249. A Study of Stereoselective Hydrolysis of Symmetrical Diesters with Pig Liver Esterase

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Summary

Pig liver esterase-(PLE) catalyzed hydrolysis of dimethyl esters of symmetrical dicarboxylic acids, including *meso*-diacids, *cis*-1,2-cycloalkanedicarboxylic acids, and diacids with a prochiral center, was studied with 14 substrates. The products of these stereoselective hydrolyses are chiral monoesters of dicarboxylic acids, with an enantiomeric excess (e.e.) from 10% to 100%. Some of these optically active monoesters are valuable synthons in natural products synthesis.

An additivity pattern of α- and β-substituents with the glutaric esters on the stereoselectivity of enzymatic hydrolysis was observed. Analysis of the experimental results leads to a model of enzyme stereoselectivity of diester hydrolysis in which the substitution pattern at α- and β-C-atoms is found to determine the absolute configuration of the resulting monoester.

The control of absolute stereochemistry is of fundamental importance for natural product synthesis [1]. Although a plethora of chemical methods has been developed for the construction of optically active compounds [2], the unique opportunity provided by enzymes as catalysts in asymmetric synthesis is being increasingly exploited [3].

It is theoretically possible, by utilizing the enantioselectivity of enzymes towards *meso*-compounds and compounds with a prochiral center to transform the total amount of starting material into a target molecule. The classical example of this kind of transformation represents the synthesis of (*R*)-mevalonolactone using the high selectivity provided by pig liver esterase (PLE) towards dimethyl 3-hydroxy-3-methylglutarate [4]. From a preparative standpoint it is important to note that by appropriate manipulation of the functional groups (*S*)-mevalonolactone can also be synthesized.

We can envisage that by using enzymes which possess low substrate selectivity but which at the same time catalyze reactions with a high degree of stereoselectivity, a large number of new chiral synthons can be provided. α-Chymotrypsin [5], horse liver alcohol dehydrogenase [6], PLE [7], and some other esterases from different microorganisms [8] have already been used to provide chiral synthons of highest optical purity for the synthesis of natural products.

This concept finds a non-enzymatic counterpart in methods developed by *Osakada et al.* [9] and *Mukaiyama et al.* [10]: cyclic *meso*-anhydrides are either reduced with chiral catalysts or they are first functionalized with chiral amines and subsequently reduced with conventional reagents. In strategies developed recently [11] [12] the *meso*-compounds are converted into a mixture of diastereoisomers by reaction with an auxiliary, enantiomerically pure reagent. The mixture is then separated by physical methods, for instance crystallization or chromatography. The non-enzymatic aminolysis of an optically active diamide of 3-methylglutaric acid, reported by *Nagao et al.* [13], proceeded with *ca.* 87% selectivity.

In connection with the synthesis of optically active verrucarinic acid [14] and the synthetic studies of cytochalasanes [15] we have examined the hydrolysis of dimethyl and diethyl 3-methylglutarate by PLE. The encouraging results prompted us to explore systematically the enantioselectivity of the hydrolysis of various *meso*- and prochiral diesters by this enzyme. By accumulating a larger number of experimental data we pursued two goals: *1.* preparation of chiral half esters as potential synthons for the construction of biologically active compounds such as macrolide and polyether antibiotics or prostaglandins; *2.* establishment of the structural requirements of the diesters for being a good substrate for PLE.

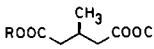
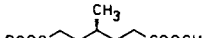
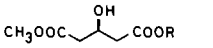
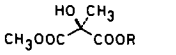
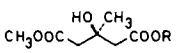
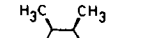
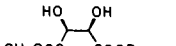
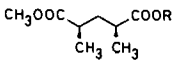
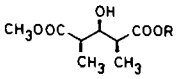
It should be mentioned that similar studies have been carried out by *Jones et al.* [16] on the oxidation of cyclic *meso*-diols with horse liver alcohol dehydrogenase (HLADH), an NAD^+-dependent enzyme. As PLE does not require a coenzyme and as the half esters obtained can be easily and specifically transformed on either the acid or the ester functionality, this enzyme might have advantages in comparison with HLADH. Of course, this is true only for substrates with similar enantioselectivities.

In this communication we present the first experimental data concerning the structural and stereochemical aspects of hydrolysis of *meso*- and prochiral diesters by PLE. *Table 1* summarizes the results which were obtained with various open-chain substrates. The diesters were either commercially available (**3a**), or prepared from the corresponding diacids (**1a**, **4a**, **6a**, **7a**, **8a**) or synthesized according to known procedures (**2a**) [17].

Diester **9a** was obtained from two equivalents of ethyl 2-bromopropionate and ethyl formate by a modified *Reformatsky* reaction yielding **9a**, the racemic form and the other possible *meso*-isomer in a ratio of *ca.* 3:3:1. This mixture was hydrolyzed to the corresponding diacids and the *xylo*-form, precursor of **9a**, was isolated by recrystallization. In all critical cases the ^{13}C-NMR spectrum was recorded (**6a**, **7a**, **8a**, **9a**) to check the isomeric purity of the substrates. The data for diester **5a** were taken from [4]. The enantiomeric excess of the half esters obtained from the enzymatic hydrolysis varies dramatically and covers a range from 10% (**2b**) to 99% (**5b**). It is interesting to note that the diesters **5a** [4] and **8a** are also hydrolyzed by α-chymotrypsin with high selectivity at the same methoxycarbonyl group – unfortunately at a slower rate – while dimethyl 3-hydroxyglutarate (**3a**) yields the half ester **3b** of opposite configuration under these conditions [18].

Table 2 contains the results of the hydrolysis of some cyclic *cis*-diesters. The substrates **10a**–**14a** were all prepared *via* their corresponding anhydrides. This allowed the compounds to be purified. Again, ^{13}C-NMR spectra were used to show the absence of the *trans*-isomer. The optical purity of the half esters seems to decrease with increasing mobility of the cyclic system in the order: cyclopropane > cyclobutane > cyclo-

Table 1. *Results of PLE-Catalyzed Hydrolysis of Diesters* **1a–9a**

Substrate (R = CH_3)		Half ester (R = H) $[\alpha]_D$	% e.e.[a]
	**1a** R = CH_3 **1b** R = H	+ 0.64°	90 [14]
	**2a** R = CH_3 **2b** R = H	+ 0.09°	10 [32]
	**3a** R = CH_3 **3b** R = H	+ 0.21° (− 1.7°)[b]) [18]	12 (100) [18]
	**4a** R = CH_3 **4b** R = H	− 5.20°[c])	46[d]) [e])
	**5a** R = CH_3 **5b** R = H	+ 0.72 [4][f])	99 (≈ 100) [4]
	**6a** R = CH_3 **6b** R = H	− 1.60°	18 [33]
	**7a** R = CH_3 **7b** R = H	− 2.60°[g])	48 [34]
	**8a** R = CH_3 **8b** R = H	− 2.71° (− 4.83°)[b])	60 (100) [35]
	**9a** R = CH_3 **9b** R = H	− 8.6°	98[h]) [40]

[a]) Enantiomeric excess was determined by comparison with the optical rotation values of half esters **1b–3b** and **5b–8b** reported in the literature.

[b]) Values in parentheses were obtained after the enzymatic hydrolysis with α-chymotrypsin.

[c]) The optical rotation was measured on the acetoxy-derivative.

[d]) The enantiomeric excess was determined by a GC analysis of the (*S*)-ethyl lactate derivative of the acetylated half ester.

[e]) Absolute configuration presumed, not proved.

[f]) According to [4] **5a** can also be hydrolyzed with α-chymotrypsin in high optical yield.

[g]) This experiment was carried out by Dr. *V.S. Parmar*, whose collaboration is gratefully acknowledged.

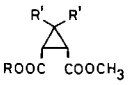
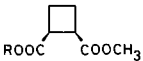
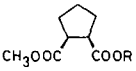
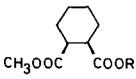
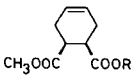
[h]) Enantiomeric excess was determined by comparison with the optical value of the hydrazide derivative of **9c** reported in the literature.

hexene ≈ cyclohexane. In contrast, the cyclopentane derivative, which exists in different conformations of nearly the same energy [19], was hydrolyzed with virtually no selectivity, whereas the 3,3-dimethylcyclopropanediester **11a** was found to be a bad substrate. It showed very slow reactivity.

Whereas α-chymotrypsin has been intensively studied with respect to the topography of the active site and its structural and stereochemical consequences [3a], very little information is available for PLE [20]. From our experimental data the following preliminary conclusions can be drawn by restricting ourselves to ester groups bound to sp^3-C-atoms.

1. To achieve high stereoselectivity the distance of the prochiral center from the ester group has to be restricted to the α- or β-position.

Table 2. *Results of PLE-Catalyzed Hydrolysis of* cis-*Diesters* **10a–15a**

Substrate		Half ester (R = H) $[\alpha]_D$	Lactone $[\alpha]_D$	% e.e.[a]
	**10a** R = CH_3; R′ = H			
	10b R = R′ = H	− 11.0°	+ 62.0°	100 [16c]
	11a R = R′ = CH_3			
	11b R = H; R′ = CH_3	− 11.2°	+ 39.0°	43 [10]
	**12a** R = CH_3			
	12b R = H	+ 2.7°	− 107.0°	90 [16c]
	**13a** R = CH_3			
	13b R = H	+ 1.1°	+ 8.5°	9 [16c]
	**14a** R = CH_3			
	14b R = H	+ 5.23°[b]	+ 45.0°	78[c] [39]
	**15a** R = CH_3			
	15b R = H	+ 14.6°	+ 51.1°[d]	85[c]

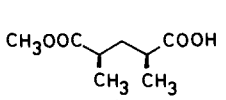
[a] Enantiomeric excess was determined by comparison with the optical rotation values of lactones **10c–13c** and **15c**, and of half ester **14b**, reported in the literature.

[b] $[\alpha]_{578}$, not $[\alpha]_D$.

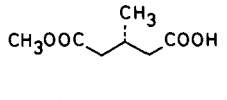
[c] For comparison the lactone **15c** was transformed to the enantiomer of **14c** by catalytic hydrogenation. $[\alpha]_D = -48.4°$ was thereby found. The value reported in [16c] for **14c** seems to be too low.

[d] The half ester **15b** was reduced with $LiBH_4$ to yield the (1 *S*,6 *R*)-lactone **15c**.

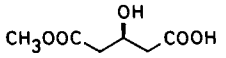
2. Approximate additivity of structural parameters on enzyme stereoselectivity is observed. This is demonstrated by comparison of substituted glutaric esters **5a** and **9a**. The diesters carrying more substituents (**5a**, **9a**) are hydrolyzed with higher stereoselectivity than their less substituted counterparts (**1a**, **3a**, **8a**).



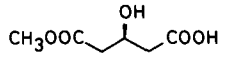
8b moderate e.e.



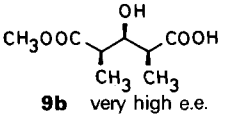
1b high e.e.



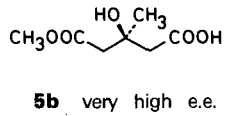
3b low e.e.



3b low e.e.



9b very high e.e.



5b very high e.e.

3. As expected, the rigid conformation of a substrate, imposed by a cyclic structure, affects higher stereoselectivity as compared to an acyclic analogue. Open-chain diesters usually exist in different conformations of similar energy. Some are attacked at the

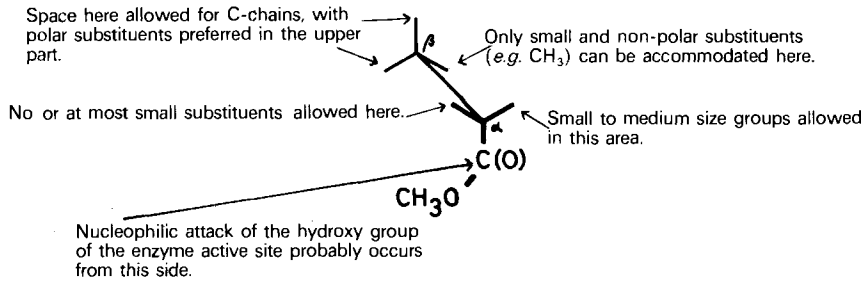
pro(*R*)-, the others at the pro(*S*)-methoxycarbonyl group by the nucleophilic hydroxy function of the enzyme. This effect is best demonstrated by the dramatically increased selectivity of hydrolysis of **12a** as compared with **6a**.

The behavior of the six-membered ring substrates **14a** and **15a**, albeit surprising at first sight, can easily be rationalized assuming that the ester group must be in an equatorial position. In sharp contrast, the cyclopentane derivative **13a** is attacked with almost no selectivity. It appears to be just a boundary case in going from the cyclobutane-(*S*)-acid produced to the cyclohexane-(*R*)-acid produced.

4. Substituents of different polarity and different size, *i.e.* hydroxy and methyl groups, show opposite effects on the selectivity of enzyme hydrolysis. In the methyl-diester **1a** the pro(*S*)-group is hydrolyzed with high optical yield, while in the hydroxy-diester **3a** the pro(*R*)-group is preferably attacked. Similar observations were also made on the substrates **6a** and **7a**.

Interestingly, *Ohno et al.* [7a] observed, that in the case of dimethyl 3-aminoglutarate the pro(*S*)-methoxycarbonyl group is cleaved, in contrast to the 3-hydroxy analog **3a**, while the (*Z*)-protected amino-ester was hydrolyzed with excellent selectivity at the pro(*R*)-group.

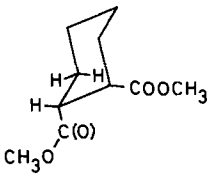
These conclusions allow us to propose the following general formula which summarizes the structural and stereochemical requirements which an ester must meet to fit into the cavity of the active site of the enzyme.



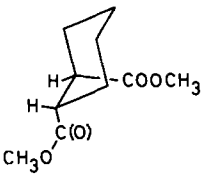
This model is illustrated below using the cyclohexane-derivative **14a**, and dimethyl 2,4-dimethyl-3-hydroxyglutarate (**9a**) as examples. Both proved to be good substrates for PLE. Looking at the $C_\alpha - C_\beta$-bond in the chair form of **14a**, we see that this diester can assume only one allowed conformation (**A**) in which the (*R*)-methoxycarbonyl group is being hydrolyzed in the equatorial position. The conformation **B** leading to the (1*R*, 2*S*)-half ester is apparently less favored due to the presence of a methoxycarbonyl group in the area where only small substituents can be accommodated. Similar reasoning can be applied to the open chain substrate **9a**. Of the most stable conformations which can be envisaged, only **C** (pro(*S*)-methoxycarbonyl group being hydrolyzed) is in agreement with the general formula depicted above.

In **D** the methyl group is on the wrong side, whereas in **E** the substituent in the α-position is too large – both **D** and **E** would lead to the hydrolysis of the pro(*R*)-methoxycarbonyl group.

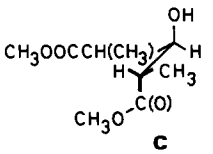
Of course, this model does not reflect the topography of the enzyme pocket itself, but just summarizes in a general formula those cases, in which we have observed good



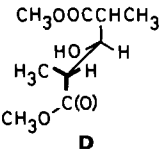
A



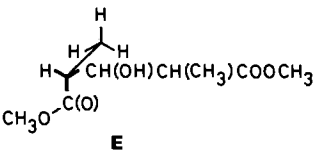
B



C

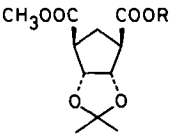


D

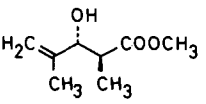


E

selectivity. It has to be refined further for the prediction and rationalization of subtle effects. We still cannot explain the different behavior of 3-hydroxy- and 3-amino-glutarate [7a] or why the 3-methylglutarate (**1a**) is a much better substrate than the 3-hydroxy-ester **3a**. But the model correctly predicts that the *meso*-diester **16a** is preferably cleaved to **16b** [7c] and that the (2*S*,3*R*)-enantiomer of (±)-**17** is preferentially hydrolyzed by PLE [7d].



16a R = CH_3
16b R = H



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Experimental Part

1. *General Remarks.* Water- and air-sensitive reactions were carried out in an Ar-atmosphere, CH_2Cl_2 and Et_2O were dried by passing through an Al_2O_3-column, THF by distilling it over $LiAlH_4$. All org. extracts were dried over $MgSO_4$ and evaporated under reduced pressure below 50°. Pig liver esterase (EC 3.1.1.1) and chymotrypsin A_4 (EC 3.4.21.1) were purchased from *Boehringer* and *Sigma*, respectively. Capillary GC analyses were carried out with a *Perkin-Elmer Sigma 3 B* chromatograph on a *SE 54* column. TLC were prepared with silica gel *60* F_{254} (*Merck*) and the spots were observed by spraying with 10% H_2SO_4 in MeOH. For CC silica gel *60* (0.063–0.200 mm, *Merck*) was used. The melting points (m.p.) were determined on a *Kofler* block and are corrected. The boiling points (b.p.) for bulb-to-bulb distillations refer to uncorrected oven temperatures. Optical rotations and IR (cm^{-1}) were measured with a *Perkin-Elmer* model *141* polarimeter and a *Perkin-Elmer* model *177* grating spectrometer, 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. Chemical shifts are reported in ppm downfield from internal $SiMe_4$.

2. *Preparation of Diesters* **2a–4a** *and* **6a–15a**. *Dimethyl 4-methylheptanedioate* (**2a**) was prepared from 3-methyl-1,5-pentanediol as reported [17]: b.p. 95°/2 Torr. ^{1}H-NMR (60 MHz, CCl_4): 0.9 (*m*, 3H, CH_3–C(4)); 1.5 (*m*, 5H, $H_2C(3)$, $H_2C(5)$, H–C(4)); 2.3 (*t*, 4H, $H_2C(2)$, $H_2C(6)$); 3.65 (*s*, 6H, $2COOCH_3$).

Dimethyl 3-hydroxyglutarate (**3a**) was commercially available and *dimethyl 2-hydroxy-2-methylmalonate* (**4a**) was prepared from corresponding diacid by esterification.

Dimethyl meso-*2,3-dimethylsuccinate* (**6a**) was prepared from *meso*-2,3-dimethylsuccinic acid (m.p. 207–210°) with ethereal diazomethane. ^{1}H-NMR (60 MHz, CCl_4): 1.1 (*d*, *J* = 6.5, 6H, $CH_3-C(2)$, $CH_3-C(3)$); 2.6 (*m*, 2H, H–C(2), H–C(3)); 3.6 (*s*, 6H, $2\,COOCH_3$). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 14.9, 42.8, 51.6, 174.8 ([21]).

Dimethyl meso-*tartarate* (**7a**) was obtained by esterification of a solution of *meso*-tartaric acid in MeOH with CH_2N_2 in Et_2O. ^{1}H-NMR (60 MHz, CD_3COCD_3): 3.7 (*s*, 6H, $2\,COOCH_3$); 4.4 (*s*, 4H, H–C(2), H–C(3); 2OH). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 52.3, 74.2, 172.1.

Dimethyl meso-*2,4-dimethylglutarate* (**8a**). The *meso*-anhydride, m.p. 88–90°, obtained from the mixture of *meso*- and *dl*-2,4-dimethylglutaric acid [22] was hydrolyzed in hot MeOH and subsequently treated with CH_2N_2 in Et_2O. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.15 (*d*, *J* = 6.5, $CH_3-C(2)$, $CH_3-C(4)$); 1.2–2.7 (*m*, 4H, H–C(2), H–C(4), $H_2C(3)$); 3.6 (*s*, 6H, $2\,COOCH_3$). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 17.3, 37.5, 51.5, 176.4 (Ref: [23] and [24]).

Dimethyl xylo-*3-hydroxy-2,4-dimethylglutarate* (**9a**). The modified *Reformatsky* reaction [25] of ethyl 2-bromopropionate (0.3 mol), ethyl formate (0.15 mol) and Zn (100 g) gave 16.8 g (48%) of the mixture of isomeric esters, b.p. 96–100°/0.5 Torr. This mixture (13 g) was hydrolyzed with 5 g of NaOH and 80 ml of H_2O overnight at r.t. and 3 h at 80–90°. The solution was acidified with 6N HCl, saturated with NaCl and extracted continuously with Et_2O. The extracts were dried and evaporated to give 95% of the semisolid mixture of diacids. Recrystallization from Et_2O/CH_2Cl_2 gave 4.0 g of crystalline product with m.p. 127–131°. Repeated recrystallization from acetone/CH_2Cl_2 gave 3.5 g of pure *xylo*-diacid; m.p. 138–139°. ^{13}C-NMR (22.63 MHz, $CDCl_3$ (D_5)pyridine): 12.5, 42.8, 72.6, 178.7.

The *xylo*-diacid was esterified with CH_2N_2 in Et_2O. The product gave a single peak on GC (10% *DEGS*/*Chromosorb W/AW* at 135°). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.25 (*d*, *J* = 7, 6H, $CH_3-C(2)$, $CH_3-C(4)$); 2.6 (*m*, 2H, H–C(2), H–C(4)); 3.15 (*s*, 1H, OH); 3.75 (*s*, 6H, $2\,COOCH_3$); 4.15 (*t*, *J* = 6, 1H, H–C(3)) ([26]). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 12.2, 42.7, 51.8, 72.3, 175.8.

The *xylo*-diacid was converted to the corresponding anhydride by stirring it overnight at r.t. with excess Ac_2O. The solvents were removed under reduced pressure and the product recrystallized from benzene/pentane; m.p. 121–123°. ^{1}H-NMR ($CDCl_3$/(D_5)pyridine): 1.45 (*d*, *J* = 6.5, 6H, $CH_3-C(2)$, $CH_3-C(5)$); 2.7 (*dq*, *J* = 10.5, *J* = 6.5, 2H, H–C(2), H–C(5)); 3.6 (*t*, *J* = 10.5, 1H, H–C(3)). ^{13}C-NMR (22.63 MHz, $CDCl_3$/(D_5)pyridine): 12.8, 45.1, 71.0, 168.6.

Dimethyl cis-*1,2-cyclopropanedicarboxylate* (**10a**). *cis*-1,2-Cyclopropanedicarboxylic anhydride, prepared from commercial (*cis*/*trans*-mixture) diethyl 1,2-cyclopropanedicarboxylate following the procedure of *McCoy* [27], was first refluxed in MeOH and the product obtained was then esterified with CH_2N_2 in Et_2O. The diester was purified by preparative GC on 10% *OV-17*/*Chromosorb P* at 180°. ^{1}H-NMR (60 MHz, CCl_4): 0.9–2.2 (*m*, 4H, H–C(1), $H_2C(3)$, H–C(2)); 3.65 (*s*, 6H, $2\,COOCH_3$). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 11.7, 21.4, 52.0, 170.3.

Dimethyl cis-*3,3-dimethyl-1,2-cyclopropanedicarboxylate* (**11a**). *cis*-3,3-Dimethyl-1,2-cyclopropanedicarboxylic anhydride[1]) was converted to the diester (see **10a**). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.2 (*s*, 3H, $CH_3-C(3)$); 1.4 (*s*, 3H, $CH_3-C(3)$); 1.9 (*s*, 2H, H–C(1), H–C(2)); 3.65 (*s*, 6H, $2COOCH_3$). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 15.5, 26.0, 32.0, 51.5, 169.4.

Dimethyl cis-*1,2-cyclobutanedicarboxylate* (**12a**). Commercial *cis*-1,2-cyclobutanedicarboxylic acid anhydride was recrystallized from benzene/hexane, hydrolyzed and esterified (see **10a**). ^{1}H-NMR (60 MHz, CCl_4): 1.8–2.6 (*m*, 4H, $H_2C(3)$, $H_2C(4)$); 3.1–3.45 (*m*, 2H, H–C(1), H–C(2)); 3.6 (*s*, 6H, $2\,COOCH_3$). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 22.2, 40.7, 51.6, 173.6 ([28]).

Dimethyl cis-*1,2-cyclopentanedicarboxylate* (**13a**). *trans*-1,2-Cyclopentanedicarboxylic acid was converted into *cis*-1,2-cyclopentanedicarboxylic anhydride by heating it at 200° for 1.5 h [29]. The anhydride so obtained was hydrolyzed with H_2O on a steam bath to *cis*-1,2-cyclopentanedicarboxylic acid; after twofold recrystallization from hot H_2O a product with m.p. 136–139° ([30]: 137–139°) was obtained. The *cis*-diacid was dissolved in MeOH and esterified with CH_2N_2. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.8–2.3 (*m*, 6H, $H_2C(2)$, $H_2C(3)$, $H_2C(4)$); 2.9–3.2 (*m*, 2H, H–C(1), H–C(2)); 3.7 (*s*, 6H, $2\,COOCH_3$). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 24.0, 28.8, 47.1, 51.6, 174.3 ([21]).

Dimethyl cis-*1,2-cyclohexanedicarboxylate* (**14a**). *cis*-1,2-Cyclohexanedicarboxylic anhydride was hydrolyzed in hot H_2O and the diacid so obtained (m.p. 195–197°) was esterified with CH_2N_2 in Et_2O. ^{1}H-NMR (60 MHz, CCl_4): 1.1–2.2 (*m*, 8H, $H_2C(3)$, $H_2C(4)$, $H_2C(5)$, $H_2C(6)$); 2.5–2.9 (*m*, 2H, H–C(1), H–C(2)); 3.6 (*s*, 6H, $2\,COOCH_3$). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 23.9, 26.4, 42.8, 51.5, 174.1 ([21] [28]).

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[1]) The anhydride was kindly provided by Dr. *P. A. Verbrugge*, (*Shell*, Amsterdam).

Dimethyl cis-*1,2-cyclohex-4-enedicarboxylate* (**15a**). *cis*-1,2-Cyclohex-4-enedicarboxylic anhydride was hydrolyzed to the diacid (m.p. 160–161°; [31]: m.p. 166°) and esterified (see **14a**). ^{1}H-NMR (60 MHz, $CDCl_3$): 2.0–2.8 (*m*, 4H, $H_2C(3)$, $H_2C(6)$); 2.8–3.2 (*m*, 2H, H–C(1), H–C(2)); 3.7 (*s*, 6H, $2COOCH_3$); 5.65 (br. *s*, 2H, H–C(4), H–C(5)); ^{13}C-NMR (22.63 MHz, $CDCl_3$): 26.0, 39.9, 51.7, 125.2, 173.6.

3. *PLE-Catalyzed Hydrolysis of Diesters* **2a–4a** *and* **6a–15a**. *1-Methyl hydrogen (4*R*)-4-methylheptanedioate* (**2b**). To 10 mmol of **2a** suspended in 50 ml of 0.1M phosphate buffer of pH 8 were added 500 units of PLE with vigorous stirring. The pH-value was kept within the 7.5–8.0 range by addition of 1N NaOH. After consumption of 1 mol-equiv. of base the mixture was homogeneous. The pH-value was adjusted to 9 and the aq. phase extracted with Et_2O. The org. layer was washed with H_2O and the combined aq. solutions acidified to pH 2.5. These were again extracted with Et_2O, dried and evaporated *i.v.* to yield 96% of the half ester **2b**; $[\alpha]_D^{20} = +0.09°$ (neat). Optically pure half ester with (*R*)-configuration had $[\alpha]_D^{21} = +0.9°$ (neat) [32]. ^{1}H-NMR (60 MHz, $CDCl_3$): 0.9 (*m*, 3H, CH_3–C(4)); 1.55 (*m*, 5H, $H_2C(3)$, $H_2C(5)$, H–C(4)); 2.35 (*m*, 4H, $H_2C(2)$, $H_2C(6)$); 3.65 (*s*, 3H, $COOCH_3$); 10.5 (*s*, 1H, COOH).

1-Methyl hydrogen (3S)-3-hydroxyglutarate (**3b**). Diester **3a** (10 mmol) in 25 ml of 0.1M phosphate buffer was hydrolyzed with 200 units of PLE. The reaction was complete after 2 h. The pH-value was adjusted to 9 and the mixture was extracted with Et_2O. The combined aq. solutions were acidified to pH 2.5 and the solvents were evaporated *i.v.* at 30°. The semisolid was washed with three portions of AcOEt. The extracts were dried and evaporated to give 95% of the half ester **3b**; $[\alpha]_D^{20} = +0.21°$ ($c = 12.9$, $CHCl_3$). Reported for (3*R*)-half ester **3b**; $[\alpha]_D^{20} = -1.7°$ ($c = 12.5$, $CHCl_3$) [18]. ^{1}H-NMR (60 MHz, $CDCl_3$): 2.6 (*d*, $J = 6$, 4H, $H_2C(2)$, $H_2C(4)$); 3.7 (*s*, 3H, $COOCH_3$); 4.45 (*quint.*, $J = 6$, 1H, H–C(3)); 7.45 (br. *s*, 2H, OH, COOH).

1-Methyl hydrogen (2S)-2-hydroxy-2-methylmalonate (**4b**). Diester **4a** (1.7 mmol) was hydrolyzed in 1/2 h with 900 units of PLE. After adjusting the pH to 2.5 and evaporation of the solvent the residue was thoroughly extracted with Et_2O. Yield 82.2%. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.65 (*s*, 3H, CH_3–C(2)); 3.75 (*s*, 3H, $COOCH_3$); 6.85 (br. *s*, 2H, OH, COOH).

The half ester **4b** (1.4 mmol) was dissolved in 1 ml of pyridine and 1 ml of Ac_2O. 4-(Dimethylamino)pyridine (DMAP) (10 mg) was added and the mixture was stirred at r.t. overnight. It was poured into ice-water and extracted with Et_2O, washed with 1N HCl and dried: *1-methyl hydrogen (2S)-2-acetoxy-2-methyl-malonate* in 96.3% yield; $[\alpha]_D^{20} = -5.20°$ ($c = 4.8$, $CHCl_3$). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.8 (*s*, 3H, CH_3–C(2)); 2.15 (*s*, 3H, CH_3COO–C(2)); 3.8 (*s*, 3H, $COOCH_3$); 9.7 (br. *s*, 1H, COOH).

The protected half ester (248 mg, 1.3 mmol) was dissolved in 5 ml of CH_2Cl_2. (*S*)-Ethyl lactate (229 µl, 2 mmol) and 20 mg DMAP were added. The mixture was cooled to 0° and dicyclohexylcarbodiimide (DCC) (330 mg, 1.6 mmol) was added. Stirring was continued for an additional 2 h at r.t. The precipitated urea was filtered off. The solution was diluted with Et_2O and washed with 2N Na_2CO_3, 1N HCl and brine. The product was purified on a silica gel column (petrol ether/Et_2O 1 : 1). Yield 275 mg (77%). Further purification was possible by bulb-to-bulb distillation (180°/0.2 Torr). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.28 (*t*, $J = 7$, 3H, CH_2–CH_3); 1.51 (*d*, $J = 7$, 3H, CH_3–CH); 1.85 (*s*, 3H, CH_3–C); 2.16 (*s*, 3H, $COCH_3$); 3.81, 3.82 (2*s*, 3H, $COOCH_3$); 4.20 (*q*, $J = 7$, 2H, CH_2–CH_3); 5.25, 5.26 (2*q*, $J = 7$, 1H, CH_3–CH–O). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 14.1, 16.7, 20.7, 21.1, 53.1, 61.5, 70.1, 80.1, 166.5, 167.5, 169.4, 169.7.

The enantiomeric excess has been evaluated from 360-MHz. ^{1}H-NMR spectra as 36% ± 10%. It was possible to separate the (*S*)-ethyl lactate derivatives on a capillary column (*Carbowax*) and to determine more precisely the e.e. value as 46%.

1-Methyl hydrogen (2R,3S)-2,3-dimethylsuccinate (**6b**). Diester **6a** gave under standard working conditions (see **2a** → **2b**) the half ester **6b** in 94% yield; $[\alpha]_D^{20} = -1.60°$ ($c = 14$, EtOH). Reported for the resolved half ester $[\alpha]_D^{20} = +8.93°$ ($c = 14.6$, EtOH) [33]. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.2 (*m*, 6H, CH_3–C(2), CH_3–C(3)); 2.8 (*m*, 2H, H–C(2), H–C(3)); 3.65 (*s*, 3H, $COOCH_3$); 10.1 (*s*, 1H, COOH).

1-Methyl hydrogen (2S,3R)-tartarate (**7b**). Compound **7a** was hydrolyzed and worked up as in **4a** → **4b** (10 mmol substrate, 500 units PLE, 8 h). Yield 92%; $[\alpha]_D^{20} = -2.60°$ ($c = 3.3$, H_2O) ([34]: $[\alpha]_D^{17} = -5.43°$ ($c = 9.2$, H_2O)). ^{1}H-NMR (60 MHz, $CDCl_3$): 3.7 (*s*, 3H, $COOCH_3$); 4.5 (*m*, 2H, H–C(2), H–C(3)); 5.7 (*s*, 3H, 2OH, COOH). ^{13}C-NMR (22.63 MHz, CD_3COCD_3): 52.3, 74.2, 172.1.

1-Methyl hydrogen (2R,4S)-2,4-dimethylglutarate (**8b**). Diester **8a** was hydrolyzed and worked up (see **2a** → **2b**); yield 98%; $[\alpha]_D^{20} = -2.71°$ ($c = 7$, $CHCl_3$) ([35]: $[\alpha]_D^{25} = -4.61°$ ($c = 7$, $CHCl_3$); [36]: $[\alpha]_D^{22} = -4.8°$; for the (2*S*,4*R*)-half ester with an e.e. value of 98%: $[\alpha]_D^{25} = +4.0$ ($c = 5$, $CHCl_3$) [8a]). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.2 (*d*, $J = 6.5$, 6H, CH_3–C(2), CH_3–C(4)); 1.2–2.9 (*m*, 4H, $H_2C(3)$, H–C(2), H–C(4)); 3.65 (*s*, 3H, $COOCH_3$); 9.8 (*s*, 1H, COOH).

1-Methyl hydrogen (3S,2R,4S)-3-hydroxy-2,4-dimethylglutarate (**9b**). Diester **9a** gave after usual work up (**2a** → **2b**) 95% of half ester **9b**; $[\alpha]_D^{20} = -8.60°$ ($c = 6$, EtOH). A sample recrystallized from Et_2O/pentane had

m.p. 91–92°. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.3 (*d*, *J* = 7, 6 H, CH_3–C(2), CH_3–C(4)); 2.7 (*m*, 2 H, H–C(2), H–C(4)); 3.75 (*s*, 3 H, $COOCH_3$); 4.2 (*t*, *J* = 6, 1 H, H–C(3)); 7.0 (br. *s*, 2 H, OH, COOH). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 12.0, 12.2, 42.4, 52.0, 72.1, 175.9, 180.6.

*1-Methyl hydrogen (1*R,*2*S*)-1,2-cyclopropanedicarboxylate* (**10b**). Yield 92% (same as **2a** → **2b**). $[\alpha]_D^{20} = -11.0°$ (*c* = 7, EtOH). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.1–1.55 (*m*, 1 H, H–C(3)); 1.55–1.9 (*m*, 1 H, H–C(3)); 1.95–2.4 (*m*, 2 H, H–C(1), H–C(2)); 3.7 (*s*, 3 H, $COOCH_3$); 11.0 (*s*, 1 H, COOH) ([37]).

*1-Methyl hydrogen (1*S,*2*R*)-3,3-dimethyl-1,2-cyclopropanedicarboxylate* (**11b**). Diester **11a** (3.2 mmol) was hydrolyzed in 40 ml of phosphate buffer with 1000 units of PLE. The reaction was extremely slow and it was interrupted and worked up after one week. Yield 22.7% of **11b**; $[\alpha]_D^{20} = -11.2°$ (*c* = 0.06, EtOH); ([38]: $[\alpha]_D^{20} = +29.95°$ (EtOH)). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.2 (*s*, 3 H, CH_3–C(3)); 1.4 (*s*, 3 H, CH_3–C(3)); 1.9 (*s*, 2 H, H–C(1), H–C(2)); 3.6 (*s*, 3 H, $COOCH_3$); 9.7 (br. *s*, 1 H, COOH).

*1-Methyl hydrogen (1*R,*2*S*)-1,2-cyclobutanedicarboxylate* (**12b**). Diester **12a** was hydrolyzed and worked up under standard conditions (see **2a** → **2b**). Yield 99%; $[\alpha]_D^{25} = +2.68°$ (*c* = 5, EtOH). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.9–2.7 (*m*, 4 H, H_2C (3), H_2C (4)); 3.2–3.6 (*m*, 2 H, H–C(1), H–C(2)); 3.7 (*s*, 3 H, $COOCH_3$); 7.9 (*s*, 1 H, COOH). ([37]).

*1-Methyl hydrogen (1*S,*2*R*)-1,2-cyclopentanedicarboxylate* (**13b**). Diester **13a** was hydrolyzed and worked up under standard conditions (see **2a** → **2b**). Yield 80%. $[\alpha]_D^{20} = +1.1°$ (*c* = 4, EtOH). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.6–2.2 (*m*, 6 H, H_2C(3), H_2C(4), H_2C(5)); 2.8–3.1 (*m*, 2 H, H–C(1), H–C(2)); 3.6 (*s*, 3 H, $COOCH_3$); 9.2 (*s*, 1 H, COOH).

*1-Methyl hydrogen (1*S,*2*R*)-1,2-cyclohexanedicarboxylate* (**14b**). Following the standard procedure (**2a** → **2b**) the half ester **14b** was obtained in 98% yield. $[\alpha]_D^{20} = +5.0°$; $[\alpha]_{578}^{20} = +5.23°$ (*c* = 5.5, EtOH). Resolved monoester had $[\alpha]_{578} = -6.7°$ (*c* = 0.1, EtOH) [39]. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.1–2.4 (*m*, 8 H, H_2C(3), H_2C(4), H_2C(5), H_2C(6)); 2.6–3.1 (*m*, 2 H, H–C(1), H–C(2)); 3.7 (*s*, 3 H, $COOCH_3$); 8.2 (*s*, 1 H, COOH).

*1-Methyl hydrogen (1*S,*2*R*)-1,2-cyclohex-4-enedicarboxylate* (**15b**). From **15a** (same as **2a** → **2b**). Yield 95%; $[\alpha]_D^{20} = +14.6°$ (*c* = 0.2, EtOH). ^{1}H-NMR (60 MHz, $CDCl_3$): 2.0–2.8 (*m*, 4 H, H_2C(3) and H'_2C(6)); 2.8–3.2 (*m*, 2 H, H–C(1), H–C(2)); 3.7 (*s*, 3 H, $COOCH_3$); 5.65 (br. *s*, 2 H, H–C(4), H–C(5)); 10.1 (br. *s*, 1 H, COOH).

4. *α-Chymotrypsin-Catalyzed Hydrolysis of Dimethyl* meso*-2,4-Dimethylglutarate* (**8a**). Diester **8a** (5 mmol) in 10 ml of phosphate buffer was stirred with chymotrypsin (50 mg in 10 ml of H_2O) for 4 days at pH 7.5–8.0. After this time more chymotrypsin was added (50 mg in 10 ml of H_2O) and stirring continued for another 4 days. The reaction was interrupted and worked up in the usual way (**2a** → **2b**). Yield 48%; $[\alpha]_D^{20} = -4.83°$ (*c* = 7, $CHCl_3$).

5. *Preparation of lactones* **6c** *and* **9c–14c**. *(3*R,*4*S*)-3,4-Dimethyltetrahydrofuran-2-one* (**6c**). The half ester **6b** (2.8 mmol) in 2 ml of THF was treated at −20° under Ar with 5.5 ml of 1M borane-methylsulfide complex in THF. After addition the solution was allowed to warm to r.t. overnight. H_2O (1 ml) was added at 0° followed by solid K_2CO_3. After stirring for 1 h Et_2O and more K_2CO_3 were added and the solution was filtered through a short column of silica gel. After removal of the solvent the oily residue was dissolved in 10 ml of benzene. TsOH monohydrate (5 mg) was added and the mixture was refluxed by simultaneous removal of benzene (8 ml). The solution was diluted with benzene, filtered through silica gel, evaporated and the residue purified by bulb-to-bulb distillation; yield 49%; $[\alpha]_D^{20} = -8.5°$ (*c* = 4.5, $CHCl_3$). Reported for optically pure (*3*S,*4*R)-lactone: $[\alpha]_D^{20} = +39.9°$ (*c* = 11.3, $CHCl_3$) [16c]. ^{1}H-NMR (60 MHz, CCl_4): 1.05, (*d*, *J* = 6.5, 3 H, CH_3–C(4)); 1.15 (*d*, *J* = 6.5, 3 H, CH_3–C(3)); 2.4–3.1 (*m*, 2 H, H–C(3), H–C(4)); 3.9 (*dd*, *J* = 9, 2.5, 1 H, H–C(5)); 4.3 (*dd*, *J* = 9, 5.5, 1 H, H–C(5)).

*(3*R,*5*R,*4*S*)-3,5-Dimethyl-4-hydroxytetrahydro-2-pyrone* (**9c**). The half ester **9b** was reduced with 1M borane-methylsulfide complex in THF as for **6b** (yield 70%). The hydroxy-ester so obtained was dissolved in CH_2Cl_2 containing one drop of CF_3COOH and left overnight. The solution was diluted 1:1 with Et_2O and filtered through silica gel. Lactone **9c** was isolated with 96% yield. After crystallization from CH_2Cl_2/pentane the lactone had m.p. 88–90°; $[\alpha]_D^{20} = -4.4°$ (*c* = 5, MeOH) ([40]: m.p. 88–88.5°; $[\alpha]_D^{25} = -5.0°$ (*c* = 2, MeOH) ([41]: $[\alpha]_D = +5.5°$ (*c* = 1.1, MeOH)). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.1 (*d*, *J* = 7, 3 H, CH_3–C(5)); 1.45 (*d*, *J* = 7, 3 H, CH_3–C(3)); 2.0 (*m*, 1 H, H–C(5)); 2.5 (*m*, 1 H, H–C(3)); 3.3 (*t*, *J* = 8.5, 1 H, H–C(4)); 3.6 (*s*, 1 H, OH); 3.9 (*dd*, *J* = 11.5, 9.5, 1 H, H–C(6)); 4.4 (*dd*, *J* = 11.5, 4.5, 1 H, H–C(6)). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 13.6, 13.8, 36.7, 44.3, 70.7, 75.7, 174.3.

Lactone **9c** was dissolved in abs. MeOH and the solution was heated with six drops of anh. hydrazine in a closed vessel at 90° for 18 h. The solvent and excess hydrazine were removed under reduced pressure, and the solid residue was crystallized from EtOH/Et_2O; m.p. 138–139°; $[\alpha]_D^{20} = -41.0°$ (*c* = 1.9, MeOH) ([40]: m.p. 140–141°; $[\alpha]_D = -42°$ (*c* = 0.55, MeOH)).

(1R)-3-Oxabicyclo[3.1.0]hexan-2-one (**10c**). The half ester **10b** was reduced (yield 63%) and lactonized (b.p. 70°/8 Torr; yield 70%) as described for **6b** → **6c**; $[\alpha]_D^{20} = +62.0°$ ($c = 2.5$, $CHCl_3$). Reported for optically pure (1*S*)-lactone $[\alpha]_D^{20} = -61.8°$ ($c = 6.6$, $CHCl_3$) [16c].

(1S)-6,6-Dimethyl-3-oxabicyclo[3.1.0]hexan-2-one (**11c**). To a solution of 0.72 mmol of **11b** in 10 ml of THF were added dropwise 75 µl (0.75 mmol) of borane-methylsulfide complex. After stirring at r.t. for 1.5 h, H_2O (0.5 ml) was added and the mixture was then concentrated *i.v.* The residue was taken up in benzene and stirred with a catalytic amount of TsOH overnight. The mixture was filtered through silica gel, the solvents evaporated *i.v.* and the residue purified by bulb-to-bulb distillation (b.p. 140°/20 Torr). Yield 32.8%; $[\alpha]_D^{20} = +39.0°$ ($c = 0.03$, $CHCl_3$). Reported for (1*R*)-lactone with 81% e.e. $[\alpha]_D^{25} = -72.8°$ ($c = 1.4$, $CHCl_3$) [10]. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.1 (*s*, 6 H, $CH_3-C(6)$, $CH_3-C(6)$); 1.7–2.3 (*m*, 2 H, H–C(1), H–C(5)); 3.8–4.5 (*m*, 2 H, $H_2C(4)$).

(1R)-3-Oxabicyclo[3.2.0]heptan-2-one (**12c**). The half ester **12b** was reduced with borane-methylsulfide complex in THF (yield 94%) and lactonized (yield 95%) as for **6b** → **6c**, except that for lactonization a solution of the hydroxy-ester in CH_2Cl_2 (conc. 0.5M) was treated at r.t. overnight with one drop of CF_3COOH. The lactone **12c** was purified by distillation at 60–65°/1 Torr and GC on 10% *OV-17/Chromosorb P* at 190°; $[\alpha]_D^{20} = -107°$ ($c = 2.6$, $CHCl_3$). Reported for optically pure (1*S*)-lactone $[\alpha]_D^{20} = +118.7°$ ($c = 10$, $CHCl_3$) [16c]. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.8–2.8 (*m*, 4 H, $H_2C(6)$, $H_2C(7)$); 2.8–3.6 (*m*, 2 H, H–C(1), H–C(5)); 4.1–4.6 (*m*, 2 H, $H_2C(4)$).

(1S,5R)-3-Oxabicyclo[3.3.0]octan-2-one (**13c**)[2]. The half ester **13b** was reduced with borane-methylsulfide complex in THF (yield 86%) and lactonized with TsOH in CH_2Cl_2. The product was purified by distillation at 130°/0.4 Torr (yield 60%). $[\alpha]_D^{20} = +8.5°$ ($c = 1$, $CHCl_3$). Reported for optically pure (1*S*, 5*R*)-lactone: $[\alpha]_D^{25} = +96.9°$ ($c = 1$, $CHCl_3$ [16c]). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.2–2.2 (*m*, 6 H, $H_2C(6)$, $H_2C(7)$, $H_2C(8)$); 2.8–3.1 (*m*, 2 H, H–C(1), H–C(5)); 3.8–4.7 (*m*, 2 H, $H_2C(4)$).

(1R,6S)-8-Oxabicyclo[4.3.0]nonan-7-one (**14c**)[2]. The half ester **14b** was reduced as for **12b** → **12c** and the lactone **14c** was prepared by dissolving the hydroxy ester in 5 ml of MeOH/0.5 ml conc. HCl and stirring for 2 h at r.t. The mixture was diluted with Et_2O, washed with H_2O and brine and dried. After evaporation of solvents the residue was purified by a bulb-to-bulb distillation (170°/1 Torr). Yield 82%; $[\alpha]_D^{20} = +45°$ ($c = 1$, $CHCl_3$). Reported for (1*R*, 6*S*)-lactone $[\alpha]_D^{25} = +48.8°$ [16c]. ^{1}H-NMR (60 MHz, $CDCl_4$): 1.0–2.7 (*m*, 10 H, H–C(1), $H_2C(2)$, $H_2C(3)$, $H_2C(4)$, $H_2C(5)$, H–C(6)); 3.9 (br. *d*, $J = 9$, 1 H, H–C(9)); 4.15 (*dd*, $J = 9, 5$, 1 H, H–C(9)).

(1S,6R)-8-Oxabicyclo[4.3.0]non-3-ene-7-one (**15c**)[2]. The half ester **15b** (4.5 mmol) was dissolved in 10 ml of H_2O containing 4.6 mmol of LiOH. After standing at r.t. for a few minutes, the solution was evaporated *i.v.*, and the residue was dried *i.v.* (0.1 Torr). The so obtained Li-salt was suspensed in 10 ml of dry THF under Ar. To this suspension were added 8 mmol of $LiBH_4$ in 10 ml of Et_2O, and the mixture was heated for 2 h at 50°. Excess hydride was quenched by the addition of MeOH (2 ml) and the mixture was heated for 30 min at 50°. After evaporation of the solvent under reduced pressure, the contents were diluted with H_2O, brought to pH 2.0, and extracted with AcOEt. The dried extracts were evaporated *i.v.* and the residue was dissolved in benzene containing a catalytic amount of TsOH. After 1 h at r.t. the mixture was filtered through silica gel and eluted with Et_2O. Yield 68%; b.p. 140°/0.5 Torr; $[\alpha]_D^{20} = +51.1°$ ($c = 1.5$, $CHCl_3$). Reported for (1*R*, 6*S*)-lactone $[\alpha]_D^{20} = -67.1°$ ($c = 1$, $CHCl_3$) [16c]. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.4–3.0 (*m*, 6 H, H–C(1), H–C(6), $H_2C(2)$, $H_2C(5)$); 3.95 (*dd*, $J = 9, 1$, 1 H, H–C(9)); 4.3 (*dd*, $J = 9, 4$, 1 H, H–C(9)); 5.75 (br. *s*, 2 H, H–C(3), H–C(4)).

(1S,6R)-8-Oxabicyclo[4.3.0]nonan-7-one (**14c**)[2]. (1*S*, 6*R*)-Lactone **15c** (3 mmol) was dissolved in 10 ml of AcOEt and hydrogenated with 10% Pd/C (0.020 g) under atmospheric pressure at r.t. After 1 h the catalyst was filtered of and the solvents evaporated *i.v.* The residue was distilled (140°/0.4 Torr). Yield 99%; $[\alpha]_D^{20} = -48.4°$ ($c = 0.6$, $CHCl_3$). ^{1}H-NMR (60 MHz, $CDCl_3$): 0.9–2.8 (*m*, 10 H, H–C(1), H–C(6), $H_2C(2)$, $H_2C(3)$, $H_2C(4)$, $H_2C(5)$); 3.95 (br. *d*, $J = 9$, 1 H, H–C(9)); 4.2 (*dd*, $J = 9, 5$, 1 H, H–C(9)).

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[2]) According to IUPAC nomenclature the lactones **13c**, **14c** and **15c** are named as derivatives of 1*H*-cyclopenta-[*c*]furan and isobenzofuran, respectively.

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