184. Stereoselective Hydrolysis of Substituted Cyclopropanedicarboxylates with Pig Liver Esterase

by **Paula Walser, Peter Renold, Victor N'Goka, Fatemeh Hosseinzadeh,** and **Christoph Tamm***

Institut für Organische Chemie der Universität Basel, St. Johanns-Ring 19, CH–4056 Basel

(29.VIII.91)

The hydrolysis of the *meso*-cyclopropane-1,2-dicarboxylates **1a**–**3a**, **4**, **5a**, **6a**, and **9**, containing various substituents at C(3), and of the *rac*-3-phenylcyclopropane-1,2-dicarboxylates **7a**, **8a**, and **10** with pig liver esterase (PLE) is described. The stereoselectivity and absolute configurations of the products were determined. An interpretation of results was attempted on the basis of a recent active-site model for PLE.

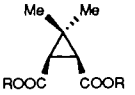
Introduction. – The efficient synthesis of biologically active compounds, either of natural or unnatural origin, frequently requires chiral synthons. Enzymes as chiral catalysts are now widely used for their preparation [1–4], because it often is rather difficult to introduce centres or chirality or perform regiospecific transformations by the application of purely 'chemical methods'. Especially esterases, such as pig liver esterase (PLE, *E.C. 3.1.1.1*), a serine hydrolase, have been studied extensively in recent years [5–8]. We have used PLE successfully in resolving racemic esters [9] and for the preparation of versatile chirons [5] [6] [9] [10]. Stability, low costs, and the ability of hydrolyse a wide range of substrates with high stereoselectivity represent additional advantages of this enzyme which operates without the need for co-enzymes. Until now, more than one hundred different esters, mainly *meso*- and *prochiral*-diesters have been subjected to the treatment with PLE [8]. To be able to fully exploit the potential of this enzyme, it is indispensable to understand the factors which are responsible for the specificity. Accordingly, we as well as other research groups have initiated investigations for securing a large number of data on hydrolyses, allowing to gain more insight into the relationship between substrate structure and enzymic activity of PLE. Until recently, it appeared to be very difficult to reach this goal, not only because the physiological role of PLE is unknown [11], but also because commercially available PLE preparations are mixtures of at least six isoenzymes [12] [13] which, however, were found to exhibit essentially the same stereospecificity [14]. These findings justify the attempt to rationalize the results of the hydrolyses by an active-site model which is mainly based on the measured ee values and the absolute configuration of the hydrolysis products. Several approaches to such a model have been reported [14–18]. The most recent proposal made by *Jones* and coworkers which is based on cubic-space descriptors, is at present the most precise published active-site model [19].

Here, we report on the results of the hydrolysis of a series of structurally related cyclopropane-1,2-carboxylates with PLE. These substrates were chosen for the following reasons: *1*) The cyclopropane ring provides rigidity. Therefore, only one preferred conformation has to be accounted for the analysis of the substrate/active-site interac-

tions. *2*) Cyclopropanedicarboxylates have been studied only rarely inspite of the fact that cyclopropane derivatives have become versatile building blocks for the synthesis of various natural products [20–22]. *3*) Cyclopropane rings also occur as structural elements of natural products, *e.g.* cyclopropaneamino acids [23] [24], cyclopropane fatty acids [25], and steroids [26] [27]. Many mono- and sesquiterpenes contain a cyclopropane ring [25]. *4*) Asymmetric catalytic cyclopropanations of alkenes with carbenoid transition-metal complexes yield excellent ee values.

Results. – Some time ago we reported the hydrolysis of dimethyl cyclopropane-1,2-dicarboxylate (**1a**) and dimethyl 3,3-dimethylcyclopropane-1,2-dicarboxylate (**2a**) showing ee values of 100% and 43%, respectively [15]. We now have repeated the hydrolyses, synthesized the new cyclopropane derivatives **3a**, **4**, **5a**–**8a**, **9**, and **10** and subjected to the hydrolysis with PLE. All substrates have been prepared according to procedures which were described in the literature but had to be modified considerably in order to reach optimal yields. The details are described in the *Exper. Part.* The results of the PLE hydrolyses of the prochiral diesters **1a**–**3a**, **4**, **5a**, **6a**, **9**, and **10** are summarized in *Table 1* and *Scheme 1*. The diesters (1.5–5.5 mmol) were suspended at room temperature in 0.1M phosphate buffer (pH 8) and treated with PLE (500–1000 units) under vigorous stirring.

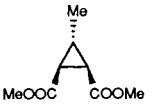
1a



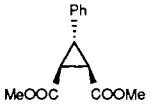
2a R = Me

3a R = Et

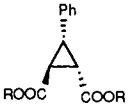
4 R = Pr



5a



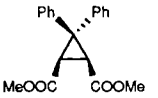
6a



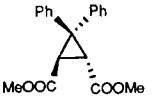
(±)

7a R = Me

8a R = Et



9



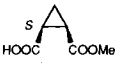
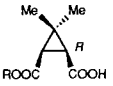
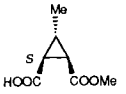
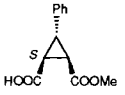
(±)

10

The decreasing pH indicated the course of the hydrolysis. It was adjusted and kept constant to the value of 8 by the continuous addition of 1N NaOH. Only one of the ester groups was cleaved. The reaction was ended after 1 equiv. of base had been consumed. The half-esters formed (*Table 1* and *Scheme 1*) were derivatized with (−)-(*S*)-1-phenylethylamin (*Scheme 2*), the ee values determined on the basis of the ratio of the diastereoisomers of the amides formed, either by ^{1}H-NMR spectroscopy or by GC.

The absolute configuration of the half ester **1b**, which was formed by the hydrolysis of **1a** as only product, as well as of half-ester **2b**, which was the main product obtained from **2a**, was determined by comparison of the values of the optical rotation with known data [15] (*Table 1*). In the case of the hitherto unknown half-esters **5b** and **6b**, we first attempted to prepare crystals of the (−)-(*S*)-1-phenylethyl- and (−)-(*S*)-1-naphthylethyl-

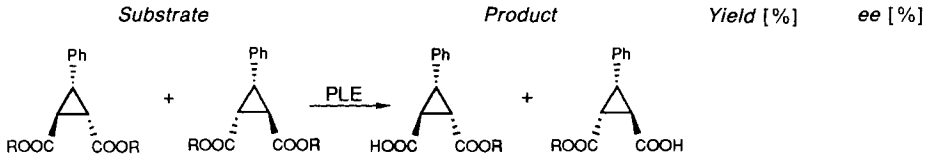
Table 1. *Results of PLE-Catalyzed Hydrolysis of Diesters* **1a–3a, 4, 5a, 6a, 9,** *and* **10**

Substrate	Major product	Yield [%]	$[\alpha]_D$ of half-ester (EtOH)	ee [%]
1a	 **1b**	99	–11.0 ($c = 0.06$)	100
2a	 **2b** R = Me	95	–13.0 ($c = 0.06$)	74[a])
3a	**3b** R = Et	80	-4.6 ($c = 0.06$)	45[a])
4	no hydrolysis			
5a	 **5b**	90	-9.9 ($c = 1$)	91[b])
6a	 **6b**	99	–13.0 ($c = 1$)	88[b])
9	no hydrolysis			
10	no hydrolysis			

[a]) Determined by GC after conversion of the mixture of the enantiomeric half-esters into the mixture of the diastereoisomeric amides with (–)-(*S*)-1-phenylethylamine.

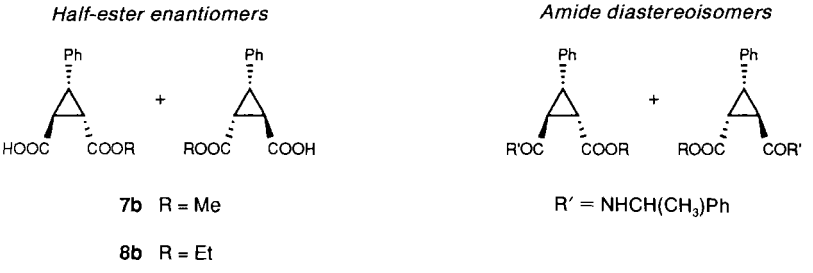
[b]) Determined by ^{1}H-NMR after conversion of the mixture of the enantiomeric half-esters into the mixture of the diastereoisomeric amids with (–)-(*S*)-1-phenylethylamine.

Scheme 1. *PLE-Catalyzed Hydrolysis of the* rac-*Diesters* **7a** *and* **8a**

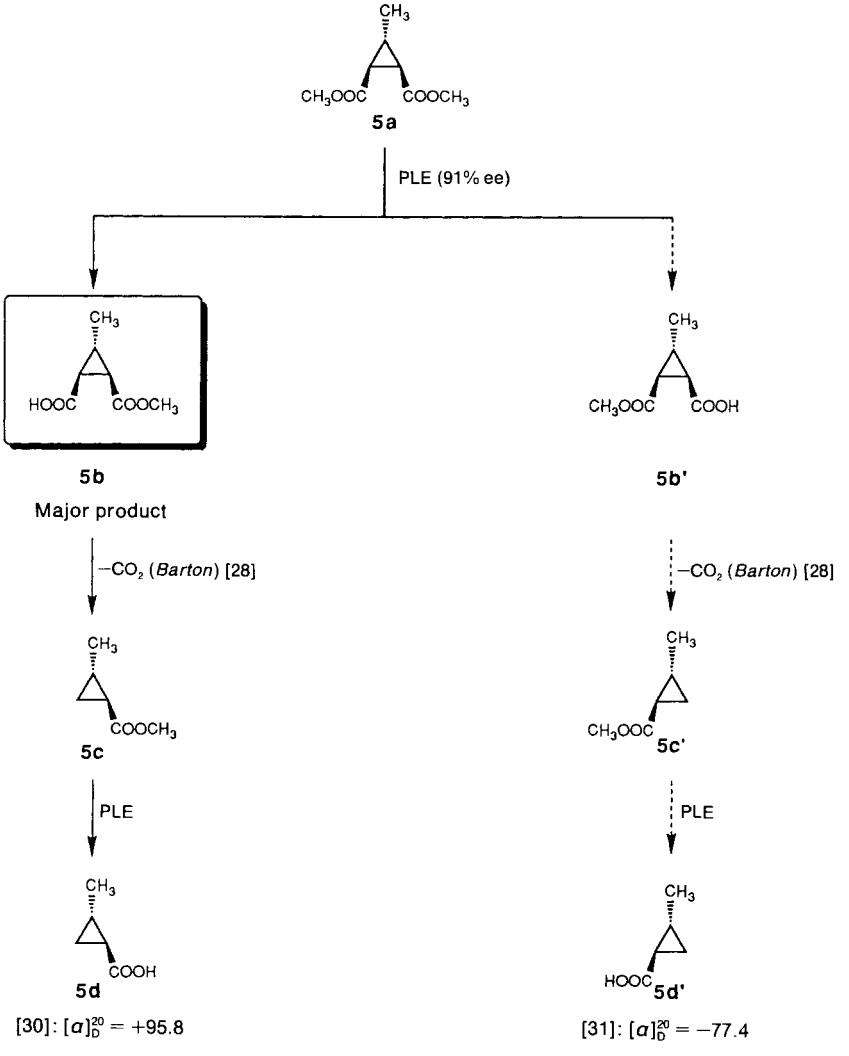


[a]) Determined by GC after conversion of the mixture of the enantiomeric half-esters into the mixture of the diastereoisomeric amides with (–)-(*S*)-phenylethylamine.

Scheme 2. *Derivatization of the Hydrolysis Products* **7b** *and* **8b** *with (−)-(S)-1-Phenylethylamine*

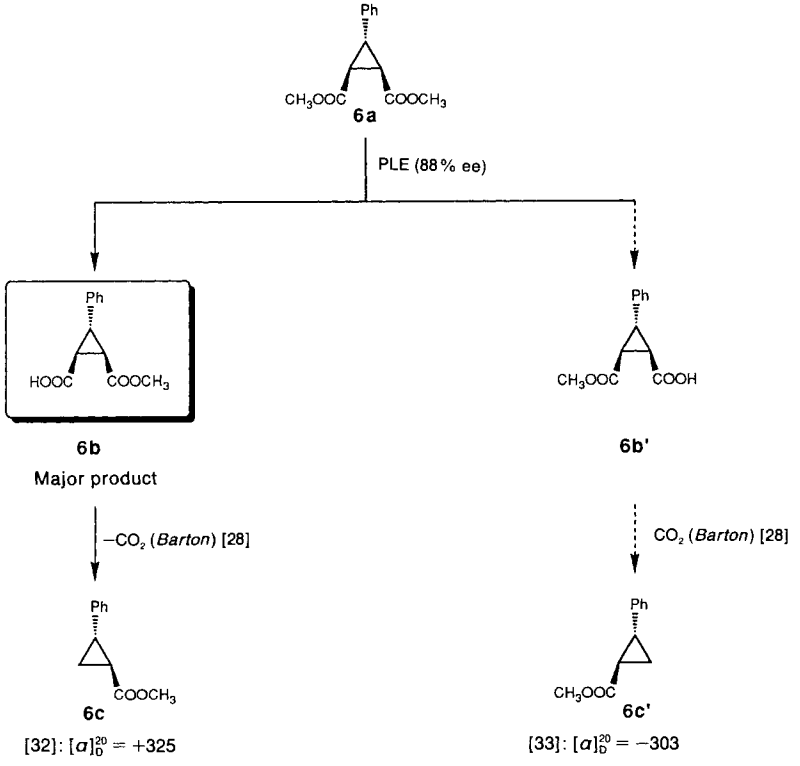


Scheme 3. *Conversion of the Hydrolysis Products of* **5a** (**5b** *and* **5b′**) *to the 2-Methylcyclopropane-1-carboxylic Acids* **5d** *and* **5d′**



amine suitable for X-ray diffraction. The absolute configurations of the hydrolysis products were finally established by the conversion of the half-ester obtained from **5a**, which was either **5b** or the enantiomer **5b'**, into the monoester **5c** or **5c'**, respectively, by a *Barton* decarboxylation [28] [29] (*Scheme 3*). Subsequent treatment of the mono-ester formed with PLE gave a carboxylic acid whose optical rotation clearly indicated that **5d** and not the enantiomer **5d'** had been formed. The absolute configuration of **5d** is known [30]. The major product of the PLE hydrolysis of **6a**, **6b** or **6b'**, was subjected to the same

Scheme 4. *Conversion of the Hydrolysis Products of* **6a** (**6b** *and* **6b'**) *to the Mono-esters* **6c** *and* **6c'**



[32]: $[\alpha]_D^{20} = +325$

[33]: $[\alpha]_D^{20} = -303$

found: $[\alpha]_D^{20} = +302$ ($c = 1.07$, $CHCl_3$)

decarboxylation reaction (*Scheme 4*). The ester obtained was the enantiomer **6c** as established unambiguously by the value and sign of the optical rotation. The absolute configuration of **6c** is known [30]. These results demonstrate very clearly that in both diesters **5a** and **6a** the enzyme hydrolyzes the (*pro-S*)-ester group.

It was possible to determine the relative configuration of the hydrolysis products **7b** and **8b**, which were obtained from the unsymmetrical racemic diesters **7a** and **8a**, respectively, by ^{1}H-NMR (*Scheme 1* and *Table 2*). Comparison of **7a**/**7b** and **8a**/**8b** shows that, in the half-esters **7b** and **8b**, the signals corresponding to the *trans*-MeO and the *trans*-EtO group, respectively, are missing. According to these data, the enzyme hydrolyzes the ester groups which are *trans*-oriented with respect to the 3-Ph group.

Table 2. *^{1}H-NMR Data* (300 MHz, $CDCl_3$) *of Substrates* **7a** *and* **8a** *and Their Hydrolysis Products* **7b** *and* **8b**

7a		**7b**	
H–C(1)		H–C(1)	2.86 (*dd*, J_{trans} = 6.2, 4.7)
H–C(2)	2.4–3.3 (*m*)	H–C(2)	2.69 (*dd*, J_{cis} = 10, J_{trans} = 4.7)
H–C(3)		H–C(3)	3.14 (*dd*, J_{cis} = 10, J_{trans} = 6.3)
cis-CO_2CH_3	3.45 (*s*)	CH_3O	3.50 (*s*)
trans-CO_2CH_3	3.75 (*s*)		
H–C (arom.)	7.20 (*s*, 5 H)	H–C (arom.)	7.2–7.4 (*m*, 5 H)
8a		**8b**	
cis-OCH_2CH_3	0.99 (*t*, *J* = 7)	CH_3CH_2O	1.00 (*t*, *J* = 7)
trans-OCH_2CH_3	1.31 (*t*, *J* = 7)		
H–C(1)	2.84 (*t*, (*dd*), *J* = 6)	H–C(1)	2.86 (*dd*, J_{trans} = 6, J_{trans} = 4.7)
H–C(2)	2.61 (*dd*, J_{cis} = 10, J_{trans} = 5)	H–C(2)	2.67 (*dd*, J_{cis} = 10, J_{trans} = 4.7)
H–C(3)	3.08 (*dd*, J_{cis} = 10, J_{trans} = 5)	H–C(3)	3.13 (*dd*, J_{cis} = 10, J_{trans} = 6)
cis-OCH_2CH_3	3.92 (*q*, *J* = 7)	CH_3CH_2O	3.93 (*q*, *J* = 7)
trans-OCH_2CH_3	4.21 (*q*, *J* = 7)		
H–C (arom.)	7.2–7.3 (*m*, 5 H)	H–C (arom.)	7.2–7.4 (*m*, 5 H)

Discussion. – Our previous investigations [15] have demonstrated that substrates which possess a rigid conformation as *e.g.* in cyclic structures, are in general hydrolyzed by PLE with higher stereoselectivity as the corresponding acyclic analogues. Among all monocyclic systems, the cyclopropane ring shows no flexibility at all due to its structure. In the present study, the influence of substituents of different size at C(3) in cyclopropane-1,2-dicarboxylates was studied. Whereas the hydrolysis of the diester **1a** takes place with 100% stereoselectivity and exclusively the (*pro-S*)-methoxycarbonyl group is attacked by the nucleophilic OH group of the enzyme, the ee values of the *meso*-dicarboxylates **2a**, **5a**, and **6a** are significantly lower. In the dicarboxylate **5a**, which carries a small substituent, namely a Me group at C(3) with *cis*-orientation with respect to both ester functions, also the (*pro-S*)-ester group is hydrolyzed preferentially. In the case of the substrates **2a** and **3a**, the second Me group at C(3) causes a reversal of the PLE stereospecificity. It now is mainly the (*pro-R*)-ester group which undergoes hydrolysis. Similar changes of conformations, which are due to the increasing site of the substituents, have been observed in the past in the case of esters of malonic acid [34], aminoglutaric acid [35–37], and of a series of monocyclic diesters [15] [38]. These results indicate that, in the centre of activity of PLE, two additional binding sites of variable size are present besides both regions which bind the hydrolyzed and the non-hydrolyzed ester groups. The three-dimensional (cubic) active-site model of PLE proposed by *Jones* and coworkers [19] takes these aspects into account (*Fig.*). We summarize briefly the main features, because they are relevant for the interpretation of our results. The catalytically more important region, which is represented by a circle, contains the serine moiety which initiates the hydrolysis by the attack of the C=O group of the ester to be hydrolyzes. The binding regions, which regulate the selectivity of the enzyme, correspond to the four pockets H_L, H_S, P_B, and P_F. Whereas H_L and H_S exhibit a hydrophobic character and interact with aliphatic and aromatic substituents of the substrates, the pockets P_B and P_F accept the polar groups. P_F binds primarily *e.g.* the non-hydrolyzed ester group. An ester, to be a substrate, must be able to fit into those regions appropriately, with polar and

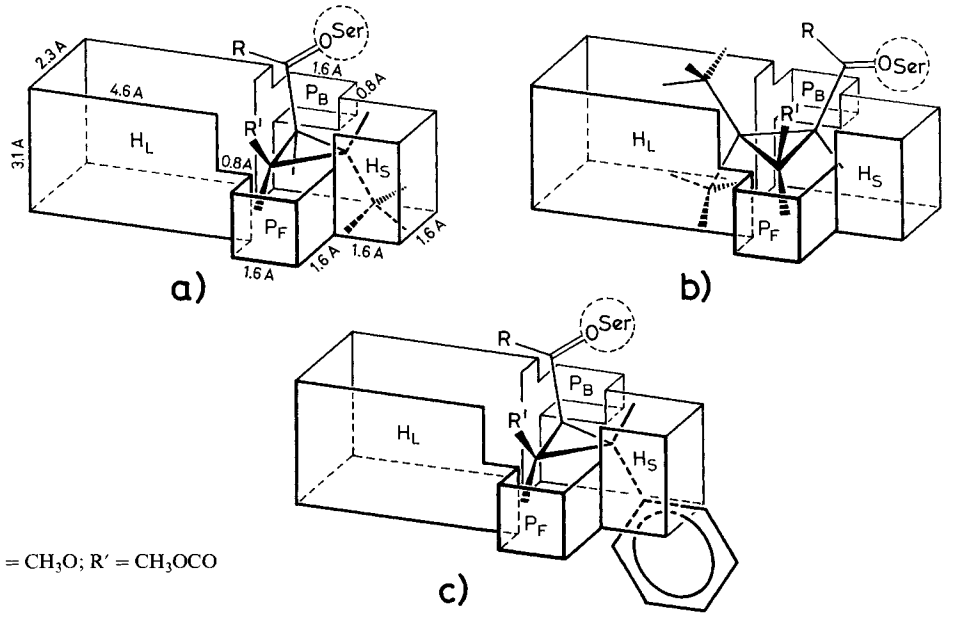


Figure. *Cubic active-site models according to* Jones *and coworkers* [19] *for the* meso-*cyclopropane-1,2-dicarboxylates* a) **5a**, b) **2a**, *and* c) **6a**

hydrophobic moieties binding into complementary sites. The stereoselectivity-determing factor is whether or not a hydrophobic group fits into H_S or H_L.

The results of the hydrolyses of the substrates **1a**, **2a**, and **5a**, as well as of the diesters **9** and **10**, which did not undergoe hydrolysis due to the large steric hindrance by both Ph groups at C(3), are compatible with the *Jones* active-site model (*Fig.*, *a* and *b*). However, regarding the configuration of the hydrolysis products of **6a** and the racemic diesters **7a** and **8a**, the results are not in agreement with the model. In the case of **6a**, one expects according to the model, that the 3-Ph moiety which is to large for the enzyme binding region H_S (*cf. Fig.*, *c*) is bound by the other hydrophobic pocket H_L. Consequently, the (*pro-R*)-ester group should have been hydrolyzed. However, according to the experimental results, it is the (*pro-S*)-group which undergoes preferentially hydrolysis, even with 91% ee. Concerning the substrates **7a** and **8a**, the ester groups, *cis*-oriented with respect to the Ph substituent, were expected to be hydrolyzed according to the model. However, very clearly the ester groups in the *trans*-position are attacked. It is important to note that PLE does not distinguish between the enantiomers of **7a** and **8a**. Both are hydrolyzed, but only the *trans*-oriented groups as pointed out already. We, therefore, are developing a modified active-site model for PLE which will also be compatible with the unexpected results mentioned.

A final remark concerns the substrates **2a**, **3a**, and **4**. It was the aim of these experiments to investigate the impact of larger alkyl rests in the ester groups on the stereoselectivity of PLE. Only the dimethyl ester **2a** is hydrolyzed with relatively high stereoselectivity (ee value 74%). The homologous diethyl ester **3a** represents a worse substrate (ee value

45%) and the dipropyl ester **4** is not converted at all. These findings fully agree with the results of the hydrolysis of other substrates [39]. Also in those cases, mainly the dimethyl esters are the best substrates for the PLE hydrolysis.

We are grateful to the *Swiss National Science Foundation* and to *Ciba-Geigy AG*, Basel, for the financial support of these investigations.

Experimental Part

1. *General.* H_2O-sensitive reactions were carried out under Ar or N_2. All solvents were distilled before use and dried whenever necessary. THF was passed through basic Al_2O_3 and freshly distilled over $LiAlH_4$ before use. All org. extracts were dried over Na_2SO_4 and the solvents removed under vacuum (*ca.* 14 Torr) at or below 40°. Solvent mixtures are indicated as *v/v* percentages. Pig liver esterase (E.C. 3.1.1.1): *Boehringer* (suspension in $(NH_4)_2SO_4$ buffer pH 6.0, 1 mg/ml). TLC: silica gel *60* F_{254} (*Merck*), detection under UV light and/or developed with an aq. soln. of 2% $KMnO_4$ and 4% Na_2CO_3. Silica gel *60* (0.043–0.063 μm; *Merck*) was used for column chromatography (CC). Anal. GC: an *HP 5890 A* gas chromatograph equipped with a 'fused-silica'-capillary (25 m × 0.2 mm) coated with a 0.33-μm 5% cross-linked (phenylmethyl)silicon layer was used. A 10% *OV-17/Chromosorb P* column was used for prep. GC. M.p. were determined on a *Kofler* block and are corrected. Optical rotations and IR (cm^{-1}) were measured with a *Perkin-Elmer* model *141* polarimeter and a *Perkin-Elmer* model *781* spectrophotometer, respectively. The 60-MHz ^{1}H-NMR spectra were recorded with a *Varian EM 360* spectrometer, the 90-MHz ^{1}H-NMR and 22.63-MHz ^{13}C-NMR spectra on a *Bruker WH-90* spectrometer with *Fourier* transform, respectively. The 300-MHz ^{1}H-NMR spectra were recorded with a *Varian-Gemini 300* spectrometer and the 400-MHz ^{1}H-NMR and the 101-MHz ^{13}C-NMR spectra on a *Varian VXR-400* spectrometer with *Fourier* transform. Chemical shifts are reported in ppm downfield from internal TMS. The MS were obtained using a *VG-70-250* spectrometer.

2. *Preparation of Diesters* **1a**–**10**. *Dimethyl* meso-*Cyclopropane-1,2-dicarboxylate* (**1a**). *cis*-cyclopropane-1,2-dicarboxylic anhydride was prepared from commercial (*Aldrich*) diethyl cyclopropane-1,2-dicarboxylate (*cis/trans*-mixture) following the procedure of *McCoy* [40]. The anhydride was first refluxed in MeOH, and the product obtained was then esterified with CH_2N_2 in Et_2O. The diester obtained was purified by prep. GC. ^{1}H-NMR (60 MHz, $CDCl_3$): 0.9–2.2 (*m*, H–C(1), H–C(2), 2 H–C(3)); 3.65 (*s*, 2 CH_3CO_2). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 11.7, 21.4 (C(1), C(2), C(3)); 52.0 (2 CH_3); 170.3 (2 CO).

Dimethyl meso-*3,3-Dimethylcyclopropane-1,2-dicarboxylate* (**2a**). Compound **2a** was prepared according to the method of *Babler* and *Haack* [41]. 3,3-Dimethylglutaric acid was dissolved in abs. MeOH/toluene 1:1. A catalytic amount of conc. H_2SO_4 was added and the soln. stirred at r.t. for 24 h. Dimethyl 3,3-dimethylglutarate was obtained in quant. yield and dissolved in abs. THF. 2.5 equiv. LiN(i-Pr)$_2$ (LDA) soln. was prepared in THF and cooled to −78°. The dimethyl ester soln. was added to the LDA soln. which warmed up to 0° in 3 h. The mixture was again cooled to −78°, and 2 equiv. of AgCl were added in portions. After 1 h, the mixture was brought to r.t. and stirred for 15 h. The org. phase was first washed with 2M HCl followed by H_2O and then with sat. NaCl soln. The soln. was dried and the solvent removed to give a mixture of *cis/trans*-diastereoisomers of **2a** in 70% total yield. The required *cis*-diastereoisomer was separated from the mixture by a FC using pentane/Et_2O 20:1. The purified oil contained 4% of the *trans*-diastereoisomer. IR (film): 3040; 3000 (cyclopropane C–H); 2960; 2880; 1740 (CO). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.22 (CH_3); 1.4 (*s*, CH_3–C(3)); 1.87 (*s*, H–C(1), H–C(2)); 3.68 (*s*, 2 CH_3CO_2). ^{13}C-NMR (101 MHz, $CDCl_3$): 15.5 (CH_3–C(3)); 26.0 (C(3)); 28.0 (CH_3–C(3)); 31.9 (C(1), C(2)); 51.7 (2 CH_3O); 169.6 (2 CO). EI-MS (70 eV): 155 (18, $[M - CH_3O]^+$), 127 (100, $[M - CO_2CH_3]^+$), 111 (11), 95 (57), 83 (13), 67 (47), 55 (28), 41 (33, $[C_3H_5]^+$).

Diethyl meso-*3,3-Dimethylcyclopropane-1,2-dicarboxylate* (**3a**). The diester **3a** (an oil) was prepared by an analogous procedure as **2a** from diethyl-3,3-dimethylglutarate. The starting compound was prepared by the esterification of 3,3-dimethylglutaric acid in EtOH/toluene with catalytic amount of conc. H_2SO_4. IR (film): 3050; 3030; 3000 (cyclopropane C–H); 2960; 2940; 2880; 2850; 1730 (CO). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.23 (*s*, CH_3–C(3)); 1.26 (*t*, $J = 7$, 2 CH_3CH_2); 1.38 (*s*, CH_3–C(3)); 1.86 (*s*, H–C(1), H–C(2)); 4.15 (*q*, $J = 7$, 2 CH_3CH_2O). ^{13}C-NMR (101 MHz, $CDCl_3$): 14.2 (CH_3CH_2); 15.5 (CH_3–C(3)); 25.9 (C(3)); 28.1 (CH_3–C(3)); 32.0 (C(1), C(2)); 60.5 (2 CH_3CH_2O); 169.2 (2 CO). EI-MS (70 eV): 155 (19), 127 (100), 111 (4), 95 (53), 83 (2), 67 (36), 55 (6), 41 (17). CI-MS (NH_3): 204 (80, $[M + NH_4]^+$), 187 (4, $[M + H]^+$), 172 (16), 155 (28), 127 (100), 95 (17), 85 (5), 73 (10), 67 (3).

Dipropyl meso-*3,3-Dimethylcyclopropane-1,2-dicarboxylate* (**4**). The procedure was analogous to the preparation of **2a** and **3a** starting from dipropyl 3,3-dimethylglutarate. Oil. IR (film): 2975; 2940; 2890; 1740 (CO). ^{1}H-NMR (90 MHz, $CDCl_3$): 0.93 (*t*, *J* = 7, 2 $CH_3CH_2CH_2$); 1.21 (*s*, 2 CH_3–C(3)); 1.61 (*m*, *J* = 7, 2 $CH_3CH_2CH_2O$); 1.87 (*s*, 2 H–C(1), H–C(2)); 4.00 (*t*, *J* = 7, 2 $CH_3CH_2CH_2O$). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 10.4 (*q*, 2 $CH_3CH_2CH_2O$); 15.6 (*q*, CH_3–C(3)); 22.1 (*t*, 2 $CH_3CH_2CH_2O$); 25.8 (*s*, C(3)); 28.1 (*q*, CH_3–C(3)); 32.2 (2*d*, C(1), C(2)); 66.2 (*t*, $CH_3CH_2CH_2O$); 169 (*s*, 2 CO). EI-MS (70 eV): 183 (18), 155 (52), 141 (18), 113 (100), 95 (20), 67 (12), 59 (6), 53 (5), 43 (48). CI-MS (NH_3): 260 (100, $[M + NH_4]^+$), 243 (9, $[M + H]^+$), 217 (6), 200 (9), 183 (4), 155 (11).

Dimethyl meso-*3-Methylcyclopropane-1,2-dicarboxylate* (**5a**). Compound **5a** was synthesized by the same procedure as **2a**. 3-Methylglutaric acid was esterified in MeOH in the presence of a catalytic amount of acid. Dimethyl 3-methylglutarate was dissolved in abs. THF and slowly added to a precooled soln. of 2 equiv. LDA soln. at –78°. Then, 2 equiv. of AgCl was added: **5a** (an oil) was obtained in 75% yield after column chromatography. Only traces of *cis*/*cis* and *trans*/*trans*-isomers were detected. IR (film): 2990; 2940; 2880; 1740 (2 × CO). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.19 (*d*, *J* = 6, CH_3–C(3)); 1.84 (*d*, *J* = 6, H–C(1), H–C(2)); 2.02 (*m*, H–C(3)); 3.69 (*s*, 2 CO_2CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$): 16.8 (CH_3–C(3)); 20.6 (C(3)); 29.2 (C(1), C(2)); 52.1 (2 CH_3O); 170.3 (2 CO_2). EI-MS (70 eV): 141 (28, $[M - CH_3O]^+$), 113 (100, $[M - CO_2CH_3]^+$), 85 (10), 81 (33, $[M - CO_2CH_3 - CH_3O]^+$), 71 (7), 53 (29, $[M - 2\,CO_2CH_3]^+$), 39 (17). CI-MS (NH_3): 190 (1.5, $[M + NH_4]^+$), 173 (100, $[M + H]^+$), 158 (22), 141 (32), 126 (12), 113 (46), 85 (4), 81 (8).

Dimethyl meso-*3-Phenylcyclopropane-1,2-dicarboxylate* (**6a**). 3-Phenylglutaric acid was dissolved in abs. MeOH/toluene 1:1. Few drops of conc. H_2SO_4 were added and the soln. was stirred at r.t. for 24 h. Dimethyl 3-phenylglutarate was obtained in quant. yield. From this, **6a** was obtained as described for **2a** and **3a**. Compound **6a** was purified by silica column chromatography using pentane/Et_2O 10:1 followed by crystallization in cyclohexane (60% yield). M.p. 40–42°. IR (film): 3025–3085; 3000; 2960; 1745 (CO). ^{1}H-NMR (400 MHz, $CDCl_3$): 2.40 (*d*, *J* = 6, H–C(1), H–C(2)); 3.18 (*t*, *J* = 6, H–C(3)); 3.74 (*s*, 2 CO_2CH_3); 7.10–7.35 (*m*, 5 arom. H). ^{13}C-NMR (101 MHz, $CDCl_3$): 29.5 (C(3)); 30.0 (C(1), C(2)); 52.3 (2 CH_3O); 126.5, 127.2, 128.7, 137.5 (6 arom. C); 169.5 (2 CO). EI-MS (70 eV): 234 (2, M^+), 203 (6, $[M - CH_3O]^+$), 175 (49, $[M - CO_2CH_3]^+$), 147 (5), 131 (6), 121 (24), 115 (100, $[M - 2\,CO_2CH_3]^+$), 91 (10, $[C_3H_7]^+$), 77 (8), 63 (5), 59 (16, $[CO_2CH_3]^+$), 51 (6), 39 (6, $[C_3H_3]^+$). CI-MS (NH_3): 252 (2, $[M + NH_4]^+$), 235 (100, $[M + H]^+$), 220 (7), 203 (4), 175 (8), 115 (6).

Diethyl (*1*RS,*2*RS,*3*RS)-*3-Phenylcyclopropane-1,2-dicarboxylate* (**8a**). Diethyl cinnamate (10 ml, 60 mmol) was heated to 175°. A mixture of 28 g (160 mmol) diethyl cinnamate and 20 g (140 mmol) ethyl diazoacetate was prepared and added to the above hot soln. [42]. The oil-bath temp. was increased to 195° and the reaction mixture heated for 12 h. The soln. was cooled to r.t. and then distilled under vacuum. At 134° (0.2 Torr), the mixture of *cis,cis*-, *trans,trans*-, and *cis,trans*-dimethyl 3-phenylcyclopropane-1,2-dicarboxylate isomers was distilled off in 55% yield. The isomeric mixture was twice separated over silica using petroleum ether/AcOEt 95:5: **8a** in 18% yield. $[\alpha]_D^{23} = 0$. IR (film): 3060; 3030; 2980; 2930; 2910; 1725; 1605; 1445; 1370; 1300; 1175; 1090; 1055; 1035; 855; 770; 745; 690. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.99 (*t*, *J* = 7, *cis*-OCH_2CH_3); 1.31 (*t*, *J* = 7, *trans*-OCH_2CH_3); 2.61 (*dd*, $J_{trans} = 10$, $J_{cis} = 5$, CH(1)); 2.84 (*t*, *dd*, *J* = 6, H–C(2)); 3.08 (*dd*, $J_{trans} = 10$, $J_{cis} = 5$, H–C(3)); 3.92 (*q*, *J* = 7, *cis*-OCH_2CH_3); 4.21 (*q*, *J* = 7, *trans*-OCH_2CH_3); 7.2–7.3 (*m*, 5 arom. H).

Dimethyl (*1*RS,*2*RS,*3*RS)-*3-Phenylcyclopropane-1,2-dicarboxylate* (**7a**). Compound **8a** was refluxed for 3 h in 3N HCl to produce quantitatively the corresponding acid mixture. The dicarboxylic acid was extracted with AcOEt. The org. phase was washed with 2N NaOH soln. The aq. phase, after acidifying with HCl, was re-extracted with AcOEt. The org. phase was dried ($CaCl_2$) and the solvent removed. Pure (±)-*trans*-3-phenylcyclopropane-1,2-dicarboxylic acid was obtained in 93% yield. M.p. 172°. The dicarboxylic acid was esterified in MeOH with a few drops of conc. H_2SO_4 to give **7a**. Yield: 96%. $[\alpha]_D^{23} = 0$ ($CHCl_3$). M.p. 83°. IR (KBr): 3065; 3010; 2960; 1720; 1435; 1360; 1305; 1285; 1195; 1170; 1015; 895; 880; 805; 775; 745; 690; 650. ^{1}H-NMR (60 MHz, $CDCl_3$): 2.4–3.3 (*m*, H–C(1), H–C(2), H–C(3)); 3.45 (*s*, *cis*-OCH_3); 3.75 (*s*, *trans*-OCH_3); 7.20 (*s*, 5 arom. H).

Dimethyl meso-*3,3-Diphenylcyclopropane-1,2-dicarboxylate* (**9**). Benzophenone hydrazone reacted with 2-chloroperbenzoic acid, a procedure by *van Alphen* [43], to give 80% Ph_2CN_2. It was then dissolved in a petroleum ether/Et_2O 3:2. To this soln., 1 equiv. of maleic anhydride was added in small portions, and the mixture was cooled to 0°. After 15 min, the cooling trap was removed, when evolution of gas (N_2) started. After 30 min, precipitation started. When it was complete the precipitate was filtered and washed for several times with ether. The product obtained, 1,2-didehydro-5,5-diphenylpyrazolin-3,4-dicarboxylic anhydride (74% yield), was dried and dissolved in abs. toluene and kept for 12 h at 80–90°. The solvent was removed, the residue washed with Et_2O and dissolved in MeOH. Some drops of conc. H_2SO_4 were added, and the mixture was refluxed for 10 h. The obtained diester **9** was then chromatographed over silica using petroleum ether/Et_2O 2:1. Total yield: 46.8%. M.p. 74–75.5° ([43]: M.p. 72°). IR (KBr): 3040–3100; 2900–3000; 1780, 1760 (CO ester). ^{1}H-NMR (60 MHz, $CDCl_3$): 2.75 (*s*, H–C(1),

H–C(2)); 3.5 (*s*, 2 CO_2CH_3); 7.1–7.35 (*m*, 10 arom. H). ^{13}C-NMR (101 MHz, $CDCl_3$): 32.0 (C(1), C(2)); 43.9 (C(3)); 52.0 (2 C, 2 CH_3O); 127.2, 127.5, 127.8, 128.1, 130.4, 145.3 (arom. C); 168.5 (2 CO). EI-MS (70 eV): 250, 191 (100), 165, 115, 105, 77, 59, 51. CI-MS (NH_3): 328 ($[M + NH_4]^+$), 311 (100, $[M + H]^+$), 279, 250, 191, 165.

Dimethyl (1RS,2RS)-3,3-Diphenylcyclopropane-1,2-dicarboxylate (**10**). A soln. of Ph_2CN_2 (see procedure for **9**) in petroleum ether/Et_2O 3:2 was prepared. To this soln., 1.2 equiv. dimethyl fumarate (or dimethyl maleate) were added and stirred at r.t. for 8 h. After some time, the mixture became bright, and simultaneously a precipitate had settled. The solvent was removed and the colorless residue washed with MeOH. Then, it was dissolved in toluene and refluxed for 20 h, when N_2 was evolved to give **10**. The diester (an oil) was purified by chromatography over silica gel. Total yield: 25%. M.p. 176.3–177° ([43]: M.p. 158°). IR (KBr): 3060–3080; 3000–3040; 2960; 1730; 1485; 1340; 1160. ^{1}H-NMR (60 MHz, $CDCl_3$): 3.3 (*s*, H–C(1), H–C(2)); 3.5 (*s*, 2 CH_3O); 7.15–7.4 (*m*, 10 H). ^{13}C-NMR (101 MHz, $CDCl_3$): 32.1 (C(1), C(2)); 47.0 (C(3)); 52.0 (2 CH_3O); 127.3, 128.5, 128.6, 140.1 (arom. C); 169.1 (2 CO). EI-MS (70 eV): 250, 218, 191 (100), 165, 115, 105, 89, 77, 59, 51, 39. CI-MS (NH_3): 328 ($[M + NH_4]^+$), 311 ($[M + H]^+$), 279, 250, 218, 191, 165, 115.

3. *General Procedure for PLE-Catalyzed Hydrolysis of Diesters* **1a–3a** *and* **5a–8a** *to the Corresponding Half-esters.* To 10 mmol of the diester suspended in 50 ml of 0.1M phosphate buffer (pH 8.0) were added at r.t. 500 units of PLE (*ca.* 1.5 ml of the PLE suspension, see *General*) with vigorous stirring. The pH value was kept within the 7.5–8.0 range by addition of 1M NaOH. After consumption of 1 equiv. of base, the reaction was stopped by adjusting pH at 9. The unreacted diester was recovered by extracting with Et_2O. The half-ester was obtained as follows: the aq. soln. was acidified to pH 2.5 and extracted with Et_2O. The org. phase was washed with H_2O followed by sat. NaCl soln. It was then dried and solvent removed.

(1S,2R)-2-(Methoxycarbonyl)cyclopropane-1-carboxylic Acid (**1b**). Yield 92%. $[\alpha]_D^{23} = -11.2$ (*c* = 7, EtOH). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.1–1.55 (*m*, H–C(3)); 1.55–1.9 (*m*, H–C(3)); 1.95–2.4 (*m*, H–C(1), H–C(2)); 3.7 (*s*, CO_2CH_3); 11.0 (*s*, CO_2H).

(1R,3S)-3-(Methoxycarbonyl)-2,2-dimethylcyclopropane-1-carboxylic Acid (**2b**). Yield 95%. $[\alpha]_D^{23} = -13.0 \pm 2$ (*c* = 0.06, EtOH). Oil. IR (film): 2500–3500 (CO_2H); 1740 (CO ester); 1715 (CO acid). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.3 (*s*, CH_3–C(3)); 1.4 (*s*, CH_3–C(3)); 1.96 (*d*, *J* = 9, CH); 2.02 (*d*, *J* = 9, CH); 3.76 (*s*, CO_2CH_3); 7.4–8.8 (br., CO_2H). ^{13}C-NMR (101 MHz, $CDCl_3$): 15.3 (CH_3–C(3)); 27.6 (C(3)); 28.3 (CH_3–C(3)); 32.7 (C(2)); 33.6 (C(1)); 52.6 (CH_3O); 172.1 (CO); 172.7 (CO). EI-MS (70 eV): 155 (1, $[M - OH]^+$), 141 (25, $[M - CH_3O]^+$), 127 (83, $[M - CO_2H]^+$), 113 (100, $[M - CO_2CH_3]^+$), 95 (82, $[M - CO_2CH_3 - H_2O]^+$), 85 (6), 81 (8), 73 (22), 67 (91), 59 (30), 55 (22), 51 (8), 41 (79). CI-MS (NH_3): 190 (6, $[M + NH_4]^+$), 173 (100, $[M + H]^+$), 155 (14), 127 (12), 95 (5), 73 (2), 67 (3).

(1R,3S)-3-(Ethoxycarbonyl)-2,2-dimethylcyclopropane-1-carboxylic Acid (**3b**). Yield 80%. $[\alpha]_D^{23} = -4.6 \pm 2$ (*c* = 0.06, EtOH). Oil. IR (film): 2550–3500 (br. COOH); 2980; 2880; 1700–1750 (CO ester and acid). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.29 (*t*, *J* = 7, CH_3CH_2O); 1.3 (*s*, CH_3–C(3)); 1.39 (*s*, CH_3–C(3)); 1.94 (*d*, *J* = 9, CH); 2.00 (*d*, *J* = 9, CH); 4.20 (*q*, *J* = 7, CH_3CH_2O); 7.6–8.40 (br., OH). ^{13}C-NMR (101 MHz, $CDCl_3$): 14.1 (CH_3CH_2O); 15.3 (CH_3–C(3)); 27.5 (C(3)); 28.3 (CH_3–C(3)); 32.9 (C(2)); 33.5 (C(1)); 61.7 (CH_3CH_2O); 171.7 (CO); 173.0 (CO). EI-MS (70 eV): 141 (44, $[M - CO_2H]^+$), 128 (4), 113 (100, $[M - CO_2C_2H_5]^+$), 95 (52), 87 (10), 67 (50), 59 (18), 53 (22), 43 (71), 39 (29). CI-MS (NH_3): 204 (9, $[M + NH_4]^+$), 187 (100, $[M + H]^+$), 171 (15), 158 (10), 144 (7), 126 (7), 112 (3), 96 (8), 58 (4), 44 (8).

(1S,2R,3R)-2-(Methoxycarbonyl)-3-methylcyclopropane-1-carboxylic Acid (**5b**). Yield 90%. $[\alpha]_D^{23} = -9.9 \pm 2$ (*c* = 1, EtOH). Oil. IR (film): 2550–3500 (several, br., COOH); 2970; 1710–1750 (CO ester and acid). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.20 (*d*, *J* = 6, CH_3–C(3)); 1.80–1.95 (2*dd*, *J* = 9, 6, H–C(1), H–C(2)); 2.05 (*m*, H–C(3)); 3.70 (*s*, CO_2CH_3); 8.10 (br., OH). ^{13}C-NMR (101 MHz, $CDCl_3$): 16.9 (CH_3–C(3)); 21.8 (C(3)); 29.3 (C(2)); 30.1 (C(1)); 52.4 (CH_3O); 170.8 (CO_2CH_3); 175.1 (CO_2H). EI-MS (70 eV): 141 (2, $[M - OH]^+$), 127 (44, $[M - CH_3O]^+$), 113 (78, $[M - CO_2H]^+$), 99 (100, $[M - CO_2CH_3]^+$), 81 (32), 71 (11), 59 (39), 43 (49, $[C_3H_7]^+$), 39 (27, $[C_3H_3]^+$). CI-MS (NH_3): 176 (18, $[M + NH_4]^+$), 159 (100, $[M + H]^+$), 141 (17), 126 (6), 113 (12).

(1S,2R,3R)-2-(Methoxycarbonyl)-3-phenylcyclopropane-1-carboxylic Acid (**6b**). Yield 99%. M.p. 90–92°. $[\alpha]_D^{23} = -13 \pm 2$. IR (film): 2800–3550 (CO_2H); 3040; 3010; 2965; 1740 (CO acid); 1695 (CO ester); 1610; 1590. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.41–2.28 (2 *dd*, *J* = 10, 6, H–C(1), H–C(2)); 3.21 (*dd*, H–C(3)); 3.76 (*s*, CO_2CH_3); 7.1–7.35 (*m*, 5 arom. H); 9.23 (*s*, CO_2H). ^{13}C-NMR (101 MHz, $CDCl_3$): 30.0 (C(3)); 30.3 (C(2)); 30.6 (C(1)); 5.26 (CH_3O); 126.6, 127.5, 128.8, 137.0 (arom. C); 169.7 (CO_2CH_3); 174.6 (CO_2H). EI-MS (70 eV): 220 (8, M^+), 188 (8, $[M - CH_3OH]^+$), 175 (28, $[M - CO_2H]^+$), 161 (21, $[M - CO_2CH_3]^+$), 144 (22), 133 (17), 115 (100), 103 (7), 91 (15), 59 (13), 51 (10), 39 (10). CI-MS (NH_3): 238 (18, $[M + NH_4]^+$), 221 (100, $[M + H]^+$), 203 (7), 175 (10), 144 (9), 115 (18).

(1RS,2SR,3SR)-2-(Methoxycarbonyl)-3-phenylcyclopropane-1-carboxylic Acid (**7b**). Yield 99%. M.p. 128°. IR (film): 2400–3600 (COOH); 1740 (CO acid); 1690 (CO ester); 1470; 1440. ^{1}H-NMR: see *Table 2*. EI-MS (70

eV): 220 (4.7, M^+), 188 (5.1, $[M - CH_3OH]^+$), 175 (22.6, $[M - CO_2H]^+$), 161 (17.4), 144 (17.7), 133 (14.7), 115 (100), 105 (5.6), 91 (14.3), 77 (13.3), 59 (11.2), 51 (10.2), 45 (4.1), 39 (12.0). CI-MS (NH_3): 238 (59.9, $[M + NH_4]^+$), 221 (40.8, $[M + H]^+$), 203 (12, $[M - OH]^+$), 188 (11.1, $[M - CH_3OH]^+$), 175 (47.5, $[M - CO_2H]^+$), 160 (11.7), 144 (32.7), 133 (12.0), 115 (100), 105 (6.9), 91 (16.0), 78 (3.0), 63 (3.7), 39 (3.6).

(1RS,2SR,3SR)-2-(Ethoxycarbonyl)-3-phenylcyclopropane-1-carboxylic Acid (**8b**). Yield 90%. M.p. 80°. IR (film): 2400–3600 (COOH); 1735 (CO acid); 1690 (CO ester); 1460; 1443. ^{1}H-NMR: see *Table 2*. EI-MS (70 eV): 234 (5.3, M^+), 189 (34.1, $[M - OCH_2CH_3]^+$), 161 (24.2), 144 (13.8), 133 (33.2), 115 (100), 105 (8.5), 91 (12.6), 77 (11.7), 63 (7.6), 51 (7.7), 39 (9.1). CI-MS (NH_3): 252 (100, $[M + NH_4]^+$), 235 (94.99, $[M + H]^+$), 219 (7.9, $[M - CH_3]^+$), 206 (4.2, $[M + 1 - CH_2CH_3]^+$), 189 (27.7, $[M - OCH_2CH_3]^+$), 177 (8.3), 160 (10.6), 144 (13.8), 133 (10.6), 115 (40.0), 105 (3.8), 91 (7.4), 44 (8.0).

4. *General Procedure for the Derivatization of 2-(Alkoxycarbonyl)cyclopropanecarboxylic Acids* (**1b–3b** and **5b–8b**) *with (–)-(S)-1-Phenylethylamine.* A soln. of 1 equiv. of half-ester, 1.2 equiv. of 2-chloro-1-methylpyridinium iodide, 2.4 equiv. of Et_3N, and 1.2 equiv. of (–)-(*S*)-1-phenylethylamine in abs. CH_2Cl_2 was prepared. It was refluxed (with simultaneous stirring) for 2 h. The mixture was added to H_2O and extracted with small portions of Et_2O. The org. phase was washed with 1M HCl, followed by a 5% $NaHSO_4$ and a sat. $Na_2S_2O_3$ soln. After drying and removing of the solvent, the amide (mostly oil) was obtained. The purity was checked and the ee value determined by GC.

5. *Conversion of* **5b** *to (1S,2S)-2-Methylcyclopropanecarboxylic Acid* (**5d**). 5.1. *Decarboxylation of* **5b** *to Methyl (1S,2S)-2-Methylcyclopropanecarboxylate* (**5c**). To a soln. of **5b** in dry THF, under Ar at –15°, 1 equiv. each of *N*-methylmorpholine and isobutyl chloroformate were dropwise added, and stirred for 5 min. A soln. of 1.2 equiv. of *N*-hydroxy-2-thiopyridone and Et_3N was prepared in appropriate amount of dry THF and was added to the mixture in dark. The stirring continued at –15° for another 2 h in dark, and the precipitated *N*-methylmorpholine hydrochloride was filtered off. To the yellow filtrate, 2.3 equiv. of *t*-BuSH were added and the mixture was irradiated with a high-pressure Hg lamp for 30 min r.t. Et_2O was added to the mixture. This soln. was first washed with 0.1N $NaHCO_3$ soln., followed by H_2O, 0.5N HCl, and again H_2O and sat. NaCl soln. The org. phase was dried (Na_2SO_4) and most of the solvent removed under vacuum at r.t. The residue was further distilled, and the volatile fraction was collected in a cooling trap at 30 Torr and bath temp. till 100°. The condensate was analyzed by GC/MS and was found to be a mixture of **5c**, ether, and THF. It was directly used for PLE hydrolysis.

5.2. *PLE Hydrolysis of* **5c**. The above condensate containing **5c** was emulsified in a 0.1M phosphate buffer at pH 7 and stirred with an appropriate amount of PLE suspension (see *General Procedure* for PLE hydrolysis). The pH of the soln. was maintained at 7 by addition of 0.1N NaOH soln. After completion of the hydrolysis, the pH of the soln. was increased to 9, and the reaction mixture was thrice extracted with Et_2O. The aq. phase was acidified till pH 2 and extracted with Et_2O. The combined Et_2O extracts was washed with sat. NaCl soln., dried (Na_2SO_4), and the solvent was removed to obtain a colorless oil. GC of the oil showed that it contained 80% of **5d**. Yield: 30%. For characterization, part of the product was purified by bulb-tube distillation (110°/25 Torr). $[\alpha]_D^{25} = +97.3$ ($c = 0.54$, EtOH. IR (film): 3450–2500 (COOH); 1695 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.74 (*m*, H–C(1)); 1.12 (*d*, $J = 6.0$, CH_3–C(2)); 1.24, 1.33 (*m*, 2 H–C(3)); 1.44 (*m*, H–C(2)); 8.9 (br. *s*, COOH). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.54, 17.82, 18.23 (CH_3–C(2), C(2), C(3)); 21.18 (C(1)); 180.90 (COOH). EI-MS (70 eV): 100 (54, M^+), 82 (22), 55 (100, $[M - CO_2H]^+$).

6. *Decarboxylation of* **6b** *to Methyl (1S,2S)-2-Phenylcyclopropanecarboxylate* (**6c**). A soln. of **6b** in dry THF was cooled to –15°. At this temp. under Ar, 1 equiv. each of *N*-methylmorpholine and isobutyl chloroformate were dropwise added to the mixture, and the mixture was stirred for 5 min. A soln. of 1.2 equiv. of *N*-hydroxy-2-thiopyridone and Et_3N was prepared in appropriate amount of dry THF and was added to the mixture in dark. The stirring continued at –15° for another 2 h in dark. The precipitated *N*-methylmorpholine hydrochloride was filtered off. To the yellow filtrate, 4.5 equiv. of *t*-BuSH were added, and the mixture was irradiated with a high-pressure Hg lamp for 40 min at r.t. Et_2O was added and the resulting mixture washed with a 0.1N $NaHCO_3$ soln., H_2O, 0.5N HCl, and again with H_2O, followed by a sat. NaCl soln. The org. phase was dried (Na_2SO_4) and the solvent evaporated. The raw product was purified over silica using petroleum ether/Et_2O 10:1: **6c**, a colorless oil, was obtained in 38% yield. $[\alpha]_D^{25} = +302.4$ ($c = 1.09$, $CHCl_3$). IR (film): 3040; 2960; 2920; 2895; 1730 (CO); 1575; 1415; 755. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.33, 1.60 (*m*, 2 H–C(3)); 1.91 (*m*, H–C(1)); 2.53 (*m*, H–C(2)); 3.72 (*s*, CH_3O); 7.09–7.31 (*m*, 5 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.0 (C(3)); 23.9, 26.3 (C(1), C(2)); 51.9 (CH_3O); 126.2, 126.5, 128.5 (arom. C); 139.9 (arom C); 173.9 (CO). EI-MS (70 eV): 176 (38, M^+), 145 (18, $[M - OCH_3]^+$), 117 (100), 91 (31).

REFERENCES

[1] G. M. Whitesides, C. H. Wong, *Angew. Chem.* **1985,** *97,* 617.
[2] J. B. Jones, in 'Asymmetric Synthesis', Ed. J. D. Morrison, Academic Press, Inc., New York, 1985, Vol. 5, pp. 309.
[3] J. B. Jones, *Tetrahedron* **1986,** *42,* 3351.
[4] S. Servi, *Synthesis* **1990,** 1.
[5] P. Mohr, M. Tori, P. Grossen, P. Herold, Ch. Tamm, *Helv. Chim. Acta* **1982,** *65,* 1412.
[6] P. Herold, P. Mohr, Ch. Tamm, *Helv. Chim. Acta* **1983,** *66,* 744.
[7] H. J. Gais, in 'Enzymes as Catalysts in org. Synthesis', Ed. M. P. Schneider, D. Reidel Publishing Co., Dordrecht, 1986, pp. 97.
[8] M. Ohno, M. Otsuka, *Org. React.* **1989,** *37,* 1.
[9] P. Mohr, L. Rösslein, Ch. Tamm, *Tetrahedron Lett.* **1989,** *30,* 2513.
[10] T. Tschamber, N. Waespe-Sarcevic, Ch. Tamm, *Helv. Chim. Acta* **1986,** *69,* 621.
[11] E. Heymann, W. Junge, *Eur. J. Biochem.* **1979,** *95,* 509.
[12] E. Heymann, W. Junge, K. Kirsch, *Hoppe-Seyler's Z. Physiol. Chem.* **1972,** *353,* 576.
[13] W. P. Jenks, D. Farb, L. Goldsmith, P. Gennzaid, *Hoppe-Seyler's Z. Physiol. Chem.* **1973,** *354,* 2.
[14] L. K. P. Lam, C. M. Brown, B. de Jeso, L. Lym, E. T. Toone, J. B. Jones, *J. Am. Chem. Soc.* **1988,** *110,* 4409.
[15] P. Mohr, N. Waespe-Sarcevic, Ch. Tamm. *Helv. Chim. Acta* **1983,** *66,* 2501.
[16] J. Zemlicka, L. E. Craine, M. J. Heeg, J. P. Oliver, *J. Org. Chem.* **1988,** *53,* 937.
[17] G. Sabbioni, J. B. Jones, *J. Org. Chem.* **1987,** *52,* 4565.
[18] M. Ohno, in 'Enzymes in Org. Synthesis, Ciba Foundation Symposium III', Pitman Publishing, London, 1985, pp. 171.
[19] E. J. Toone, M. J. Werth, J. B. Jones, *J. Am. Chem. Soc.* **1990,** *112,* 4946.
[20] C. Tarchini, M. Rohmer, C. Djerassi, *Helv. Chim. Acta* **1979,** *62,* 1210.
[21] J. Salaün, Y. Almirantis, *Tetrahedron* **1983,** *39,* 2421.
[22] J. Ollivier, J. Salaün, *Tetrahedron Lett.* **1984,** *25,* 1269.
[23] H. Staudinger, L. Ruzicka, *Helv. Chim. Acta* **1922,** *IV,* 12.
[24] L. Fowden, A. Smith, *Phytochemistry* **1969,** *8,* 437.
[25] S. Beckmann, H. Geiger, in 'Methoden der org. Chemie, Houben-Weyl', Georg Thieme Verlag, Stuttgart–New York, 1972, Vol. 4/4, p. 449.
[26] C. A. Mattia, L. Mazzarella, R. Puliti, D. Sica, F. Zollo, *Tetrahedron Lett.* **1978,** 3953.
[27] E. Fattorusso, S. Magno, L. Mayol, C. Santacroce, D. Sica, *Tetrahedron* **1975,** *312,* 1715.
[28] D. H. R. Barton, Y. Hervé, P. Potier, J. Thierry, *Tetrahedron* **1988,** *44,* 5479.
[29] M. Regitz, B. Giese, in 'Methoden der org. Chemie, Houben-Weyl', Georg Thieme Verlag, Stuttgart–New York, 1989, Vol. E19a, pp. 237–239.
[30] I. Kubo, I. Miura, K. Nakanishi, *J. Am. Chem. Soc.* **1976,** *98,* 6705.
[31] R. G. Bergman, *J. Am. Chem. Soc.* **1969,** *91,* 7405.
[32] P. E. Krieger, J. A. Landgrebe, *J. Org. Chem.* **1978,** *43,* 447.
[33] S. C. Yasui, T. A. Keiderling, *J. Am. Chem. Soc.* **1987,** *109,* 2311.
[34] F. B. Björkling, J. Boutelje, S. Gatenbeck, K. Hult, T. Norin, P. Szmulik, *Tetrahedron* **1985,** *41,* 1347.
[35] M. Ohno, S. Kobayashi, T. Jimor, Y. F. Wang, *J. Am. Chem. Soc.* **1981,** *103,* 2405.
[36] Y. F. Wang, T. Jzawa, S. Kobayashi, M. Ohno, *J. Am. Chem. Soc.* **1982,** *104,* 6465.
[37] K. Okano, T. Jzawa, M. Ohno, *Tetrahedron Lett.* **1983,** *24,* 217.
[38] G. Sabbioni, M. L. Shea, J. B. Jones, *J. Chem. Soc., Chem. Commun.* **1984,** 236.
[39] F. Hosseinzadeh, Ch. Tamm, unpublished results.
[40] L. L. McCoy, *J. Am. Chem. Soc.* **1958,** *80,* 6568.
[41] J. H. Babler, R. A. Haack, *Synth. Commun.* **1983,** *13,* 905.
[42] S. Wawzonescc, A. R. Zigman, *Org. Preparations Procedures* **1969,** *1,* 243.
[43] J. van Alphen, *Recl. Trav. Chim. Pays-Bas* **1943,** *62,* 210.