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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 961–966

Studies on enzymatic synthesis of chiral non-racemic 3-arylglutaric acid monoesters

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Received 31 January 2006; accepted 7 March 2006
Available online 4 April 2006

Abstract—The enantioselective enzymatic desymmetrization (EED) of various 3-arylglutaric anhydrides **1** with alcohols in organic media has been studied. The effect of the solvent on the stereochemical outcome of the reaction was investigated in detail. The amount of biocatalyst was optimized, and the possibility of its re-use was tested. The first example of the EED of 3-substituted glutaric anhydrides with esters as nucleophiles is reported.

1. Introduction

Desymmetrization of *meso* and prochiral compounds is a powerful approach in asymmetric synthesis.[1,2] In contrast to a kinetic resolution, a maximum yield of 100% can be achieved in a single-step reaction based on enantiofacial or enantiotopic differentiation. A number of enantioselective enzymatic syntheses have been based on this strategy.[3–5] Most enzymatic enantioselective desymmetrizations (EEDs) catalyzed by hydrolytic enzymes use substrates bearing common functional groups, such as alcohols or esters, while examples of the desymmetrization of anhydrides are less common.[3–5]

Recently, we have focused our attention on the synthesis of chiral non-racemic 3-arylglutaric acid derivatives, which are important building blocks in the synthesis of a number of biologically active compounds.[6,7] The most prominent examples are (*R*)-Baclofen **I** (Fig. 1)—a selective $GABA_B$ receptor agonist[8–10] and G-protein-coupled NK-receptor antagonist **II** (Fig. 1).[11,12] Moreover, the search for a new glycoprotein **IIb–IIIa** antagonist led to the development of compound **III** possessing improved pharmacokinetic properties, bearing a 3-phenylglutaric unit.[13]

A common enzymatic route toward optically active 3-arylglutaric acid monoesters is an enzymatic hydrolysis of the respective prochiral diesters.[9–11,14–17] The reaction usually leads to the optically active products in good yields and good to excellent enantioselectivities. Although highly efficient, this methodology involves employing an aqueous reaction media. Therefore, a tedious product separation and purification is required.

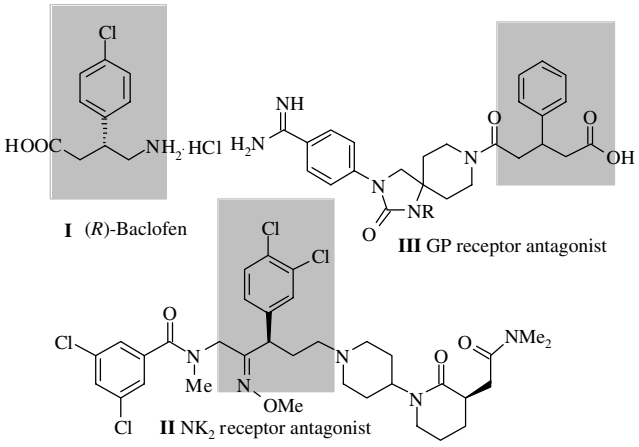

Figure 1. Biologically active compounds possessing the 3-arylglutaric unit.

Recently, we reported new methodology toward the synthesis of this class of compounds, based on the enzymatic desymmetrization of 3-arylglutaric anhydrides in organic solvents using alcohols as nucleophiles (Scheme 1).[7] This

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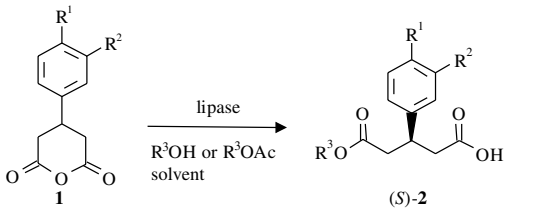
doi:10.1016/j.tetasy.2006.03.002



1a R^1 = H, R^2 = H
1b R^1 = Cl, R^2 = H
1c R^1 = Cl, R^2 = Cl
1d R^1 = OMe, R^2 = H

2a R^1 = H, R^2 = H, R^3 = Et
2b R^1 = Cl, R^2 = H, R^3 = Et
2c R^1 = Cl, R^2 = Cl, R^3 = Et
2d R^1 = OMe, R^2 = H, R^3 = Et
2e R^1 = H, R^2 = H, R^3 = *n*-Pr
2f R^1 = H, R^2 = H, R^3 = *n*-Bu
2g R^1 = H, R^2 = H, R^3 = Bn

Scheme 1. Enzymatic desymmetrization of 3-aryl glutaric acid anhydrides **1a–d**.

approach is parallel to the enzymatic hydrolysis of diesters, but the need for aqueous media is eliminated.

We found that the immobilized enzymes were efficient catalysts for the EED of anhydrides **1**, leading to the respective monoesters **2** in quantitative yields and good enantioselectivities.[7] We observed that the biocatalyst had a strong influence on both the stereoselectivity of the reaction and its kinetics. For example, Novozym 435 (CAL-B) catalyzed the formation of (*S*)-**2a** (78% ee), while Amano PS-C (*Pseudomonas cepacia*) led to the formation of (*R*)-**2a** (77% ee). Moreover, we have demonstrated that the use of short aliphatic alcohols (e.g., methanol, ethanol) as nucleophiles was advantageous for EED.

Encouraged by these results, we decided to extend this methodology to different 3-aryl substituted glutaric anhydrides and to study the scope of this biocatalytic process and the effect of solvents and nucleophile on the efficiency and enantioselectivity of the EED reaction. The influence of the amount of the biocatalyst and its re-use were investigated as well; this is of crucial importance for the potential applications of our methodology.

2. Results and discussion

In our previous study, immobilized lipases from *Candida antarctica* type B—Novozym 435 and Chirazyme L2,C3—proved to be efficient catalysts in the desymmetrization of 3-phenylglutaric anhydride **1a** in *iso*-propyl ether.[7] Although the monoester (*S*)-**2a** was obtained in approx. 80% ee, the enantiomeric excesses of other aromatic-ring substituted anhydrides **1b–c** were lower and the reaction times significantly longer. In order to find more favorable conditions for desymmetrization and to test the general applicability of the lipase-catalyzed desymmetrization, the current studies were undertaken.

A series of 3-arylsubstituted glutaric acid anhydrides **1a–d** was prepared, as described before,[7,18,19] and subjected to an enzymatic alcoholysis reaction with Novozym 435, according to Scheme 1. The absolute configurations of monoesters **2** were assigned according to the previously reported methodology.[7] The enantiomeric excesses were determined by HPLC using a Chiralcel OD-H column.

2.1. The solvent effect

It is well known that the solvent almost always affects the enantiomeric selectivity and the rate of the lipase-catalyzed reactions.[20] Our preliminary studies clearly indicated that the use of ether solvents in the EED of anhydride **1a** was superior to other solvents.[7] We extended our research to the desymmetrization of anhydrides **1b–1d**. Their enzymatic desymmetrizations catalyzed by Novozym 435 were performed in organic solvents at room temperature, affording the corresponding monoesters (*S*)-**2b–d**. The reaction times and ee values for monoesters **2b–d** are summarized in Table 1, as well as the previously reported results for monoester **2a** as a reference.

In all the cases, Novozym 435 exclusively catalyzed the formation of the respective (*S*)-monoester. As a general trend, the enantiomeric purities of the products obtained by the EED of 3-phenylglutaric anhydride **1a** were higher than those for the substituted-ring anhydrides **2b–d**.

EED of anhydride **1a** led to monoester (*S*)-**2a** with comparable enantioselectivities (75–79% ee), regardless of the ether used. On the contrary, evaluation of various ethers for the other anhydrides revealed that the choice of ether was of crucial importance. The monoester (*S*)-**2b** was obtained with moderate ee values (68%) in ethers having $\log P = 1.9$–2.9, while the ee values in more polar ethers ($\log P \leqslant 1.3$) were much lower (Table 1, entries 1, 4, 5 vs

Table 1. The effect of solvent on EED of 3-arylglutaric acid anhydrides **1a–d** with ethanol catalyzed by Novozym 435[a]

Entry	Solvent	Log *P*	(*S*)-**2a**		(*S*)-**2b**		(*S*)-**2c**		(*S*)-**2d**	
			Time[b] (days)	% ee[c]	Time[b] (days)	% ee[c]	Time[b] (days)	% ee[c]	Time[b] (days)	% ee[c]
1	*iso*-Propyl ether	2.0	2	78	5	68	4	60	22	69
2	*tert*-Butyl methyl ether	1.3	2	76	5	56	22	3	14	70
3	Ethyl ether	0.85	3	79	17	43	22	12	—	—
4	*n*-Propyl ether	1.9	4	78	17	68	11	10	—	—
5	*n*-Butyl ether	2.9	2	75	3	67	11	5	—	—
6	Cyclohexane	3.2	1	62	3	6	—	—	—	—

[a] Reaction conditions: substrate **1** (0.050 mmol), solvent (1 mL), ethanol (0.075 mmol), Novozym 435 (7.6 mg), rt.
[b] Time required for full conversion (by TLC).
[c] Ee determined by HPLC using Chiracel OD-H column.

2, 3). The best result for the monoester (*S*)-**2c** was obtained in *iso*-propyl ether (Table 1, entry 1, $\log P = 2.0$), while, for monoester (*S*)-**2d**, the use of TBME was advantageous (Table 1, entry 1, $\log P = 1.3$). It is noteworthy that the rate of EED in cyclohexane ($\log P = 3.2$) was generally high, although the enantioselectivities were poor (Table 1, entry 6).

The results indicated that the reaction time and enantiomeric excess of the product strongly depended on the structure of substrate **1**. Monoesters (*S*)-**2a–d** were obtained in moderate to good ee (60–79%). The low ee values of monoesters **2b–d** and slower reaction rates can be at least in part attributed to the reduced solubility of the anhydrides **1b–c** in comparison to **1a**. It is also known that CAL-B lipase, unlike other lipases, exhibits little to no interfacial activation.[21] However, we found no clear correlation between the solvent, the anhydride structure and the stereochemical outcome of EED. Our study demonstrates that choosing the appropriate solvent for enzymatic reaction still remains a trial-and-error process.

2.2. Studies on EED by transesterification

In an attempt to improve the enantiopurity of monoesters **2**, we undertook further studies. The aim of our research was to investigate whether it would be possible to perform EED by transesterification, according to Scheme 1. We envisioned that the use of esters both as alkoxy donors and solvents would be effective. As a model reaction, the EED of anhydride **1a** with Novozym 435 was chosen. The results are summarized in Table 2.

The enzymatic transesterification of anhydride **1a** led to formation of the respective monoesters (*S*)-**2a–g** (Table 4, entries 2–6). Without the enzyme in ethyl acetate, no product formation was observed (Table 4, entry 1). The results indicated that there was a correlation between $\log P$ of the acetate used as a solvent/nucleophile and the ee values of the monoesters **2**.

Table 2. EED of **1a** by transesterification catalyzed by Novozym 435[a]

Entry	Acetate	Log *P*	Product	% ee[b]	Time[c] (weeks)
1	Ethyl acetate[d]	0.68	—	—	5
2	Ethyl acetate[e]	0.68	(*S*)-**2a**	37	5
3	*n*-Propyl acetate	1.2	(*S*)-**2e**	33	4
4	*n*-Butyl acetate	1.7	(*S*)-**2f**	14	4
5	Benzyl acetate	1.8	(*S*)-**2g**	9	4
6	Ethyl cyanoacetate	0.02[f]	(*S*)-**2a**	0	4

[a] Reaction conditions: **1a** (0.050 mmol, 9.5 mg), acetate (1 mL), Novozym 435 (7.6 mg), rt.
[b] Ee determined by HPLC using Chiracel OD-H column.
[c] Time required for full conversion (by TLC).
[d] Blank reaction.
[e] Conversion <100%.
[f] Estimated.

We observed that higher asymmetric inductions were obtained for more polar solvents. For ethyl acetate ($\log P = 0.68$) and *n*-propyl acetate ($\log P = 1.2$), the respective monoesters **2** were obtained in 37% and 33% ee, respectively (Table 2, entries 2 and 3). The change of the solvent to water-miscible ethyl cyanoacetate (Table 2, entry 6, $\log P = 0.02$) led to a complete loss of stereodifferentiation.

We expected to obtain better results using the acetates of *n*-butyl and benzyl alcohols. These solvents are less water miscible ($\log P = 1.7$–1.8), which is usually advantageous for enzymatic reactions.[20] However, it was not the case and almost no asymmetric induction was observed (Table 2, 9–14% ee, entries 4–6). Previously, we demonstrated that short aliphatic alcohols used as nucleophiles improved the ee values of the monoesters **2**. Herein, the results may also suggest that not only the $\log P$, but the alkoxy group length influence the stereochemical course of the EED reaction.

Generally, the EED of glutaric anhydride **1a** by transesterification led to a low asymmetric induction. Moreover, the reaction times were very long (4 weeks). These unsatisfactory results can be explained by the fact that the use of esters as solvents may decrease the activity of enzymes, as well as an unfavorable equilibrium can be established. Probably, the formation of acetic acid during the reaction course can affect the enzyme activity as well. Nevertheless, we would like to emphasize the fact that, according to our knowledge, this is the first example of EED of 3-substituted glutaric anhydrides by transesterification.

2.3. Enzyme quantities and enzyme re-use

Finally, the effect of amount of the biocatalyst used in EED and possibility of its re-use were investigated. These parameters are crucial in terms of the potential large-scale applications of this methodology and, as a consequence, the process economy. We investigated the desymmetrization of anhydride **1a** with ethanol in *iso*-propyl ether as a function of Novozym 435 quantity. The results are summarized in Table 3.

Table 3. The enzyme quantity effect on EED of **1a** with ethanol catalyzed by Novozym 435 in *iso*-propyl ether[a]

Entry	Enzyme/anhydride **1a** (mg/mmol)	(*S*)-**2a** % ee[b]	Time[c] (days/weeks)
1	314	79	1/—
2	154	79	2/—
3	135	79	2.5/—
4	95	58	4/—
5	13	64	—/5[d]

[a] Reaction conditions: substrate **1a** (0.050 mmol, 9.5 mg) *iso*-propyl ether (1 mL), ethanol (0.075 mmol), Novozym 435, rt; TLC monitored until it reached full conversion.
[b] Ee determined by HPLC using Chiracel OD-H column.
[c] Time required for full conversion (by TLC).
[d] Conversion <100%.

The study revealed that the amount of enzyme does not affect the stereochemical outcome of EED, unless it is higher than 135 mg/mmol of anhydride **1a**. However, the smaller the amount of biocatalyst the longer reaction time was required to reach a full conversion, as one could expect (Table 3, entries 1–3). A further decrease in the amount

of the biocatalyst (Table 3, entries 4 and 5) led to an increased reaction time, as well as to the decreased enantiomeric purity of the monoester (*S*)-**2a**.

Since a substantial amount of Novozym 435 was required for an efficient EED of 3-arylglutaric anhydrides **1**, the possibility of the enzyme re-use was investigated. Again, the desymmetrization of anhydride **1a** with ethanol in *iso*-propyl ether was chosen as a model reaction. The results of the study are presented in Table 4.

Table 4. Studies on Novozym 435 re-circulation in EED of **1a** with ethanol in *iso*-propyl ether[a]

Cycle	Enzyme/anhydride **1a** (mg/mmol)	(*S*)-**2a** % ee[b]	Time[c] (days/weeks)
First cycle	142	78	2/—
Second cycle	133	71	3/—
Third cycle	125	55	6/—
Fourth cycle	139	36	—/4

[a] Reaction conditions: **1a** (0.50 mmol, 95.0 mg) *iso*-propyl ether (1 mL), ethanol (0.75 mmol), Novozym 435 (70 mg), rt.
[b] Ee determined by HPLC using Chiracel OD-H column.
[c] Time required for full conversion (by TLC).

The experimental data showed that Novozym 435 could be re-used up to three times, but in each cycle the enantioselectivity and activity of the biocatalyst decreased significantly. After the first cycle, the enzyme was approximately 10% less selective and 50% less active (Table 4, entries 1 and 2). In the next cycles, these changes were even more pronounced (Table 4, entries 3 and 4). Moreover, approximately 5% of enzyme was lost in every cycle due to mechanical operations.

3. Conclusions

Novozym 435-catalyzed enzymatic desymmetrization of 3-arylglutaric acid anhydrides **1** has been studied. Our results demonstrate that immobilized CAL-B lipase catalyzed the synthesis of the monoesters (*S*)-**2** with moderate to good enantiopurities. The solvent effect, as well as the nucleophilic character, were investigated in an attempt to find suitable reaction conditions. While for 3-phenylglutaric anhydride and its chloro-substituted derivatives **1a**–**c**, the enzyme showed the highest activity and enantioselectivity in *iso*-propyl ether, the use of TBME was favorable in the case of the 4-methoxy-substituted anhydride **1d**.

The use of acetates as solvents/acetoxy group donors did not lead to improved enantioselectivities. Nevertheless, the first example of 3-substituted glutaric anhydride desymmetrization by transesterification was reported.

The study on the effect of the enzyme amount demonstrated that the enantioselectivity of the reaction decreased significantly below a certain limit (135 mg of Novozym 435 per 1 mmol of anhydride **1a**). The re-use of the lipase was limited, since each cycle was accompanied by a loss of the enzyme enantioselectivity and the activity (from 10% for the first cycle to 35% for the fourth one).

Our approach undoubtedly represents a new methodology for the synthesis of chiral non-racemic glutaric acid derivatives. The water-free reaction media and the simplified work-up procedure make this process an attractive methodology for industrial purposes. The use of esters for the enzymatic desymmetrization opens new possibilities in the synthesis of 3-aryl glutaric monoacids.

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. The chemical shifts are reported in ppm (δ scale) and the coupling constants (J) are given in hertz (Hz). The MS spectra were recorded on an API-365 (SCIEX) apparatus. The IR spectra were recorded in $CHCl_3$ on a Perkin–Elmer FT-IR Spectrum 2000 apparatus. The HPLC analyses were performed on a Chiracel OD-H column (∅ 4.6 mm × 250 mm, from Diacel Chemical Ind., Ltd) equipped with a pre-column (∅ 4 mm × 10 mm, 5 μm) 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}.

Novozym 435 was purchased from Novo Nordisk. All the chemicals were obtained from commercial sources. The solvents were of analytical grade. The 3-arylglutaric anhydrides **1a**–**d** were obtained in three-step methodology from the respective aryl aldehyde, according to the literature procedures described before.[7,18,19]

4.1.1. Synthesis of monoesters (*S*)-2 by enzymatic desymmetrization catalyzed by Novozym 435. A general procedure. To a suspension of the anhydride **1** (0.50 mmol) in ether (10 mL), lipase (75 mg), and absolute ethanol (0.75 mmol, 70 μL) were added. The reaction was carried out at room temperature and its progress was monitored by TLC ($CHCl_3$/MeOH/HCOOH; 100:2:0.05). The enzyme was filtered off and the residue concentrated in vacuo to give monoester (*S*)-**2** as a colorless oil. The enantiomeric excess was determined by HPLC analysis using Chiracel OD-H column. The product was recrystallized from Et_2O/hexane.

4.1.2. Enzymatic desymmetrization of anhydride 1a with Novozym 435 by transesterification. To a suspension of anhydride **1a** (0.05 mmol, 9.5 mg) in an appropriate acetate (1 mL), Novozym 435 (7.5 mg) was added. The reaction was carried out at room temperature and the reaction progress was monitored by TLC ($CHCl_3$/MeOH/HCOOH; 100:2:0.05). The results are summarized in Table 4.

4.1.3. Studies on the amount of Novozym 435 in the synthesis of (*S*)-2a. A general procedure. To a suspension of anhydride **1a** (0.05 mmol, 9.5 mg) in *iso*-propyl ether (1 mL), appropriate amounts of Novozym 435, and absolute etha-

nol (0.075 mmol, 7 μL) were added. The reaction was carried out at room temperature and the reaction progress was monitored by TLC ($CHCl_3$/MeOH/HCOOH; 100:2:0.05). The enantiomeric excess was determined by HPLC analysis using Chiracel OD-H column. The enzyme quantities and the results are summarized in Table 3.

4.1.4. Studies on re-circulation of Novozym 435. A general procedure. To a suspension of anhydride **1a** (0.5 mmol, 95 mg) in *iso*-propyl ether (10 mL), Novozym 435 (70 mg), and absolute ethanol (0.75 mmol, 75 μL) were added. The reaction was carried out at room temperature and the reaction progress monitored by TLC ($CHCl_3$/MeOH/HCOOH; 100:2:0.05). When the reaction reached full conversion, the enzyme was filtered off, washed carefully with *iso*-propyl ether, and dried. The enzyme was re-used for the next reaction with an appropriate amount of the anhydride. The enantiomeric excess of product (*S*)-**2a** was determined by HPLC analysis using Chiracel OD-H column. The results are summarized in Table 4. Chemical yields of all the reactions were nearly quantitative (95–99%).

4.1.5. (*S*)-3-Phenylglutaric acid monoethyl ester (*S*)-2a. White crystals: mp 58–59 °C ((Et_2O/hexane; lit. 59–60[19]); $R_f = 0.24$ ($CHCl_3$/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*) = 8.3 min, t_R (*R*) = 8.9 min)]; ^1H 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), 7.27–7.32 (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%).

4.1.6. (*S*)-3-(4-Chlorophenyl)-glutaric acid monoethyl ester (*S*)-2b. White crystals: mp 56 °C (Et_2O/hexane); 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]; ^1H NMR δ 1.15 (t, $J = 7.1$ Hz, 3H), 2.67–2.80 (m, 4H), 3.50–3.70 (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, 60.6, 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.

4.1.7. (*S*)-3-(3,4-Dichlorophenyl)-glutaric acid monoethyl ester (*S*)-2e. White crystals: mp 76–77 °C (Et_2O/hexane); 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]; $R_f = 0.16$ ($CHCl_3$/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.

4.1.8. (*S*)-3-(4-Methoxyphenyl)-glutaric acid monoethyl ester (*S*)-2d. White crystals: mp 75–77 °C (Et_2O/hexane; lit. 78[22]); 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] ^1H NMR δ 1.20 (t, $J = 7.2$ Hz, 3H), 2.70–2.90 (m, 4H), 3.53–3.73 (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, 37.3, 41.1, 41.3, 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.

4.1.9. (*S*)-3-Phenylglutaric acid monopropyl ester (*S*)-2e. White crystals: mp 32 °C (Et_2O/hexane); HPLC analysis: [hexane/*i*-PrOH/CH_3COOH; 185:14:1; $\lambda = 226$ nm; 1.0 mL/min; t_R (*S*) = 7.7 min, t_R (*R*) = 8.3 min]; ^1H NMR δ 0.83 (t, $J = 7.6$ Hz, 3H), 1.42–1.63 (m, 2H), 2.54–2.85 (m, 4H), 3.52–3.72 (m, 1H), 3.92 (t, $J = 6.6$ Hz, 2H), 7.12–7.40 (m, 5H), 10.40 (s, 1H); ^{13}C NMR δ 10.6, 22.1, 38.3, 40.6, 40.9, 66.5, 127.3, 127.5, 128.9, 129.0, 142.6, 172.0, 177.9. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.19; H, 7.24.

4.1.10. (*S*)-3-Phenylglutaric acid monobutyl ester (*S*)-2f. White crystals: mp 41–43 °C (Et_2O/hexane); $R_f = 0.39$ ($CHCl_3$/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*) = 7.7 min, t_R (*R*) = 8.2 min]. ^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, 64.4, 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, $[M+Na]^+$, calcd for $C_{15}H_{20}NaO_4$: 287.1254, found (*m*/*z*): 287.1240 (100%).

4.1.11. (*S*)-3-Phenylglutaric acid monobenzyl ester (*S*)-2g. White crystals: mp 85–86 °C (Et_2O/hexane); $R_f = 0.40$ ($CHCl_3$/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 (*R*) = 9.9 min, t_R (*S*) = 10.9 min]; ^1H NMR δ 2.18–2.32 (m, 4H), 3.70 (m, 1H), 5.06 (s, 2H), 7.15–7.40 (m, 10H); ^{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.

Acknowledgment

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

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