaction reached its full conversion after 17 days to give (*S*)-**3a**, R^3 = Bu in 99% yield. After crystallization, white crystals were obtained in 93% yield: mp 41–43 °C (Et_2O/hexane); $[\alpha]_D^{20} = -2.1$ (*c* 1.50, $CHCl_3$); $R_f = 0.39$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^1H NMR δ 0.91 (t, $J = 7.2$ Hz, 3H), 1.30 (q, $J = 7.2$ Hz, 2H), 1.46–1.56 (m, 2H), 2.68–2.79 (m, 4H), 3.62–3.70 (m, 1H), 4.01 (t, $J = 6.5$ Hz, 2H), 7.27–7.32 (m, 5H); ^{13}C NMR δ 13.6, 19.0, 30.5, 38.0, 40.2, 40.6, 34.4, 127.0, 127.1, 127.3, 128.6, 128.7, 142.1, 171.6, 177.3. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.75; H, 7.83; ESI-MS HR (*m*/*z*): calcd for $C_{15}H_{20}NaO_4$ ($[M+Na]^+$): 287.1254; found 287.1240 (100%). The spectroscopic and physical data are in agreement with those obtained for the monoester synthesized chemically in 51% yield as white crystals.

4.4.5. (*S*)-3-Phenylglutaric acid monobenzyl ester (*S*)-3a, R^3 = Bn. The reaction reached its full conversion after 32 days to give (*S*)-**3a**, R^3 = Bn in 99% yield. After crystallization, white crystals were obtained in 61% yield; $[\alpha]_D^{20} = +0.6$ (*c* 0.90, $CHCl_3$); $R_f = 0.40$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^1H NMR δ 2.28 (m, 4H), 3.70 (m, 1H), 5.06 (s, 2H), 7.15–7.40 (m, 5H); ^{13}C NMR δ 38.0, 40.2, 40.6, 66.5, 127.0, 127.2, 128.1, 128.5, 128.6, 135.6, 142.1, 171.3, 177.4. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.39; H, 6.23. The spectroscopic data are in agreement with those obtained for the monoester synthesized chemically in 64% yield as white crystals: mp 84.5–86 °C (Et_2O/hexane).

4.4.6. (*S*)-3-Phenylglutaric acid monoallyl ester (*S*)-3a, R^3 = Allyl. The reaction reached its full conversion after 9 days to give (*S*)-**3a**, R^3 = Allyl as an oil in 99% yield. After crystallization from Et_2O/hexane, white crystals were obtained in 85% yield: mp 44–46 °C; $[\alpha]_D^{20} = -4.9$ (*c* 0.88, $CHCl_3$); $R_f = 0.36$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^1H NMR δ 2.76 (m, 3H), 3.63 (t, $J = 7.3$ Hz, 2H), 4.47 (d, $J = 5.8$ Hz, 2H), 5.13 (s, H), 5.2 (d, $J = 7.3$ Hz, 1H), 5.69–5.85 (m, H), 7.29 (m, 5H), 10.62 (br s 1H); ^{13}C NMR δ 38.8, 41.3, 66.2, 119.5, 128.3, 129.9, 130.1, 133.2, 143.7, 172.8, 179.5. Anal. Calcd for $C_{14}H_{16}O_4$: C, 66.76; H, 66.76. Found: C, 66.49; H, 6.43.

4.4.7. (*S*)-3-(4-Chlorophenyl)-glutaric acid monomethyl ester (*S*)-3b, R^3 = Me. The reaction reached its full conversion after 5 days to give (*S*)-**3b**, R^3 = Me in 99% yield as a colorless oil. After crystallization from Et_2O/hexane, the ester was obtained as white crystals in 34% yield: $[\alpha]_D^{20} = -9.6$ (*c* 0.88, $CHCl_3$) {lit. $[\alpha]_D^{20} = 4.1$ (*c* 2.60, $CHCl_3$), for (*R*)-enantiomer[10]}; $R_f = 0.40$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^1H NMR δ 2.66–2.70 (m, 4H), 3.50 (s, 3H), 3.40–3.60 (m, 1H), 7.14 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR δ 37.3, 40.1, 40.3, 51.7, 127.8, 128.2, 128.3, 128.6, 132.7, 140.5, 171.6, 177.2. Anal. Calcd for $C_{12}H_{13}ClO_4$: C, 56.15; H, 5.10. Found: C, 56.22; H, 5.11. The spectroscopic data are in agreement with those obtained for the monoester synthesized chemically in 75% yield as white crystals: mp 100–101.5 °C (Et_2O/hexane, lit. 100–101 °C[30]).

4.4.8. (*S*)-3-(4-Chlorophenyl)-glutaric acid monoethyl ester (*S*)-3b, R^3 = Et. The reaction reached its full conversion after 4 days to give (*S*)-**3b**, R^3 = Et as an oil in 99% yield. After crystallization, white crystals were obtained in 61% yield: mp 56 °C (Et_2O/hexane); $[\alpha]_D^{20} = -3.8$ (*c* 0.90, $CHCl_3$); HPLC analysis [hexane/*i*-PrOH/CH_3COOH 185:14:1; $\lambda = 226$ nm; 1.0 mL/min; t_R (*S*) = 9.0 min, t_R (*R*) = 9.8 min]; $R_f = 0.27$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^1H NMR δ 1.15 (t, $J = 7.1$ Hz, 3H), 2.69 (m, 4H), 3.60 (m, 1H), 4.03 (q, $J = 7.1$ Hz, 2H), 7.15 (d, $J = 8.6$ Hz, 2H), 7.34 (d, $J = 8.6$ Hz, 2H), 10.7 (s, 1H); ^{13}C NMR δ 14.2, 37.3, 40.1, 40.5, 30.6, 128.6, 128.7, 128.8, 132.7, 140.6, 171.2, 177.2. Anal. Calcd for $C_{13}H_{15}ClO_4$: C, 57.68; H, 5.59. Found: C, 57.59; H, 5.74. The spectroscopic data are in agreement with those obtained for the monoester synthesized chemically in 89% yield as white crystals: mp 69–70 °C (Et_2O/hexane).

4.4.9. (*S*)-3-(4-Chlorophenyl)-glutaric acid monobutyl ester [(*S*)-7b, R^3 = Bu]. The reaction reached its full conversion after 23 days to give (*S*)-**3b**, R^3 = Bu as an oil in 99% yield. After crystallization, white crystals were obtained in 53% yield: mp 60 °C (Et_2O/hexane); $[\alpha]_D^{20} = -2.2$ (*c* 0.90, $CHCl_3$); $R_f = 0.32$ (CH_3Cl/MeOH/HCOOH, 100:2:0.05; v/v/v); ^1H NMR δ 1.15 (t, $J = 7.0$ Hz, 3H), 1.10–1.35 (m, 2H), 1.35–1.60 (m, 2H), 2.68 (m, 4H), 3.50–3.70 (m, 1H), 3.67 (t, $J = 6.6$ Hz, 2H), 7.23 (d, $J = 8.6$ Hz, 2H), 7.35 (d, $J = 8.6$ Hz, 2H), 9.50–10.20 (br s 1H); ^{13}C NMR δ 13.6, 19.1, 30.6, 37.5, 40.2, 40.6, 64.6, 128.5, 128.6, 128.7, 129.0, 132.7, 141.6, 171.4, 177.2. Anal. Calcd for $C_{15}H_{19}ClO_4$: C, 60.30; H, 6.41. Found: C, 60.28; H, 6.35. The spectroscopic data are in agreement with those obtained for the monoester synthesized chemically in 72% yield as white crystals: mp 58–59.5 °C (Et_2O/hexane).

4.4.10. (*S*)-3-(4-Chlorophenyl)-glutaric acid monobenzyl ester (*S*)-3b, R^3 = Bn. The reaction reached its full conversion after 33 days to give (*S*)-**3b**, R^3 = Bn as an oil in 99% yield. After crystallization, white crystals were obtained in 47% yield: mp 126 °C (Et_2O/hexane); $[\alpha]_D^{20} = +0.4$ (*c* 0.90, $CHCl_3$). $R_f = 0.31$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^1H NMR δ 2.65–2.75 (m, 4H), 3.56–3.64 (m, 1H), 5.00 (s, 2H), 7.05–7.25 (m, 9H); ^{13}C NMR δ 37.4, 40.1, 40.5, 66.5, 128.2, 128.4, 128.6, 128.8, 132.8, 140.3, 171.0, 177.2. Anal. Calcd for $C_{18}H_{17}ClO_4$: C, 64.97; H, 5.15. Found: C, 64.92; H, 5.18. The spectroscopic and physical data are in agreement with those obtained for the monoester synthesized chemically in 29% yield as yellowish crystals.

4.4.11. (*S*)-3-(4-Chlorophenyl)-glutaric acid monoallyl ester [(*S*)-3b, R^3 = Allyl]. The reaction reached its full conversion after 17 days to give (*S*)-**3b**, R^3 = Allyl as an oil in 99% yield. After crystallization, white crystals were obtained in 64% yield: $[\alpha]_D^{20} = -6.3$ (*c* 0.40, $CHCl_3$); $R_f = 0.31$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^1H NMR (200 MHz, $CDCl_3$) δ 2.74 (m, 4H), 3.66 (m, 1H), 4.52 (d, $J = 5.8$ Hz, 2H) 5.20 (s, 1H), 5.27 (d, $J = 7.7$ Hz, 1H), 7.19 (d, $J = 8.6$ Hz, 2H), 7.31 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 37.9,

40.6, 40.9, 65.9, 119.0, 129.2, 129.3, 132.3, 133.4, 141.1, 171.5, 177.4. Anal. Calcd for $C_{14}H_{15}ClO_4$: C, 59.48; H, 5.35; Found: C, 59.45; H, 5.29.

4.4.12. (*S*)-3-(4-Methoxyphenyl)-glutaric acid monomethyl ester (*S*)-3c, R³ = Me. The reaction reached its full conversion after 5 days to give (*S*)-**3c**, $R^3 = Me$ in 99% yield as a colorless oil. After crystallization from Et_2O/hexane, the title product was obtained as white crystals in 95% yield: mp 55–57 °C; $[\alpha]_D^{20} = +7.6$ (*c* 0.60, EtOH); $R_f = 0.37$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^1H NMR δ 2.67 (m, 4H), 3.57 (s, 3H), 3.57 (m, 1H), 3.76 (s, 3H), 7.13 (d, $J = 8.4$ Hz, 2H), 7.45 (d, $J = 8.4$ Hz, 2H), 11.06 (s, 1H); ^{13}C NMR δ 37.2, 40.3, 40.6, 51.6, 55.1, 113.9, 128.1, 134.2, 157.3, 172.0, 177.5; IR ($CHCl_3$) ν_{max}: 3512 (OH), 2839 (Ar–OCH_3), 1732 (CO), 1713 (CO) cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.70; H, 6.57. The spectroscopic data are in agreement with those obtained for the monoester synthesized chemically in 87% yield as white crystals: mp 85 °C (Et_2O/hexane).

4.4.13. (*S*)-3-(4-Methoxyphenyl)-glutaric acid monoethyl ester (*S*)-3c, R³ = Et. The reaction reached its full conversion after 13 days to give (*S*)-**3c**, $R^3 = Et$ as an oil in 93% yield. After crystallization from Et_2O/hexane, white crystals were obtained in 71% yield: mp 75–77 °C (lit. 78[31]); $[\alpha]_D^{20} = -6.4$ (*c* 1.10, benzene); HPLC analysis [hexane/*i*-PrOH/CH_3COOH, 193:6:1; $\lambda = 226$ nm; 0.7 mL/min; t_R (*S*) = 33.3 min, t_R (*R*) = 36.3 min]: 68% ee; $R_f = 0.28$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^1H NMR δ 1.20 (t, $J = 7.2$ Hz, 3H), 2.74 (m, 4H), 3.63 (m, 1H), 3.83 (s, 3H), 4.09 (q, $J = 7.2$ Hz, 2H), 6.9 (d, $J = 7.0$ Hz, 2H), 7.19 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR δ 14.6, 41.1, 41.1, 55.9, 60.9, 114.8, 129.4, 136.0, 159.4, 172.9, 174.8. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.12; H, 6.81. The spectroscopic and physical data are in agreement with those obtained for the monoester synthesized chemically in 85% yield as white crystals: mp 76–78 °C.

4.4.14. (*S*)-3-(4-Methoxyphenyl)-glutaric acid monobutyl ester (*S*)-3c, R³ = Bu. The reaction was terminated after 25 days (conversion 44%). After crystallization, white crystals of (*S*)-**3c**, $R^3 = Bu$ were obtained in 28% yield: mp 97 °C (Et_2O/hexane); $[\alpha]_D^{20} = +2.3$ (*c* 0.50, EtOH); $R_f = 0.30$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^1H NMR δ 0.86 (t, $J = 7.2$ Hz, 3H), 1.25 (q, $J = 7.2$ Hz, 2H), 1.48 (m, 2H), 2.66 (m, 4H), 3.57 (m, 1H), 3.77 (s, 3H), 3.97 (t, $J = 6.3$ Hz, 2H), 6.81 (d, $J = 7.8$ Hz, 2H), 7.13 (d, $J = 7.8$ Hz, 2H), 10.30–10.80 (br s 1H); ^{13}C NMR δ 13.6, 19.0, 30.5, 37.3, 40.5, 40.9, 55.2, 64.3, 113.9, 128.1, 134.2, 158.3, 171.7, 177.6. Anal. Calcd for $C_{16}H_{22}O_5 + 0.1H_2O$: C, 64.89; H, 7.56. Found: C, 64.70; H, 7.78. The spectroscopic and physical data are in agreement with those obtained for the monoester synthesized chemically in 87% yield as white crystals.

4.4.15. 3-(4-Methoxyphenyl)-glutaric acid monobenzyl ester (*S*)-3c, R³ = Bn. The reaction was terminated after 33 days (63% conversion). After crystallization, white crystals of (*S*)-**3c**, $R^3 = Bn$ were obtained in 36% yield: mp 95 °C (Et_2O/hexane); $[\alpha]_D^{20} = -0.4$ (*c* 0.50, EtOH); $R_f = 0.32$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^1H NMR δ 2.67 (m, 4H), 3.58 (m, 1H), 3.76 (s, 3H), 5.00 (s, 2H), 6.76 (d, $J = 8.3$ Hz, 2H), 7.08 (d, $J = 8.3$ Hz, 2H), 7.20 (m, 5H); ^{13}C NMR δ 37.3, 40.4, 40.8, 55.1, 66.3, 114.0, 128.2, 128.4, 134.0, 174.3, 177.3; IR ($CHCl_3$) ν_{max}: 3509 (OH), 2897 (Ar–OCH_3), 1720 (CO), 1713 (CO) cm^{-1}. Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.15; H, 6.24. The spectroscopic and physical data are in agreement with those obtained for the monoester synthesized chemically in 44% yield as white crystals.

4.4.16. (*S*)-3-(4-Methoxyphenyl)-glutaric acid monoallyl ester (*S*)-3c, R³ = Allyl. The reaction was terminated after 25 days (70% conversion). After crystallization, white crystals of (*S*)-**3c**, $R^3 = Allyl$ were obtained in 67% yield. $[\alpha]_D^{20} = +7.3$ (*c* 0.65, EtOH); ^1H NMR δ 2.56–2.82 (m, 4H), 3.51–3.66 (m, 1H), 3.77 (s, 3H), 4.52 (d, $J = 5.7$ Hz, 2H), 5.10–5.28 (m, 2H), 5.70–5.89 (m, 1H), 6.82 (d, $J = 8.6$ Hz, 2H), 7.14 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR δ 37.2, 40.5, 40.8, 55.2, 65.2, 113.9, 118.2, 128.1, 131.8, 134.1, 158.3, 171.1, 177.4. Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.08; H, 6.37. The spectroscopic and physical data are in agreement with those obtained for the monoester synthesized chemically in 90% yield as white crystals: mp 71–72 °C (Et_2O/hexane).

4.4.17. (*S*)-3-(3,4-Dichlorophenyl)-glutaric acid monomethyl ester (*S*)-3d, R³ = Me. The reaction reached its full conversion after 5 days, to give the ester (*S*)-**3d**, $R^3 = Me$ in 80% yield; white crystals: mp 79–89 °C (Et_2O/hexane); $[\alpha]_D^{20} = +5.0$ (*c* 1.00, EtOH); $R_f = 0.20$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^1H NMR δ 2.55–2.88 (m, 4H), 3.55–3.75 (m, 1H), 3.61 (s, 3H), 7.13 (dd, $J = 2.0$ Hz, $J = 8.7$ Hz, 1H), 7.40–7.55 (m, 7H); ^{13}C NMR δ 32.0, 37.6, 42.6, 126.8, 128.2, 129.8, 131.4, 133.0, 134.2, 167.8, 177.0. Anal. Calcd for $C_{12}H_{12}Cl_2O_4$: C, 49.51; H, 4.15. Found: C, 49.58; H, 4.17. The spectroscopic data are in agreement with those obtained for the monoester synthesized chemically: mp 89–90 °C (EtOAc/hexane).

4.4.18. (*S*)-3-(3,4-Dichlorophenyl)-glutaric acid monoethyl ester (*S*)-3d, R³ = Et. The reaction was terminated after 25 days (76% conversion). Crystallization gave white crystals of (*S*)-**3d**, $R^3 = Bu$ ester in 38% yield: mp 76–77 °C (Et_2O/hexane); $[\alpha]_D^{20} = +3.8$ (*c* 1.00, EtOH) {lit. $[\alpha]_D^{20} = +6.9$ (*c* 1.01, EtOH), for (*S*)-enantiomer[13]}; HPLC analysis [hexane/*i*-PrOH/CH_3COOH 198:1:1; $\lambda = 225$ nm; 1.0 mL/min; t_R (*S*) = 65.0 min, t_R (*R*) = 69.8 min] 60% ee $R_f = 0.16$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^1H NMR δ 1.20 (t, $J = 7.1$ Hz, 3H), 2.55–2.88 (m, 4H), 3.55–3.75 (m, 1H), 4.03 (q, $J = 7.1$ Hz, 2H), 7.13 (dd, $J = 1.8$ Hz, $J = 8.2$ Hz, 1H), 7.37–7.42 (m, 2H); ^{13}C NMR δ 14.1, 37.2, 40.3, 40.4, 60.8, 126.8, 129.3, 130.5, 130.9, 132.5, 142.5, 169.9, 177.0. Anal. Calcd for $C_{13}H_{14}Cl_2O_4$: C, 51.17; H, 4.62. Found: C, 51.16; H, 4.78. The spectroscopic data are in agreement with those obtained for the monoester synthesized chemically in 88% yield as white crystals: mp 93–94 °C (EtOAc/hexane).

4.4.19. (*S*)-3-(3,4-Dichlorophenyl)-glutaric acid monobutyl ester (*S*)-3d, R^3 = Bu. The reaction was terminated after 5 days (conversion 40%). Crystallization gave white crystals of (*S*)-**3d**, R^3 = Bu in 16% yield: mp 76–77 °C (Et_2O/hexane); $[\alpha]_D^{20} = +1.3$ (*c* 0.50, ethanol); $R_f = 0.25$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^1H NMR δ 0.92 (t, $J = 7.2$ Hz, 3H), 1.24–1.35 (m, 2H), 1.36–1.70 (m, 2H), 2.73–2.88 (m, 4H), 3.60–3.75 (m, 1H), 4.03 (t, $J = 6.6$ Hz, 2H), 7.13 (dd, $J = 1.8$ Hz, $J = 8.2$ Hz, 1H), 7.37–7.42 (m, 2H); ^{13}C NMR δ 14.2, 19.6, 31.1, 37.8, 40.4, 40.9, 65.2, 127.4, 129.9, 131.0, 131.5, 133.0, 143.0, 171.5, 176.9. Anal. Calcd for $C_{15}H_{18}Cl_2O_4$: C, 54.07; H, 5.44. Found: C, 54.04; H, 5.69. The spectroscopic data are in agreement with those obtained for the monoester synthesized chemically in 86% yield as white crystals.

4.4.20. (*S*)-(−)-3-(3,4-Dichlorophenyl)-glutaric acid monobenzyl ester (*S*)-3d, R^3 = Bn. The reaction was terminated after 5 days (conversion 88%). Crystallization gave white crystals of (*S*)-**3d**, R^3 = Bn in 39% yield; $[\alpha]_D^{20} = +1.5$ (*c* 1.00, EtOH); $R_f = 0.24$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^1H NMR δ 2.55–2.88 (m, 4H), 3.55–3.75 (m, 1H), 5.01 (s, 2H), 6.92–7.38 (m, 8H); ^{13}C NMR δ 37.2, 40.0, 40.3, 66.8, 126.5, 126.8, 128.2, 128.3, 128.4, 128.5, 129.3, 130.5, 131.1, 132.6, 135.3, 142.2, 170.7, 177.0. Anal. Calcd for $C_{18}H_{16}Cl_2O_4$: C, 58.87; H, 4.39. Found: C, 58.94; H, 4.44. The spectroscopic data are in agreement with those obtained for the monoester synthesized chemically in 49% yield as white crystals: mp 78 °C (EtOAc/hexane).

4.4.21. (*S*)-3-(3,4-Dichlorophenyl)-glutaric acid monoallyl ester (*S*)-3d, R^3 = Allyl. The reaction was terminated after 5 days (62% conversion). Crystallization gave white crystals of (*S*)-**3e**, R^3 = Bn in 18% yield; $[\alpha]_D^{20} = +1.7$ (*c* 1.00, EtOH); $R_f = 0.24$ ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^1H NMR δ 2.60–2.80 (m, 4H), 3.55–3.75 (m, 1H), 4.49 (d, $J = 5.8$ Hz, 2H), 5.23 (m, 2H), 5.70–5.90 (m, 1H), 7.13 (dd, $J = 1.8$ Hz, $J = 8.2$ Hz, 1H), 7.37–7.42 (m, 2H); ^{13}C NMR δ 37.9, 40.4, 40.8, 66.1, 119.2, 127.0, 127.3, 129.9, 130.1, 131.1, 132.8, 142.9, 170.1, 171.1. Anal. Calcd for $C_{14}H_{14}Cl_2O_4$: C, 53.02; H, 4.45. Found: C, 53.22; H, 4.50. The spectroscopic data are in agreement with those obtained for the monoester synthesized chemically in 75% yield as white crystals: mp 65–66 °C (Et_2O/hexane).

4.4.22. (*S*)-3-(4-Fluorophenyl)-glutaric acid monomethyl ester (*S*)-3e, R^3 = Me. The reaction reached its full conversion after 33 days to give (*S*)-**3e**, R^3 = Me as an oil in 99% yield. After crystallization, white crystals were obtained in 90% yield: mp 42 °C (Et_2O/hexane); $[\alpha]_D^{20} = -4.3$ (*c* 1.00, $CHCl_3$); $R_f = 0.32$ (hexane/EtOAc 6:4); ^1H NMR δ 2.53–2.84 (m, 4H), 3.58 (s, 3H), 3.61–3.72 (m, 1H), 6.92–7.04 (m, 2H), 6.96 (d, $J = 8.75$ Hz, 2H), 7.18 (d, $J = 8.56$ Hz, 2H); ^{13}C NMR δ 37.2, 40.1, 40.5, 51.7, 115.6 (d, $J = 21.5$ Hz), 128.7 (d, $J = 7.9$ Hz), 137.4 (d, $J = 2.9$ Hz), 161.2 (d, $J = 244.0$ Hz), 171.7, 177.1; IR ($CHCl_3$) ν_{max}: 1733 (CO), 1715 (CO) cm^{-1}. Anal. Calcd for $C_{12}H_{13}FO_4$: C, 60.00; H, 5.45. Found: C, 59.82; H, 5.79. The spectroscopic data are in agreement with those obtained for the monoester synthesized chemically in 85% yield as white crystals: mp 90–91 °C (EtOAc/hexane, lit. 97–98 °C[30]).

4.4.23. (*S*)-3-(4-Fluorophenyl)-glutaric acid monoethyl ester 3e, R^3 = Et. The reaction reached its full conversion after 20 days to give (*S*)-**3e**, R^3 = Et as an oil in 99% yield. After crystallization, white crystals were obtained in 89% yield: mp 59–60 °C (Et_2O/hexane); $[\alpha]_D^{20} = -4.7$ (*c* 1.00, $CHCl_3$); $R_f = 0.38$ (hexane/EtOAc, 6:4); ^1H NMR δ 1.14 (t, $J = 7.1$ Hz, 3H), 2.51–2.82 (m, 4H), 3.58–3.64 (m, 1H), 4.03 (q, $J = 7.1$ Hz, 2H), 6.88–7.02 (m, 2H), 7.10–7.26 (m, 2H); ^{13}C NMR δ 14.1, 37.3, 40.3, 40.7, 60.6, 115.4 (d, $J = 21.3$ Hz), 128.6 (d, $J = 7.9$ Hz), 137.8 (d, $J = 2.9$ Hz), 161.7 (d, $J = 245.1$ Hz), 171.3, 177.1. Anal. Calcd for $C_{13}H_{15}FO_4$: C, 61.41; H, 5.95. Found: C, 61.16; H, 5.95. The spectroscopic data are in agreement with those obtained for the monoester synthesized chemically in 91% yield as white crystals: mp 35–36 °C (EtOAc/hexane).

4.4.24. (*S*)-3-(4-Fluorophenyl)-glutaric acid monobutyl ester (*S*)-3e, R^3 = Bu. The reaction reached its full conversion after 25 days to give (*S*)-**3e**, R^3 = Bu as an oil in 99% yield. After crystallization, white crystals were obtained in 44% yield: mp 44–46 °C (Et_2O/hexane); $[\alpha]_D^{20} = -2.2$ (*c* 0.50, $CHCl_3$); $R_f = 0.46$ (hexane/EtOAc 6:4); ^1H NMR δ 0.87 (t, $J = 7.3$ Hz, 3H), 1.16–1.36 (m, 2H), 1.40–1.58 (m, 2H), 2.51–2.82 (m, 4H), 3.52–3.70 (m, 1H), 3.97 (t, $J = 6.6$ Hz, 2H), 6.90–7.05 (m, 2H), 7.12–7.28 (m, 2H); ^{13}C NMR δ 13.6, 19.0, 30.5, 37.4, 40.3, 40.7, 64.4, 115.4 (d, $J = 21.2$ Hz), 128.7 (d, $J = 7.5$ Hz), 137.8 (d, $J = 2.8$ Hz), 161.2 (d, $J = 245.0$ Hz), 171.4, 177.0; IR ($CHCl_3$) ν_{max}: 1767 (CO), 1720 (CO) cm^{-1}. Anal. Calcd for $C_{15}H_{19}FO_{44}$: C, 63.82; H, 6.78. Found: C, 63.18; H, 6.98. The spectroscopic data are in agreement with those obtained for the monoester synthesized chemically in 86% yield as white crystals: mp 63–64 °C (EtOAc/hexane).

4.4.25. (*S*)-3-(4-Fluorophenyl)-glutaric acid monobenzyl ester (*S*)-3e, R^3 = Bn. The reaction reached its full conversion after 7 days to give (*S*)-**3e**, R^3 = Bn as an oil in 99% yield. After crystallization, white crystals were obtained in 40% yield; $[\alpha]_D^{20} = -1.7$ (*c* 0.80, $CHCl_3$); $R_f = 0.37$ (hexane/EtOAc 6:4); ^1H NMR δ 2.54–2.84 (m, 4H), 3.54–3.72 (m, 1H), 5.01 (s, 2H), 6.85–7.02 (m, 2H), 7.06–7.40 (m, 7H); ^{13}C NMR δ 37.2, 40.2, 40.6, 66.3, 115.4 (d, $J = 21.12$ Hz), 128.1, 128.4, 128.7 (d, $J = 7.89$ Hz), 135.4, 138.2 (d, $J = 2.90$ Hz), 161.0 (d, $J = 245.0$ Hz), 171.1, 177.0. Anal. Calcd for $C_{18}H_{17}FO_4$: C, 68.35; H, 5.42. Found: C, 68.39; H, 5.57. The spectroscopic data are in agreement with those obtained for the monoester synthesized in 40% yield as white crystals: mp 114–115 °C (EtOAc/hexane).

4.4.26. (*S*)-3-(4-Fluorophenyl)-glutaric acid monoallyl ester (*S*)-3e, R^3 = Allyl. The reaction reached its full conversion after 7 days to give (*S*)-**3e**, R^3 = Allyl in 99% yield as an oil. After crystallization, white crystals were obtained in 76% yield: mp 44–50 °C (Et_2O/hexane); $[\alpha]_D^{20} = -2.5$ (*c* 0.90, $CHCl_3$); $R_f = 0.47$ (hexane/EtOAc 6:4); ^1H NMR δ 2.55–2.88 (m, 4H), 3.51–3.72

(m, 1H), 4.48 (d, $J = 5.7$ Hz, 2H), 5.10–5.28 (m, 2H), 5.68–5.90 (m, 1H), 6.90–7.05 (m, 2H), 7.10–7.28 (m, 2H); ^{13}C NMR δ 38.1, 41.0, 41.4, 66.2, 115.4 (d, $J = 21.3$ Hz), 128.6 (d, $J = 7.9$ Hz), 137.8 (d, $J = 2.9$ Hz), 161.7 (d, $J = 245.1$ Hz), 172.5, 179.4; IR ($CHCl_3$) ν_{max}: 3516 (OH), 1818 (CH=CH_2), 1729 (CO) cm^{-1}. Anal. Calcd for $C_{14}H_{15}FO_4$: C, 63.15; H, 5.68. Found: C, 62.88; H, 5.90. The spectroscopic data are in agreement with those obtained for the monoester synthesized chemically in 89% yield as white crystals: mp 63–64 °C (EtOAc/hexane).

4.4.27. Assigning the absolute configuration of chiral 3-arylglutaric acid monoesters. All the chiral monoesters (3*S*)-**3** were transformed to lactones (4*R*)-**4** according to General procedure 1 described for (4*R*)-(4-fluorophenyl)tetrahydro-2*H*-pyran-2-one (4*R*)-**4d**. The reaction yields and optical rotary dispersion values ($[\alpha]_D^{20}$) of lactones are summarized in Table 3.

4.4.28. (4*R*)-(4-Fluorophenyl)tetrahydro-2*H*-pyran-2-one (4*R*)-4d. *General procedure 1*: To the cooled (0 °C) solution of monoester (3*S*)-**3e** (R^2 = Me) (0.058 g, 0.24 mmol) in dry THF, potassium *tert*-butoxide (0.027 g, 0.24 mmol) was added. The mixture was allowed to warm up to room temperature and lithium borohydride (0.011 g, 0.51 mmol) was added. The mixture was refluxed for 1 h and after cooling concd hydrochloric acid (0.5 mL) was added dropwise. The solution was extracted with methylene chloride (3 × 5 mL). Combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo to give a transparent oil. The crude mixture was dissolved in toluene (5 mL) with catalytic amount of *p*-toluenesulfonic acid. The solvents were evaporated in vacuo along with formed water. The last operation (lactonization) was repeated three times. Triethylamine was added (0.1 mL) and its excess was evaporated in vacuo. The resulting oil was purified by column chromatography (hexane/EtOAc, 8:2) to give lactone (4*R*)-**4e** (0.023 g, 0.19 mmol) in 49% yield as a colorless oil. $[\alpha]_D^{20} = -3.2$ (*c* 1.90, $CHCl_3$); $R_f = 0.32$ (hexane/EtOAc, 6:4) ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.82–2.13 (m, 2H), 2.50 (dd, $J = 10.6$ Hz, $J = 17.5$ Hz, 1H), 2.80 (ddd, $J = 1.5$ Hz, $J = 5.9$ Hz, $J = 17.5$ Hz, 1H), 3.05–3.22 (m, 1H), 4.20–4.45 (m, 2H), 6.92–7.14 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 37.2, 40.2, 40.4, 51.7, 115.4 (d, $J = 21.1$ Hz), 128.6 (d, $J = 7.9$ Hz), 137.8 (d, $J = 3.2$ Hz), 161.7 (d, $J = 245.0$ Hz), 170.8; IR ($CHCl_3$) ν_{max}: 1734 (CO) cm^{-1}. Anal. Calcd for $C_{11}H_{11}FO_2$: C, 68.03; H, 5.71. Found: C, 68.01; H, 5.81. The spectroscopic and physical data are in agreement with those obtained for the racemic lactone (±)-**4e** synthesized according to *General procedure 1* in 76% yield.

4.4.29. (4*S*)-(4-Fluorophenyl)tetrahydro-2*H*-pyran-2-one (4*S*)-4e. To the vigorously stirred solution of (3*S*)-**3d** (R^2 = Me) (0.061 g, 0.24 mmol) in dry THF at 0 °C, potassium *tert*-butoxide (0.027 g, 0.24 mmol) was added. The mixture was allowed to warm up to room temperature and lithium aluminum hydride (0.011 g, 0.51 mmol) was added. The mixture was refluxed for 1 h and after cooling 33% hydrochloric acid (2 mL) was added dropwise. The solution was extracted with methylene chloride (3 × 5 mL). Combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo to give a transparent oil. The crude mixture was dissolved in toluene (5 mL) with catalytic amount of *p*-toluenesulfonic acid. The solvent was evaporated in vacuo and the procedure was repeated 3 times. Triethylamine was added (0.1 mL) and its excess was evaporated in vacuo. The resulting oil was purified by column chromatography (hexane/EtOAc, 8:2) to give lactone (4*S*)-**4e** (0.023 g, 0.19 mmol) in 49% yield as a colorless oil. $[\alpha]_D^{20} = +3.3$ (*c* 1.25, $CHCl_3$). The spectroscopic and physical data are in agreement with those obtained for racemic lactone (±)-**4e**.

4.4.30. (4*R*)-4-Phenyltetrahydro-2*H*-pyran-2-one 4a. Lactone (4*R*)-**4a** was synthesized according to General procedure 1 in 52% yield as a colorless oil. $[\alpha]_D^{20} = -5.7$ (*c* 2.10, $CHCl_3$), {lit. $[\alpha]_D^{20} = +3.8$ (*c* 7.2, $CHCl_3$), for (*S*)-enantiomer[32]}; $R_f = 0.39$ (hexane/EtOAc, 6:4) ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.94–2.12 (m, 2H), 2.56 (dd, $J = 10.6$ Hz, $J = 17.6$, 1H), 2.86 (ddd, $J = 1.5$ Hz, $J = 5.8$ Hz, $J = 17.2$ Hz, 1H), 3.08–3.28 (m, 1H), 4.30 (dt, $J = 3.6$ Hz, $J = 11.4$ Hz, 1H), 4.42 (ddd, $J = 3.7$ Hz, $J = 4.8$ Hz, $J = 11.3$ Hz, 1H), 7.15 (d, $J = 7.2$ Hz, 2H), 7.28 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.1, 31.2, 38.2, 69.5, 127.7, 128.5, 130.2, 171.1; IR ($CHCl_3$) ν_{max}: 1730 (CO) cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.94; H, 7.89. The spectroscopic and physical data are in agreement with those obtained for racemic lactone (±)-**4a** synthesized according to General procedure 1 from monoester (±)-**3a**, R^3 = Et in 19% yield.

4.4.31. (4*R*)-4-(4-Chlorophenyl)tetrahydro-2*H*-pyran-2-one (4*R*)-4b. The lactone (4*R*)-**4b** was synthesized according to General procedure 1 from (3*S*)-**3b**, R^3 = Et in 36% yield as white crystals: mp 80 °C; $[\alpha]_D^{20} = -8.7$ (*c* 1.38, $CHCl_3$) {lit. $[\alpha]_D^{20} = +8.4$ (*c* 1.38, $CHCl_3$), for (*S*)-enantiomer[33]}; $R_f = 0.34$ (hexane/EtOAc, 6:4); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.70–2.15 (m, 2H), 2.51 (dd, $J = 10.6$ Hz, $J = 17.6$ Hz, 1H), 2.85 (ddd, $J = 1.5$ Hz, $J = 5.8$ Hz, $J = 17.2$ Hz, 1H), 3.05–3.28 (m, 1H), 4.28 (dt, $J = 3.6$ Hz, $J = 11.4$ Hz, 1H), 4.46 (ddd, $J = 3.7$ Hz, $J = 4.8$ Hz, $J = 11.3$ Hz, 1H), 7.07 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.8, 37.5, 38.0, 69.0, 127.4, 127.7, 128.3, 128.5, 128.9, 129.0, 129.3, 129.4, 129.7, 141.7, 170.7; IR ($CHCl_3$) ν_{max}: 1732 (CO) cm^{-1}. Anal. Calcd for $C_{11}H_{11}ClO_2$: C, 62.72; H, 5.26. Found: C, 62.86; H, 5.21. The spectroscopic data are in agreement with those obtained for racemic lactone (±)-**4b** synthesized according to General procedure 1 from monoester (±)-**3b**, R^3 = Et as white crystals in 43% yield: mp 79–80 °C (lit. 81–83[6]).

4.4.32. (4*R*)-4-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-2-one (4*R*)-4c. The lactone (4*R*)-**4c** was synthesized according to General procedure 1 in 71% yield as white crystals: mp 75–77 °C; $[\alpha]_D^{20} = -7.7$ (*c* 3.20, $CHCl_3$) {lit. $[\alpha]_D^{20} = -7.0$ (*c* 0.96, $CHCl_3$), for (*R*)-enantiomer[34]}; $R_f = 0.32$ (hexane/EtOAc, 6:4); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.91–2.26 (m, 2H), 2.61 (dd, $J = 10.6$ Hz,

$J = 17.6$, 1H), 2.95 (ddd, $J = 1.6$ Hz, $J = 5.9$ Hz, $J = 17.2$ Hz, 1H), 3.12–3.31 (m, 1H), 3.82 (s, 1H), 4.37 (dt, $J = 3.9$ Hz, $J = 11.4$ Hz, 1H), 4.48 (ddd, $J = 3.8$ Hz, $J = 4.8$ Hz, $J = 11.3$ Hz, 1H), 6.92 (d, $J = 8.8$ Hz, 2H), 7.16 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.1, 37.2, 38.3, 55.9, 69.2, 114.8, 128.0, 135.5, 159.2, 171.3; IR ($CHCl_3$) ν_{max}: 1731 (CO) cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.73; H, 6.72. The spectroscopic data are in agreement with those obtained for racemic lactone (±)-**4c** synthesized according to General procedure 1 as white crystals in 45% yield: mp 79–80 °C (lit. 83.4–83.6[34]).

4.4.33. (4*R*)-(3,4-Dichlorophenyl)tetrahydro-2*H*-pyran-2-one (4*R*)-4d. The lactone (4*R*)-**4d** was synthesized according to General procedure 1 in 35% yield as a colorless oil. $[\alpha]_D^{20} = -8.1$ (*c* 1.60, $CHCl_3$); $R_f = 0.32$ (hexane/EtOAc, 6:4); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.80–2.15 (m, 2H), 2.48 (dd, $J = 10.8$ Hz, $J = 17.5$ Hz, 1H), 3.15 (ddd, $J = 1.6$ Hz, $J = 6.0$ Hz, $J = 17.8$ Hz, 1H), 4.20–4.50 (m, 3H), 6.80 (dd, $J = 2.2$ Hz, $J = 8.3$ Hz, 1H), 7.25 (d, $J = 2.1$ Hz, 1H), 7.35 (d, $J = 8.3$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.6, 37.3, 37.7, 68.8, 126.4, 129.2, 131.5, 131.9, 133.6, 143.5, 170.2; IR ($CHCl_3$) ν_{max}: 1735 (CO) cm^{-1}. Anal. Calcd for $C_{11}H_{10}Cl_2O_2$: C, 53.90; H, 4.11. Found: C, 53.78; H, 4.13. The spectroscopic and physical data are in agreement with those obtained for racemic lactone (±)-**4d** synthesized according to General procedure 1 from monoester (±)-**3d**, $R^3 = Et$ in 47% yield.

Acknowledgements

This work was supported by Polish State Committee for Scientific Research, grant PZB-MIN-007/P04/2003.

References

1. Liu, L. T.; Hong, P. C.; Huang, H. L.; Chen, S. F.; Wang, C. L. J.; Wen, Y. S. *Tetrahedron: Asymmetry* **2001**, *12*, 419–426.
2. Yu, M. S.; Lantos, I.; Peng, Z. Q.; Lu, J.; Cacchio, T. *Tetrahedron Lett.* **2000**, *41*, 5647–5651.
3. Pifferi, G.; Nizzola, R.; Cristoni, A. *Il farmaco* **1994**, *49*, 453–455.
4. Kubota, H.; Kakefuda, A.; Okamoto, Y.; Fujii, M.; Yamamoto, O.; Yamagiwa, Y.; Orita, M.; Ikeda, K.; Takeuchi, M.; Shibanuma, T. Y. I. *Chem. Pharm. Bull.* **1998**, *46*, 1538–1544.
5. Dorn, P. C.; Finke, P. E.; Oates, B.; Budhu, R. J.; Mills, S. G.; MacCoss, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 259–264.
6. Chen, L. Y.; Zaks, A.; Chackalamannil, S.; Dugar, S. *J. Org. Chem.* **1996**, *61*, 8341–8343.
7. Berglund, P.; Hults, K. In *Stereoselective Biocatalysis*; Patel, R., Ed.; Marcel Dekker: New York, 1999, pp 633–657.
8. Schmid, R. D.; Verger, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1608–1633.
9. Wong, C. H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: New York, 1994.
10. Chenevert, R.; Desjardins, M. *Can. J. Chem.* **1994**, *72*, 2312–2317.
11. Chenevert, R.; Desjardins, M. *Tetrahedron Lett.* **1991**, *32*, 4249–4250.
12. Francis, C. J.; Jones, J. B. *J. Chem. Soc., Chem. Commun.* **1984**, *9*, 579–580.
13. Homann, M. J.; Vail, R.; Morgan, B.; Sabesan, V.; Levy, C.; Dodds, D. R.; Zaks, A. C. *Adv. Synth. Catal.* **2001**, *343*, 744–749.
14. Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Chemistry*; Wiley-VHC: Weinheim, 1999.
15. Yamamoto, Y.; Iwasa, M.; Sawada, S.; Oda, J. *Agric. Biol. Chem.* **1990**, *54*, 3269–3274.
16. Yamamoto, Y.; Yamamoto, K.; Nishioka, T.; Oda, J. *Agric. Biol. Chem.* **1988**, *52*, 3087–3092.
17. Yamamoto, K.; Nishioka, T.; Oda, J.; Yamamoto, Y. *Tetrahedron Lett.* **1988**, *29*, 1717–1720.
18. Ozegowski, R.; Kunath, A.; Schick, H. *Liebigs Ann. Chem.* **1993**, *7*, 805–808.
19. Harusawa, S.; Takemura, S.; Yoneda, R.; Kurihara, T. *Tetrahedron* **1993**, *49*, 10577–10586.
20. Ostaszewski, R.; Portlock, D. E.; Fryszkowska, A.; Jeziorska, K. *Pure Appl. Chem.* **2003**, *75*, 413–419.
21. Fryszkowska, A.; Ostaszewski, R.; Frelek, J. *Tetrahedron* **2005**, *61*, 6064–6072.
22. Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542–9543.
23. Perregaard, J.; Moltzen, E. K.; Meier, E.; Sanchez, C. *J. Med. Chem.* **1995**, *38*, 1998–2008.
24. Burger, A.; Hofstetter, A. *J. Org. Chem.* **1959**, *24*, 1290–1293.
25. Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 142–146.
26. Koer, A. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 147–151.
27. Jackson, J. G.; Kenner, J. *J. Chem. Soc., Chem. Commun.* **1928**, 1657–1662.
28. Genge, T. *J. Indian. Chem. Soc.* **1959**, *36*, 677.
29. Sato, M.; Nagashima, S.; Furuya, T.; Kaneko, C. *Chem. Pharm. Bull.* **1992**, *40*, 1972–1974.
30. Gootjes, J.; Nauta, W. T. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 1183–1199.
31. Chitre, L. *J. Univ. Bombay Sci.* **1935**, *4/2*, 94–96.
32. Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* **1979**, *44*, 2250–2256.
33. Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047–4056.
34. Enders, D.; Rendenbach, B. E. M. *Chem. Ber.* **1987**, *120*, 1223–1227.