Enzyme-Catalyzed Asymmetric Synthesis. 8.[1] Enantioselectivity of Pig Liver Esterase Catalyzed Hydrolyses of 4-Substituted Meso Cyclopentane 1,2-Diesters

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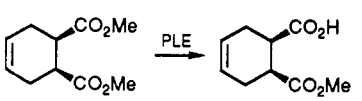
Hydrolyses of *meso*-1,2-cyclopentanedicarboxylic acid bis(methyl esters) bearing in the 4-position an oxo, methylene, *cis*-hydroxy, *trans*-hydroxy, *cis*-acetoxy, *trans*-acetoxy, *cis*-methoxy, *cis*-*tert*-butoxy, ethylenedioxy, propylenedioxy, dimethyl propylenedioxy, and butylidenedioxy substituent, respectively (see **3–14**), catalyzed by pig liver esterase (PLE), are enantioselective, giving acid–esters (see **18–29**) with ee values ranging from 0 to 87%. There are substrate-induced enantioselectivity reversals depending on the configuration and nature of the substituent in the 4-position. Whereas, e.g., in the hydroxy diester **5** the *R*-center ester group is hydrolyzed preferentially it is the *S*-center ester group in the *tert*-butoxy diester **8**. The meso cyclopentane diester derivatives **4–14** are all derived from meso keto diester **3**, which in turn can be prepared from meso cyclohexene diester **1** on a preparative scale by routine procedures. PLE-catalyzed hydrolysis of the substituted cyclopentanoid and cyclohexanoid diesters **15** and **16**, respectively, whose ester groups are separated by a CH_2 group from the stereogenic ring atoms proceeds with opposite selectivity as compared to diesters **3** and **1** to give acid–esters **30** and **31**, respectively. On the other hand, hydrolysis of diesters **15** and **16** catalyzed by α-chymotrypsin (α-CT) yielded the enantiomeric acid–esters *ent*-**30** and *ent*-**31**, respectively. Interpretation of the enantioselectivities within currently proposed selectivity models for PLE was not satisfactory. Some of the acid–esters obtained (see **18**, **20**, **23**, **30**, *ent*-**30**, and *ent*-**31**) are of potential or demonstrated value as chiral educts for the synthesis of biologically active cyclopentanoids.

Introduction

The ability of enzymes to differentiate enantiotopic groups in meso or other prochiral compounds provides excellent opportunities for asymmetric synthesis.[3,4] Esterases and lipases are among the most attractive enzymes in this regard because they do not need coenzymes and lipases act on such substrates even in organic solvents of low water content.[5] Pig liver esterase (PLE),[6] although a complex mixture of trimeric isoenzymes which behave more or less differently in regard to substrate specifity,[6e] pH dependence,[6e,f] inhibition or activation by organic solvents[6e] or other compounds,[6b] and enantioselectivity,[6i] is one of the most useful hydrolases for discrimination between enantiotopic ester groups.[7-9] This has been amply demonstrated and is impressively exemplified by the PLE-catalyzed enantioselective hydrolysis of meso diester **1**, which proceeds on a 100-mol scale,[10] to give in high chemical and optical yield acid–ester **2**.[7g,h,o] We have demonstrated its usefulness as a chiral educt by synthesizing[11] optically active brefeldins,[12a,c] prostaglandin precursors,[12b-d] carbacyclins,[12e-g] and isocarbacyclins.[12h] From a synthetic point of view it seems worthy to recall that by appropriate chemoselective transformations acid–esters like **2** can give access to both enantiomers of target compounds.[7h,l,o,q,u]



1 **2**

A two-faced aspect of PLE besides its beneficially low substrate specifity and frequently met high enantioselectivity is the substrate structure induced reversal of the latter which has been observed in both the monocyclic[7b,g,h,k-m,p] and acyclic series[7b,z,8a,d,g,l] of substrates. While a possible disadvantage for the general use of PLE in asymmetric synthesis, it can provide a synthetic oppor-

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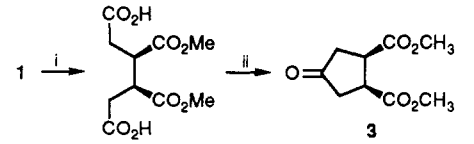
tunity for obtaining both enantiomers with one enzyme[13] by a "synthetically reversible" substrate modification[8a] and a tool for the development or refinement of enantioselectivity models for PLE.[3f,7g,l,8k] An illustrative example is the PLE-catalyzed hydrolysis of unsubstituted monocyclic meso compounds with a 1,2-bis(alkoxycarbonyl) moiety[7g,h,k,l] where there is a reversal of selectivity on going from the 3- to the 6-membered ring, with the 5-membered ring not only representing the changeover point but also the system with the lowest selectivity. *meso*-1,2-Cyclopentane diesters bearing in the 1/2-, 3/5- or 4-position substituents which differ in respect to stereochemistry, size, and/or polarity should be therefore interesting probes for the enantioselectivity of PLE, and in case of synthetically useful enantiomeric excesses (ee's), valuable educts for the synthesis of cyclopentanoids.[12,14] Related studies with prochiral malonates[7s,8g] and conformationally more flexible prochiral glutarates[7z,8a,l,n] have already been reported.

In this paper we describe the results of the PLE-catalyzed hydrolyses of the more rigid and conformationally restricted cyclopentanoid *meso*-1,2-dicarboxylic acid diesters **3**–**14** having different and preparative useful substituents in the 4-position. PLE-catalyzed hydrolysis has been extended to the cyclopentanoid and cyclohexenoid meso diesters **15** and **16**, respectively, which have a 1,2-bis[(methoxycarbonyl)methyl] moiety. Their hydrolysis catalyzed by α-chymotrypsin (α-CT) was also investigated because of synthetic reasons.

Scheme I[a]



17 3

[a] Reagents: (i) $KMnO_4$, H_2O; (ii) Ac_2O, NaOAc, reflux.

Results

The meso keto diester **3**,[15a] which served as a key intermediate for the synthesis of all but two diesters, was prepared by a two-step route optimized for a mole scale from meso diester **1**[16] using unexceptional methods (Scheme I). Thus, oxidative cleavage of the double bond in **1** with potassium permanganate in water gave a 89% yield of meso diacid **17**.[17] Decarboxylative cyclization[18]

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(13) This seems to be generally possible with lipases where via selective esterification of prochiral diols in organic solvents and hydrolysis of the corresponding diacetates in water both enantiomeric monoacetates are available, see: ref 5b–d.

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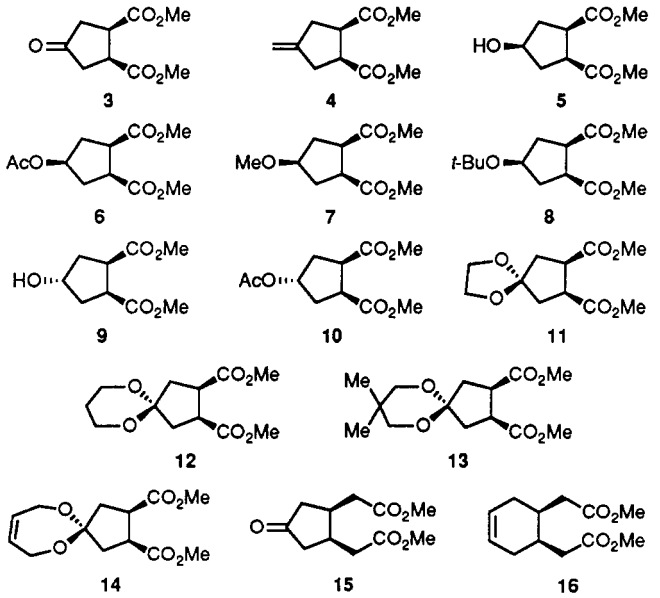
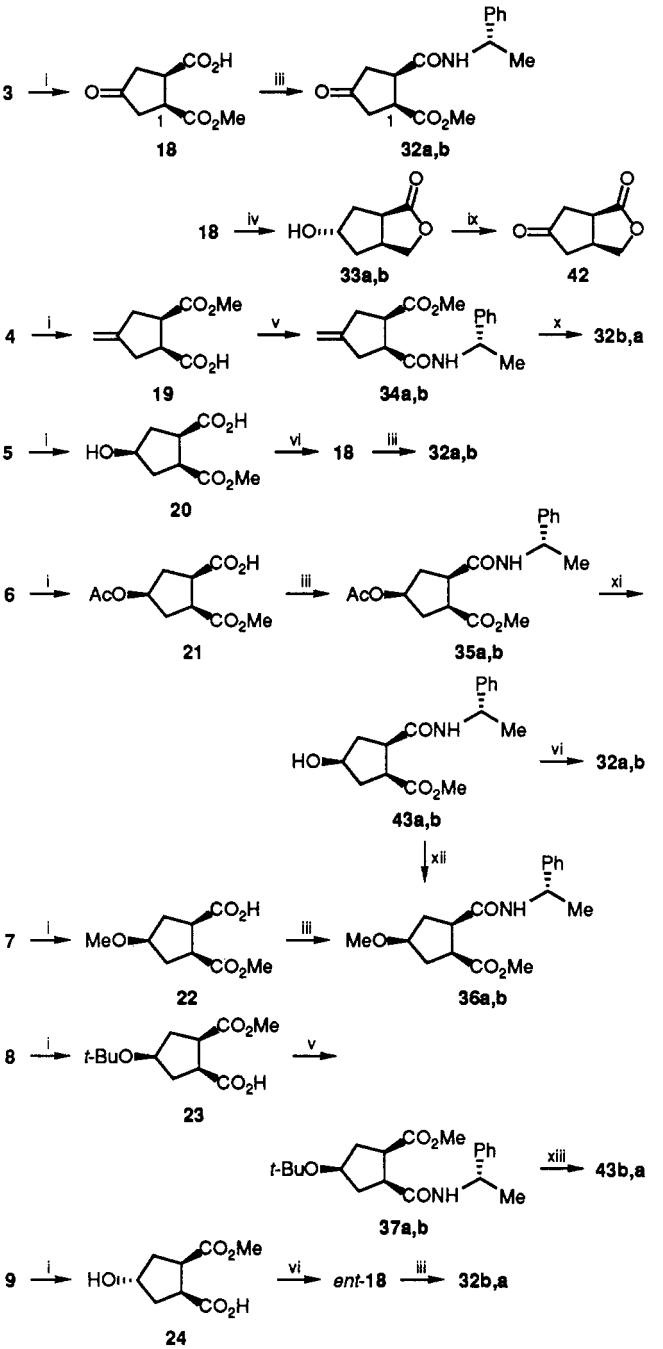
of **17** in acetic anhydride with sodium acetate led after distillative workup to **3** contaminated with approximately 5% of its racemic C_2 isomer. Crystallization from ether furnished pure **3** in 73% yield. A prerequisite for keeping isomerization of **3** to its C_2 isomer to a minimum is the removal of sodium acetate before distillative workup. Conversion of the keto diester **3** into the methylene diester **4**[19] could be accomplished in acceptable yield by treatment with a $Zn-CH_2Br_2-TiCl_4$ mixed reagent.[20] *cis*-Hydroxy diester **5** was obtained from **3** by catalytic hydrogenation with 92% de, whereas the trans hydroxy diester **9** was derived from **5** by Mitsunobu reaction[21] via the trans acetoxy diester **10**. The meso diesters **6–8** and **11–14** were prepared from **5** and **3**, respectively, by routine procedures. Via a published route[4e] which was optimized for preparative scale, the meso diacetic acid diester **16** was obtained from **1**. Meso diester **15**[15] was prepared from **16** in two steps analogous to those used in the synthesis of **3**.



The PLE- and α-CT-catalyzed hydrolyses of **3–16** were carried out in 0.15 M aqueous phosphate buffer at pH 7.0 and pH 8.0, respectively, and room temperature.[7h] Organic cosolvents were generally not added (see later) although all diesters except hydroxy diesters **5** and **9** have only a low solubility in water. The pH was held at this level by the addition of 0.5 M aqueous sodium hydroxide from an autoburett. Each reaction was worked up after 1 equiv of base had been consumed, and the half esters **18–25**, **29**, **30**, *ent*-**30**, **31**, and *ent*-**31** were isolated in good yield (Scheme II and III). In case of the ketal acid–esters **26–28** acidic workup caused extensive deketalization to *rac*-**18** and *ent*-**18**, respectively. Purification of *rac*-**26** and **27** was not easily executed.

The ee's of acid–esters **18**, **19**, **21**, **22**, **23**, **25**, **30**, *ent*-**30**, **31**, and *ent*-**31** were determined by conversion into the corresponding (*S*)-1-phenylethyl amides with (1*S*)-phenylethylamine[22] and analyzed by ^1H NMR spectroscopy and are accurate to ≤±3%. In each diastereomeric amide mixture (**a**, **b**) the methoxycarbonyl signals were separated. The acetoxy signals of **35a,b** and **38a,b**, the methoxy signals of **36a,b**, and the *tert*-butoxy signals of **37a,b** were separated too. In all cases base-line separation of the methoxycarbonyl signals and the methyl signals for the (1-phenylethyl)carbamyl group could be achieved in the ^1H NMR spectra in the presence of 0.8 equiv of Eu(fod)$_3$. NMR measured ee's were checked in the case of **32a,b** by HPLC (accuracy ≤±1%); the two assays compared favorably. In the case of acid–esters **30** and *ent*-**30**

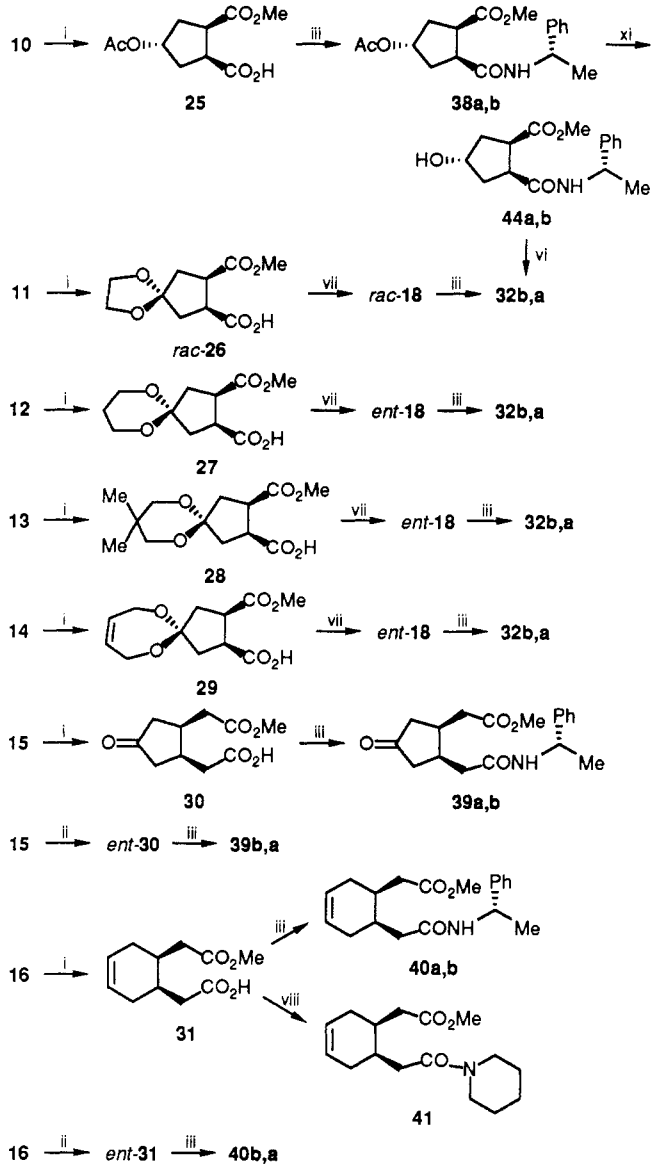
Scheme II[a,b]



[a] Reagents: (i) PLE, H_2O, pH 7.0; (ii) α-CT, H_2O, pH 8.0; (iii) $(COCl)_2$, CH_2Cl_2; (*S*)-$H_2NCH(Ph)CH_3$; (iv) Na, EtOH, NH_3; H_3O^+; (v) Im_2CO, THF; (*S*)-$H_2NCH(Ph)CH_3$; (vi) Me_2SO, $(COCl)_2$, CH_2Cl_2; NEt_3; (vii) H_3O^+; (viii) $SOCl_2$, CH_2Cl_2; piperidine; (ix) Py·HCl·CrO_3, CH_2Cl_2; (x) O_3, CH_2Cl_2; Me_2S; (xi) MeOH, TsOH·H_2O; (xii) CH_2N_2, BF_3·Et_2O; (xiii) CF_3COOH. [b] For all acid–esters except **26** and amide **41** the confirmation shown is that of the major enantiomer. In the case of diastereomers (**a**, **b**) the configuration shown is that of the diastereomer designated as **a**, and the first listed in the formula number is the major one except the amides formed from *rac*-**18**.

(17) Akermark, B. *Ark. Kem.* **1967**, *27*, 11.
(18) Minssen-Guette, M.; Jacques, J.; Rettenmaier, R.; Wakmunski, F. S.; Jonston, D. B. R.; Windholz, T. B. *J. Med. Chem.* **1969**, *12*, 388.
(19) Binger, P.; Schuchardt, U. *Chem. Ber.* **1981**, *114*, 3313.
(20) Lombardo, L. *Org. Synth.* **1986**, *65*, 81.
(21) Mitsunobu, O. *Synthesis* **1981**, 1.
(22) Rosen, T.; Waranabe, M.; Heathcock, C. H. *J. Org. Chem.* **1984**, *49*, 3657.

Scheme III[a]



[a] See footnotes *a* and *b* of Scheme II.

^{1}H NMR determination of ee values was also possible by observing different methoxycarbonyl signals for the diastereomeric salts formed upon addition of 1 equiv of (−)-ephedrine.[7h]

Hydroxy acid–esters **20**, **24**, and ketal acid–esters *rac*-**26** and **27**–**29** were converted to *rac*-**18** and *ent*-**18**, respectively, as outlined in Schemes II and III, and as such analyzed. Control experiments with racemic acid–esters established that no enantiomer differentiation occurred during amide formation and that deketalization of acid–esters **27**–**29** was not accompanied by racemization. The results are summarized in Table I.

Amides **32a** and **39a** could be obtained diastereomerically pure by recrystallization, and amides **32a,b** and **34a,b** were separated by MPLC[23] which should be possible in the case of the other amides, too.

The (1*R*)-[(*S*)-1-phenylethyl] amides **32b**, **34a**, **35b**, **38a**, **43b**, and **44a** exhibit the ^{1}H NMR signal for the methoxycarbonyl group at significantly higher field than the diastereomeric (1*S*)-[(*S*)-1-phenylethyl] amides **32a**, **34b**, **35a**, **38b**, **43a**, and **44b**. Judging from the generally preferred conformation of the (1-phenylethyl)carbamyl group, this should be due to the anisotropic effect exerted by the phenyl group. The opposite situation, however, is encountered with the diastereomeric amides **36a,b** and **37a,b** where the ester group in the (1*S*)-[(*S*)-1-phenylethyl] amides **36a** and **37b** resonates at higher field.

Table I. Enzyme-Catalyzed Hydrolyses of Diesters 3–16

entry	enzyme	diester	acid–ester	ee, %	$t_{1/2}$, h
1	PLE	**3**	(+)-(1*S*-*cis*)-**18**	72 (82)[a]	6.4
2	PLE	**4**	(+)-(1*R*-*cis*)-**19**	22	30
3	PLE	**5**	(+)-(1*S*-*cis*)-**20**	80	24.2
4	PLE	**6**	(+)-(1*S*-*cis*)-**21**	52	18.5
5	PLE	**7**	(+)-(1*S*-*cis*)-**22**	58	29
6	PLE	**8**	(−)-(1*R*-*cis*)-**23**	84	22
7	PLE	**9**	(−)-(1*R*-*cis*)-**24**	22	182
8	PLE	**10**	(−)-(1*R*-*cis*)-**25**	27	9.8
9	PLE	**11**	(±)-**26**	0	7.3
10	PLE	**12**	(2*R*-*cis*)-**27**	48	9.4
11	PLE	**13**	(−)-(2*R*-*cis*)-**28**	16	72
12	PLE	**14**	(−)-(2*R*-*cis*)-**29**	47	5.6
13	PLE	**15**	(−)-(1*S*-*cis*)-**30**	80 (87)[b]	8.0
14	α-CT	**15**	*ent*-**30**	83	
15	PLE	**16**	(−)-(1*S*-*cis*)-**31**	68	7.0
16	α-CT	**16**	*ent*-**31**	86	

[a] In the presence of 10% methanol. [b] In the presence of 2% acetonitrile.

The absolute configuration of acid–ester **18** and thus of amides **32a,b** was determined by chemical correlation with the (+)-(3a*S*-*cis*)-lactone **42**.[12a] Reduction of acid–ester **18** with sodium and ethanol in liquid ammonia[7h] gave after acidic workup the hydroxy lactones **33a,b** as a 4:1 mixture, which was oxidized to the brefeldin precursor **42** in 57% overall yield. Correlation of the other amides as shown in Schemes II and III led to the assignment of the absolute configuration of **19**–**29**. The absolute configuration of **30** was determined by chemical correlation.[24] Acid–ester **31** was converted to the amide **41** of known absolute configuration.[25]

Discussion

The cyclopentanoid diesters **3**–**15** and the cyclohexanoid diester **16** are all substrates for PLE (entries 1–13 and 15 in Table I). Further hydrolysis of the acid–esters **18**–**29** to the corresponding meso diacids was very slow. In fact, hydrolysis came practically to a complete halt after the consumption of 1 equiv of sodium hydroxide. Further hydrolysis to the corresponding meso diacids occurred to a small extent only in the case of the acid–esters **30** and **31**. Large differences in rates of PLE-catalyzed hydrolysis of dicarboxylic acid diesters and the corresponding acid-esters (as salt) have been noted in almost all cases described thus far in the literature.[6a,7,8] The half-life time for PLE-catalyzed hydrolysis of diesters **3**–**16** varies considerably. The two extremes are the unsaturated ketal diester **14** and the *trans*-hydroxy diester **9** for which $t_{1/2}$ values of 5.6 and 182 h (entries **12** and **7**), respectively, were noted. Interestingly, the *cis*-hydroxy diester **5** (entry 3) is hydrolyzed much faster than its trans isomer **9**. No obvious correlation exists between the $t_{1/2}$ value for diester

(23) G. Helmchen, B. Glatz, *Ein einfaches System und Säulen höchster Trennleistung zur präparativen Mitteldruck-Flüssigkeitschromatrographie*, Addendum to Habilitation Thesis, G. Helmchen, Stuttgart (FRG), 1980.

(24) Acid–ester **30** was converted into (−)-[3′a*R*-(3′aα,4′α,6′aα]-hexahydro-5,5-dimethyl-5′-oxospiro[1,3-dioxane-2,2′(1′*H*)-pentalene]-4′-carboxylic acid methyl ester (*cup*. Mori, K.; Tsuji, M. *Tetrahedron* **1986**, *42*, 435) by a route similar to the one described in ref 25a: Zatorski, A., Gais, H.-J., unpublished results.

(25) (a) Nagao, Y.; Nakamura, T.; Ochiai, M.; Fuji, K.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1987**, 267. (b) Nagao, Y.; Nakamura, T.; Kume, M.; Ochiai, M.; Fuji, K.; Fujita, E. J. *Ibid.* **1987**, 269.

hydrolysis and the ee value of the acid-ester.

As anticipated, not only the rate but also the enantioselectivity of the PLE-catalyzed hydrolysis of diesters **3–14** is influenced heavily by the nature and configuration of the substituent in the 4-position. We made similar observations in the porcine pancreas lipase catalyzed hydrolysis of structurally related *meso*-1,2-cyclopentanedimethanol diacetates.[5c] Hydrolysis of the keto diester **3** proceeds preferentially at the *R*-center ester group producing the keto acid–ester **18** with an ee value of 72% (Scheme II) which could be raised to 96% by recrystallization from ethyl acetate as shown by HPLC analysis of **32a,b**; ee enhancement by preferential crystallization of racemate has been observed in the case of acid–ester **2**.[7h] PLE-catalyzed hydrolysis of the racemic C_2 isomer of **3**, however, was reported to give with high enantiomer selectivity the corresponding 1*S*,2*S*-acid–ester besides the 1*R*,2*R*-diester.[9o] Hydrolysis of **3** is slower than that of its 1*S*,2*S*-isomer.[2a]

Replacing the oxo substituent of **3** by a methylene substituent leads to a preferential *S*-center ester group hydrolysis of diester **4** to give acid–ester **19** but having only an ee of 22%. For the isomeric olefinic diester **1**, the selectivity of PLE is opposite and very high.[7g,h,o] Enantioselectivity reversal of PLE caused by the presence or absence of a heteroatom has been noted before in the case of *meso*-cyclopentane-1,3-dicarboxylates.[7p]

A *cis*-hydroxy group in the 4-position again results in a *R*-center ester group selective hydrolysis. The acid–ester **20** was isolated with 80% ee from diester **5**. The situation doesn't change much with the acetoxy and methoxy diesters **6** and **7** except the ee values of the acid–esters **21** and **22** are lower (entries 4 and 5). There is a clear reversal of selectivity, however, in the case of the cis-configurated *tert*-butoxy diester **8** (entry 6). Here the *S*-center ester group is preferentially hydrolyzed by PLE, which leads to the acid–ester **23** having an ee of 84%. Similar findings have been made in the case of the methyl and *tert*-butyl ethers of dimethyl (hydroxymethyl)methylmalonate.[8g] The attainment of **23** demonstrates that both enantiomeric hydroxy acid–esters **20** and *ent*-**20** are accessible starting from *meso*-diester **5** with PLE.

Introduction of a substituent in the 4-position trans to the ester groups also causes a reversal of selectivity as exemplified by the hydrolysis of the diesters **9** and **10** to the acid–esters **24** and **25**, respectively (entries 7 and 8). Selectivities, however, are only marginal. It is worth noting that in the case of the PLE-catalyzed hydrolysis of the acetoxy diesters **6** and **10** the acetoxy group remains intact (entries 4 and 8).

In the series composed of the keto diester **3** and the ketal diesters **11–14** the ethylene ketal diester **11** represents the changeover point (entries 1 and 9–12). Whereas in **3** the *R*-center ester group is hydrolyzed preferentially no selectivity is observed with **11** and in the sterically more demanding ketal diesters **12–14** the *S*-center ester group is the one which is attacked preferentially. In the above series only acid–esters **18**, **20**, and **23** (entries 1, 3, and 6) were obtained with half-way acceptable ee values.

Attempts to raise the ee's of acid–esters **18–31** to higher levels by variation of the ester alkoxy group[7e,8m,9d] in **3–16** or by adding organic solvents[7s,y,z,8c,e,9l] were with the exemption of diesters **3** and **15** not made. Thus, PLE-catalyzed hydrolysis of **3** in the presence of 10% acetone, 10% *tert*-butyl alcohol, 2% acetonitrile, and 2% pyridine, respectively, was found to be much slower and less enantioselective (60–65% ee). With 10% methanol, hydrolysis was slower, too, but the ee value of acid–ester **18** was raised to 82%. In the case of **15** selectivity and reaction time were also influenced by cosolvent. Thus, with 2% acetonitrile or 10% *tert*-butyl alcohol longer reaction times and slightly higher ee values (84–87%) were encountered.

Interestingly, selectivity reversal is observed when the ester groups are separated by a CH_2 group from the stereogenic ring atoms as exemplified by the hydrolysis of **15** and **16** (entries 13 and 15) compared to **3** and **1**. Whereas in **1** and **3** the *R*-center ester group is attacked by PLE, it is the opposite enantiotopic ester group in **15** and **16** (because of a priority change of ligands, also designated as *R*-center ester group) which is hydrolyzed preferentially, leading to the acid–esters **30** and **31** having ee values of 80 and 68%, respectively. No such reversal was noted, however, in the case of the PLE-catalyzed hydrolysis of dimethyl *meso*-epoxysuccinate[8d] and *meso*-epoxyadipate.[7l]

Hydrolysis of **15** and **16** with large amounts of α-CT led to the enantiomeric acid–esters *ent*-**30** and *ent*-**31**, respectively (entries 14 and 16). Small amounts of the corresponding *meso* diacids were formed, too. Reversal of selectivity on switching from PLE to α-CT for a given substrate has been noted before, e.g., in the case of prochiral 3-hydroxyglutarates.[8d,h,l]

While acid–ester *ent*-**31**, previously obtained by a less efficient nonenzymatic route, has already been used as an educt for the synthesis of carbacyclin[25a] and isocarbacyclin,[25b] acid–esters **30** and *ent*-**30** may eventually serve the same purpose.[24]

Conclusion

The results presented here on the enantioselectivity of PLE-catalyzed hydrolyses of functionalized cyclopentanoid and cyclohexanoid diesters (see **3–15** and **16**, respectively) extend further the usefulness of PLE in asymmetric synthesis. Some of the acid–esters **18–30**, *ent*-**30**, and *ent*-**31** obtained should be useful building blocks for cyclopentanoid natural product synthesis. The remarkable feature of PLE to induce selectivity reversals within a series of structurally related substrates has again surfaced. Some obvious correlations between substrate structure and selectivity can be derived from an inspection of the data for the PLE-catalyzed hydrolysis of diesters **3–16** (Table I). Compared to the parent dimethyl *meso*-1,2-cyclopentanedicarboxylate,[7g,l] polar substituents like oxo and *cis*-hydroxy cause the hydrolysis to be much more selective for the *R*-center ester group. Changing the *cis*-hydroxy group to a *cis*-methoxy or *cis*-acetoxy group leads to a diminished selectivity, perhaps because of their reduced polarity and/or increased size. The reversal of selectivity observed in the case of the *cis*-*tert*-butoxy group would thus fit into this picture. Introduction of a nonpolar substituent like methylene or changing the hydroxy and acetoxy groups from cis to the ester groups to trans reverses the stereoselectivity. The ketals **11–14** have essentially both a *cis*- and *trans*-alkoxy substituent, and therefore low selectivity compared to **6** and **10** might naively be expected. We were, however, unable to explain the selectivity reversals and differing $t_{1/2}$ values recorded in the enzymatic hydrolysis of **3–16** within currently proposed substrate[7g] or active-site[3f,7l,8k] oriented enantioselectivity models for PLE. The opposing selectivities found for the enantiomeric and enantiomer differentiation, respectively, in the group composed of the structurally related diesters **1**, **3**, **15**, **16** and dimethyl *meso*-cyclopropanedicarboxylate,[7g,l] and the C_2 isomers of **3**,[9o] dimethyl 1,2-cyclopentanedicarboxylate,[9m] and dimethyl 1,2-cyclohexanedicarboxylate[7s] may serve to illustrate the interpretative difficulties connected with PLE. The iso-

enzyme composition of PLE may well be a major obstacle for the development of selectivity models like the Cohen model for α-CT[26] or the Prelog–Dutler–Jones model[27] for horse liver alcohol dehydrogenase. A perhaps even greater handicap is the complete lack of information on the three-dimensional structure of PLE. Incidentally, its physiological role is also unknown.[6d,e]

Experimental Section

Melting points are uncorrected. Bath temperatures are given for Kugelrohr distillations. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ unless otherwise stated. Mass spectra were recorded utilizing electron impact (EI) ionization and/or chemical ionization (CI) techniques. Optical rotations were obtained in MeOH unless otherwise stated. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} analytical plates using the same solvents as for column chromatography. Column chromatography was performed on Merck silica gel, 0.040–0.063 mm, and MPLC on Merck silica gel, 15–25 μm, with the indicated solvents. High-pressure liquid chromatography (HPLC) was performed on a Macherey-Nagel-120, 4 × 300 mm, 5 μm silica gel column with *tert*-butyl methyl ether/*n*-hexane/2-propanol, 75:20:5 (flow rate 1 mL/min), as eluent (UV detection at 254 nm). All enzymatic hydrolysis reactions were carried out with a Metrohm pH-stat. Pig liver esterase (PLE, EC 3.1.1.1, 130 units/mg protein, suspension in 3 M $(NH_4)_2SO_4$ solution) was purchased from Boehringer GmbH, Mannheim, and α-chymotrypsin (α-CT, EC 3.4.21.1, 59 units/mg protein, type II) from Sigma GmbH (FRG). The general purification and analytical procedures used were as described previously.[7h]

***meso*-3,4-Bis(methoxycarbonyl)hexanedioic Acid (17).** To a well-stirred solution of $KMnO_4$ (1 kg, 6.3 mol) in water (3.6 L) was slowly added at 0 °C alkene **1** (396 g, 2.0 mol). The temperature of the reaction mixture should not exceed 5 °C (ice–NaCl cooling bath). After being stirred for 3–4 h at room temperature, gaseous SO_2 was passed into the well-stirred mixture at 5 °C (ice–NaCl cooling bath) until all MnO_2 was reduced. The pink solution was carefully acidified to pH 2.0 by the addition of concentrated HCl (evolution of SO_2!), salts were removed by decantation, and the aqueous phase was extracted with THF/EtOAc (1:1, 5 × 200 mL). The combined extracts were dried with $MgSO_4$ and concentrated in a rotary evaporator. The solid residue was recrystallized from EtOAc/*n*-hexane (dissolution in hot EtOAc and addition of *n*-hexane until a turbidity appeared) to give **17** (470 g, 89%) as white crystals: mp 147 °C; ^1H NMR (250 MHz, $CDCl_3/CD_3OD$, 1:1) δ 2.17 (dd, J = 17.0, 4.2 Hz, 2 H), 2.49 (dd, J = 17.0, 9.5 Hz, 2 H), 3.02 (m, 2 H), 3.46 (s, 6 H), 4.39 (br s, 2 H); ^{13}C NMR ($CDCl_3/CD_3OD$, 1:1) δ 32.71, 42.13, 51.78, 172.83, 173.31. Anal. Calcd for $C_{10}H_{14}O_8$ (262.2): C, 45.80; H, 5.38. Found: C, 45.74; H, 5.35.

***cis*-4-Oxo-1,2-cyclopentanedicarboxylic Acid Bis(methyl ester) (3).** A well-stirred suspension of dicarboxylic acid **17** (470 g, 1.79 mol) and anhydrous NaOAc (120 g) in Ac_2O (2.2 L) was heated under reflux. After CO_2 evolution had ceased (1–2 h), the reaction mixture was cooled and stored for 10 h at 5 °C in a cold room. Precipitated NaOAc was filtered off, and Ac_2O was removed under reduced pressure. After removal of an additional crop of NaOAc, the oily residue was purified by short-path distillation (bath temperature 120 °C, 10^{-3} Torr) using a saberlike distilling head. It is important to remove NaOAc as completely as possible before distillation in order to prevent partial epimerization of **3** to its racemic C_2 isomer. After recrystallization of the semicrystalline material from Et_2O, **3** (263 g, 73%) was obtained as white needles (the mother liquor consists mainly of **3**, its racemic C_2 isomer, and the corresponding enol acetates): mp 58 °C (a lower melting point indicates the presence of the C_2 isomer); ^1H NMR (250 MHz) δ 2.50 (ddd, J = 18.9, 7.0, 2.5 Hz, 2 H), 2.76 (ddd, J = 18.9, 5.2, 1.7 Hz, 2 H), 3.46 (m, 2 H), 3.74 (s, 6 H); ^{13}C NMR (75 MHz) δ 40.33, 43.24, 52.25, 172.68, 213.18; MS (EI, 70 eV) m/z (%) 200 (M^+, 15), 169 (54), 168 (32), 140 (36), 114 (93), 113 (44), 71 (76), 59 (48), 55 (100); IR (KBr) 2960, 1740, 1442, 1410, 1370, 1333, 1290, 1251, 1224, 1200, 1175, 1119, 1087, 1029, 1014, 988, 925, 892, 850, 836 cm^{-1}. Anal. Calcd for $C_9H_{12}O_5$ (200.2): C, 53.99; H, 6.05. Found: C, 54.06; H, 6.10.

***cis*-4-Methylene-1,2-cyclopentanedicarboxylic Acid Bis(methyl ester) (4).** In a 250-mL round-bottomed flame-dried flask were placed under nitrogen in the strict exclusion of moisture-activated Zn[20] (2.88 g, 44 mmol), dry THF (25 mL), and dry CH_2Br_2 (1 mL, 14 mmol). To the stirred mixture was added dropwise at −40 °C freshly distilled $TiCl_4$ (1.15 mL, 10.3 mmol) over a 15-min period. After the cooling bath was removed, the mixture was stirred at 0 °C in a cold room for 3 days under nitrogen. The gray slurry was diluted with dry CH_2Cl_2 (5 mL) and cooled to 0 °C. To the stirred mixture was added slowly a solution of **3** (2.00 g, 10 mmol) in dry CH_2Cl_2 (8 mL) within 10 min. After having stirred at room temperature for 1 h, the resulting dark gray mixture was diluted with EtOAc (40 mL) and quenched by careful addition of aqueous $NaHCO_3$ (5 g in 10 mL) over a period of 30 min. The organic layer was separated, dried with $MgSO_4/NaHCO_3$, and concentrated. Chromatography (EtOAc/*n*-hexane, 1:1; R_f (**3**) 0.41; R_f (**4**) 0.59) and Kugelrohr distillation (90 °C, 10^{-3} Torr) gave **4** (1.3 g, 65%) as a colorless oil: ^1H NMR (250 MHz) δ 2.57–2.71 (m, 2 H), 2.74–2.87 (m, 2 H), 3.17 (m, 2 H), 3.67 (s, 6 H), 4.94 (quin, J = 2.3 Hz, 2 H); ^{13}C NMR (20 MHz) δ 35.31, 46.41, 51.78, 107.40, 147.58, 173.61; MS (EI, 70 eV) m/z (%) 198 (M^+, 4), 167 (54), 166 (41), 138 (100), 107 (41), 79 (100), 78 (56), 77 (50), 59 (38); IR (film) 3075, 2980, 2955, 1840, 1740, 1660, 1436, 1360, 1290, 1250, 1200, 1170, 1034, 917, 884 cm^{-14}, HRMS calcd for $C_{10}H_{14}O_4$ 198.0893, obsd 198.0894.

(1α,2α,4α)-4-Hydroxy-1,2-cyclopentanedicarboxylic Acid Bis(methyl ester) (5). Ketone **3** (15.0 g, 75 mmol) dissolved in dry EtOAc (150 mL) was hydrogenated at normal pressure after addition of PtO_2 (1.0 g). After usual workup and separation of unreacted **3** (5%) and a small amount of **9** by chromatography (EtOAc/*n*-hexane, 2:1; R_f (**3**) 0.67, R_f (**5**) 0.31, R_f (**9**) 0.35), **5** (12.0 g, 79%) was obtained as a colorless oil: ^1H NMR (250 MHz) δ 2.10 (m, 2 H), 2.31 (m, 2 H), 3.09 (m, 2 H), 3.24 (br s, 1 H), 3.71 (s, 6 H), 4.36 (tt, J = 7.4, 3.7 Hz, 1 H); ^{13}C NMR (100 MHz) δ 38.43, 45.80, 52.08, 72.09, 174.68; MS (EI, 70 eV) m/z (%) 202 (M^+, 0.7), 171 (8), 116 (66), 87 (100), 55 (55); IR (film) 3700–3060, 2960, 1740, 1442, 1363, 1285, 1245, 1208, 1184, 1032 cm^{-1}. Anal. Calcd for $C_9H_{14}O_5$ (202.2): C, 53.46; H, 6.98. Found: C, 53.19; H, 6.97.

(1α,2α,4α)-4-Acetoxy-1,2-cyclopentanedicarboxylic Acid Bis(methyl ester) (6). To a solution of alcohol **5** (3.03 g, 15 mmol), NEt_3 (3.33 g, 30 mmol), and 4-(dimethylamino)pyridine (10 mg) in dry CH_2Cl_2 (50 mL) was slowly added at 0 °C Ac_2O (1.61 g, 15.7 mmol). The mixture was stirred for 4 h at room temperature and diluted with EtOAc (80 mL). Standard workup and purification by chromatography (EtOAc/*n*-hexane, 4:1; R_f (**6**) 0.65, R_f (**5**) 0.42) gave **6** (3.26 g, 89%) as a colorless oil: ^1H NMR (250 MHz) δ 2.02 (s, 3 H), 2.18 (m, 2 H), 2.40 (m, 2 H), 3.07 (m, 2 H), 3.69 (s, 6 H), 5.11 (tt, J = 7.5, 5.7 Hz, 1 H); ^{13}C NMR (20 MHz) δ 21.01, 34.90, 44.70, 51.87, 73.78, 170.58, 173.20; MS (EI, 70 eV) m/z (%) 171 (20), 152 (30), 125 (18), 124 (30), 116 (24), 87 (27), 55 (16), 43 (100); MS (CI, NH_3) m/z (%) 263 (12), 262 (100, MNH_4^+), 245 (3); IR (film) 2960, 1739, 1440, 1367, 1247, 1207, 1122, 1029 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_6$ (244.2): C, 54.09; H, 6.60. Found: C, 54.11; H, 6.59.

(1α,2α,4α)-4-Methoxy-1,2-cyclopentanedicarboxylic Acid Bis(methyl ester) (7). A dried ethereal solution of CH_2N_2 was dropped at 0–5 °C under stirring to a solution of **5** (2.7 g, 13.3 mmol) in dry Et_2O (50 mL) containing $BF_3{\cdot}Et_2O$ (500 μL, 4 mmol). TLC indicated only approximately 50% conversion. After concentration of the mixture in a rotary evaporator and separation by chromatography (EtOAc/*n*-hexane, 1:1; R_f (**7**) 0.46, R_f (**5**) 0.21), **7** (1.30 g, 45%) was obtained as a colorless liquid: ^1H NMR (250 MHz) δ 2.12 (m, 2 H), 2.26 (m, 2 H), 3.03, (m, 2 H), 3.28 (s, 3 H), 3.66 (s, 6 H), 3.85 (tt, J = 6.9, 6.3 Hz, 1 H); ^{13}C NMR (20 MHz) δ 34.66, 44.45, 51.78, 56.76, 80.41, 173.56; MS (EI, 70 eV) m/z (%) 216 (M^+, 2), 201 (15), 130 (25), 125 (40), 115 (24), 97 (54), 72 (100); IR (film) 2955, 1742, 1440, 1364, 1250, 1208, 1150, 1126, 1095, 1044 cm^{-1}; HRMS calcd for $C_{10}H_{16}O_5$ 216.1007, obsd 216.1016.

(1α,2α,4α)-4-*tert*-Butoxy-1,2-cyclopentanedicarboxylic Acid Bis(methyl ester) (8). To a solution of alcohol **5** (3.03 g,

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15 mmol) and isobutene (35 mL, 0.37 mol) in dry CH_2Cl_2 (40 mL) contained in a pressure bottle was added concentrated H_2SO_4 (500 μL). After stirring for 3 days at room temperature, excess isobutene was evaporated and the CH_2Cl_2 solution washed with aqueous $NaHCO_3$ solution and dried with $MgSO_4$. Standard workup, purification by chromatography (EtOAc/*n*-hexane, 1:1; R_f (**8**) 0.57), and Kugelrohr distillation (115 °C, 10^{-3} Torr) gave **8** (2.10 g, 54%) as a colorless liquid: ^{1}H NMR (250 MHz) δ 1.17 (s, 9 H), 1.92–2.06 (m, 2 H), 2.15–2.28 (m, 2 H), 2.93–3.02 (m, 2 H), 3.66 (s, 6 H), 3.97 (tt, J = 7.5, 7.4 Hz, 1 H); ^{13}C NMR (20 MHz) δ 28.49, 37.28, 43.84, 51.69, 71.30, 73.29, 173.81; MS (EI, 70 eV) m/z (%) 171 (19), 153 (24), 125 (36), 116 (67), 87 (50), 41 (37), 57 (100), 41 (37); MS (CI, isobutane) m/z (%) 259 (MH^+, 14), 203 (100), 171 (6); IR (film) 2980, 2960, 1743, 1418, 1392, 1364, 1269, 1244, 1200, 1100, 1025 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_5$ (258.3): C, 60.44; H, 8.59. Found: C, 60.37; H, 8.29.

(1α,2α,4β)-4-Hydroxy-1,2-cyclopentanedicarboxylic Acid Bis(methyl ester) (9). A solution of acetate **10** (2.02 g, 8.2 mmol) in dry MeOH (50 mL) containing $TsOH·H_2O$ (380 mg, 2 mmol) was stirred for 2 days at room temperature followed by removal of MeOH. Purification by chromatography (EtOAc/*n*-hexane, 1:1; R_f (**9**) 0.23, R_f (**10**) 0.52) gave **9** (1.42 g, 85%) as a colorless oil: ^{1}H NMR (250 MHz) δ 1.94–2.04 (m, 2 H), 2.22–2.34 (m, 2 H), 3.37 (m, 2 H), 3.67 (s, 6 H), 4.56 (tt, J = 5.6, 2.3 Hz, 1 H); ^{13}C NMR (20 MHz) δ 38.67, 44.97, 51.83, 72.12, 174.41; MS (EI, 70 eV) m/z (%) 171 (43), 116 (40), 111 (30), 87 (100), 83 (88), 59 (38), 55 (95); MS (CI, isobutane) m/z (%) 203 (MH^+, 100), 185 (6), 171 (50); IR (film) 3460, 2960, 1740, 1439, 1360, 1310, 1209, 1153, 930 cm^{-1}; HMRS calcd for $C_8H_{11}O_4$ ($M^+ - OCH_3$) 171.0662, obsd 171.0667.

(1α,2α,4β)-4-Acetoxy-1,2-cyclopentanedicarboxylic Acid Bis(methyl ester) (10). To a stirred solution of alcohol **5** (3.03 g, 15 mmol) and Ph_3P (3.93 g, 15 mmol) in dry Et_2O (100 mL) was slowly added at 0 °C a solution of $EtO_2CN{=}NCO_2Et$ (2.61 g, 15 mmol) and glacial AcOH (900 mg, 15 mmol) in dry Et_2O (100 mL). After the mixture was stirred for 4 h at room temperature, the precipitate was separated, and the solution was concentrated in a rotary evaporator. Purification by chromatography (EtOAc/*n*-hexane, 1:1; R_f (**10**) 0.52) gave **10** (2.35 g, 65%) as a colorless oil: ^{1}H NMR (250 MHz) δ 2.02 (s, 3 H), 2.00–2.12 (m, 2 H), 2.41, (m, 2 H), 3.30 (m, 2 H), 3.67 (s, 6 H), 5.32 (tt, J = 5.3, 4.2 Hz, 1 H); ^{13}C NMR (20 MHz) δ 21.16, 35.80, 45.20, 51.91, 75.11, 170.30, 173.59; MS (EI, 70 eV) m/z (%) 169 (10), 125 (15), 116 (12), 93 (13), 87 (16), 59 (13), 55 (15), 43 (100); MS (CI, NH_3) m/z (%) 263 (12), 262 (100, MNH_4^+), 247 (3), 185 (8); IR (film) 2960, 1738, 1440, 1377, 1310, 1248, 1205, 1180, 1155, 1025 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_6$ (244.2): C, 54.09; H, 6.60. Found: C, 54.39; H, 6.42.

Synthesis of Ketals 11–14 from Ketone 3. *cis*-1,4-Dioxaspiro[4.4]nonane-7,8-dicarboxylic Acid Bis(methyl ester) (11). The following procedure is representative: ketone **3** (4.00 g, 20 mmol), ethylene glycol (1.53 g, 25 mmol), and $TsOH·H_2O$ (100 mg) were dissolved in toluene (100 mL) and heated in a water aspirator for 1 day. After general workup and Kugelrohr distillation (120 °C, 10^{-3} Torr), **5** (4.0 g, 83%) was obtained as a colorless oil: ^{1}H NMR (250 MHz) δ 2.15 (m, 2 H), 2.34 (m, 2 H), 3.21 (m, 2 H), 3.69 (s, 6 H), 3.92 (s, 4 H); MS (EI, 70 eV) m/z (%) 244 (M^+, 3), 213 (54), 185 (64), 158 (100), 157 (68), 143 (60), 126 (84), 125 (52), 114 (62), 113 (55), 99 (78), 71 (56), 55 (80); IR (film) 2960, 1745, 1442, 1334, 1257, 1206, 1180, 1140, 1106, 1042 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_6$ (244.2): C, 54.09; H, 6.60. Found: C, 53.83; H, 6.56.

***cis*-6,10-Dioxaspiro[5.4]decane-2,3-dicarboxylic Acid Bis(methyl ester) (12).** Ketalization of **3** with 1,3-propanediol gave **12** in 92% yield as white crystals: mp 52 °C (Et_2O); ^{1}H NMR (250 MHz) δ 1.72 (m, 2 H), 2.30 (m, 2 H), 2.41 (m, 2 H), 3.17 (m, 2 H), 3.68 (s, 6 H), 3.84–3.92 (m, 4 H); ^{13}C NMR (20 MHz) δ 25.25, 37.78, 43.73, 51.83, 61.25, 62.07, 107.18, 173.51; MS (EI, 70 eV) m/z (%) 258 (M^+, 2), 227 (36), 199 (38), 172 (99), 171 (76), 157 (45), 140 (41), 113 (100), 71 (43), 55 (39); IR (KBr) 1990, 1880, 1724, 1448, 1393, 1332, 1284, 1245, 1215, 1192, 1150, 1108, 1065, 1030, 1012 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_6$ (258.3): C, 55.80; H, 7.03. Found: C, 55.73; H, 7.02.

***cis*-8,8-Dimethyl-6,10-dioxaspiro[5.4]decane-2,3-dicarboxylic Acid Bis(methyl ester) (13).** Ketalization of **3** with 2,2-dimethyl-1,3-propanediol gave **13** in 93% yield as white crystals: mp 51 °C (Et_2O); ^{1}H NMR (250 MHz) δ 0.96 (s, 6 H), 2.28 (m, 2 H), 2.41 (m, 2 H), 3.17 (m, 2 H), 3.47 (m, 4 H), 3.68 (s, 6 H); MS (EI, 70 eV), m/z (%) 286 (M^+, 5), 200 (100), 199 (82), 185 (42), 169 (82), 141 (63), 113 (67), 69 (95), 55 (52), 41 (45). Anal. Calcd for $C_{14}H_{22}O_6$ (286.3): C, 58.72; H, 7.75; Found: C, 58.56; H, 7.77.

***cis*-6,11-Dioxaspiro[6.4]undec-8-ene-2,3-dicarboxylic Acid Bis(methyl ester) (14).** Ketalization of **3** with (*Z*)-2-butene-1,4-diol in benzene was accompanied by polymerization and gave **14** only in 46% yield as white needles: mp 50 °C (Et_2O); ^{1}H NMR (250 MHz) δ 2.24–2.40 (m, 4 H), 3.22 (m, 2 H), 3.69 (s, 6 H), 4.18–4.25 (m, 4 H), 4.95 (m, 2 H); IR (KBr) 2955, 2872, 1750, 1442, 1364, 1330, 1288, 1270, 1255, 1208, 1140, 1083, 1044, 1012, 945, 937, 904, 800, 650 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_6$ (270.3): C, 57.76; H, 6.71. Found: C, 57.74; H, 6.62.

***cis*-4-Oxocyclopentane-1,2-diacetic Acid Bis(methyl ester) (15).** By the procedures given for the synthesis of **3** from **1**, **15** was obtained from diester **16** via *meso*-3,4-bis[(methoxycarbonyl)methyl]hexanedioic acid (mp 113 °C) in 65% overall yield as a colorless liquid which was purified by Kugelrohr distillation (150 °C, 10^{-3} Torr): ^{1}H NMR (250 MHz) δ 2.02–2.55 (m, 8 H), 2.89 (m, 2 H), 3.70 (s, 6 H); ^{13}C NMR (20 MHz) δ 34.57, 35.43, 43.46, 51.80, 172.33, 216.08; MS (EI, 70 eV) m/z (%) 228 (M^+, 3), 168 (38), 155 (93), 154 (90), 123 (34), 99 (40), 95 (100), 74 (31), 59 (70), 41 (82); MS (CI, isobutane) m/z (%) 229 (MH^+, 100), 195 (5); IR (film) 2955, 1740, 1440, 1410, 1385, 1326, 1200, 1170, 1015 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_5$ (228.2): C, 57.88; H, 7.07. Found: C, 57.53; H, 7.11.

***cis*-4-Cyclohexene-1,2-diacetic Acid Bis(methyl ester) (16).** Compound **16** was obtained from diester **1** as a colorless oil in 60% overall yield following the literature procedure with minor modifications:[4e] ^{1}H NMR (250 MHz) δ 1.74–2.36 (m, 10 H), 3.68 (s, 6 H), 5.61 (m, 2 H); ^{13}C NMR (20 MHz) δ 29.37, 32.91, 35.24, 51.55, 125.19, 173.48; MS (EI, 70 eV) m/z (%) 194 (12), 152 (18), 91 (16), 79 (18), 74 (100), 43 (26); MS (CI, isobutane) m/z (%) 227 (MH^+, 100), 195 (5); IR (film) 3030, 2960, 2920, 2840, 1740, 1437, 1384, 1354, 1330, 1310, 1280, 1260, 1210, 1160, 1018 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_4$ (226.3): C, 63.70; H, 8.02. Found: C, 63.38; H, 7.92.

PLE-Catalyzed Hydrolysis of Meso Diesters 3–16. (1*S*-*cis*)-4-Oxo-1,2-cyclopentanedicarboxylic Acid Monomethyl Ester (18). The following procedure is representative: to a stirred suspension of diester **3** (1.0 g, 5 mmol) in 0.15 M phosphate buffer solution (20 mL) of pH 7.0 was added at room temperature 100 μL of enzyme suspension (1 mg PLE, 130 units). Addition of 0.5 M aqueous NaOH at pH 7.0 which was monitored by a pH-stat proceeded until 1 equiv of base had been consumed. The pH was adjusted to 9, and the solution was extracted with Et_2O (2 × 20 mL). The aqueous layer was acidified to pH 2 by careful addition of concentrated H_2SO_4 under cooling and extracted with EtOAc (5 × 20 mL). The organic layer was dried with $MgSO_4$ and concentrated in a rotary evaporator. Purification by chromatography (EtOAc/*n*-hexane/AcOH, 10:5:1) and drying over P_2O_5 gave **18** (770 mg, 83%) as a white solid: mp 67–74 °C; $[\alpha]^{20}_{365}$ +27.5° (*c* 1.85); $[\alpha]^{20}_D$ +6.9° (*c* 1.72) (recrystallization from EtOAc gave **18** (30%) of mp 76–78 °C and $[\alpha]^{20}_{365}$ +34.6° (*c* 1.85)); ^{1}H NMR (250 MHz) δ 2.54 (m, 2 H), 2.76 (m, 2 H), 3.47 (m, 2 H), 3.72 (s, 3 H), 9.85 (br s, 1 H); ^{13}C NMR (75 MHz) δ 40.44, 40.53, 43.19, 43.48, 52.41, 173.18, 177.71, 214.48; IR (KBr) 3680–2790, 1730, 1440, 1370, 1292, 1250, 1223, 1205, 1156 cm^{-1}. Anal. Calcd for $C_8H_{10}O_5$ (186.2): C, 51.60; H, 5.41. Found: C, 51.35; H, 5.34.

(1*R*-*cis*)-4-Methylene-1,2-cyclopentanedicarboxylic Acid Monomethyl Ester (19). From diester **4** acid–ester **19** was obtained in 63% yield as a slowly crystallizing colorless oil: mp 57–64 °C; $[\alpha]^{20}_D$ +0.6° (*c* 1.25); ^{1}H NMR (250 MHz) δ 2.60–2.90 (m, 4 H), 3.13–3.25 (m, 2 H), 3.68 (s, 3 H), 4.94 (br s, 2 H), 8.21 (br s, 1 H); HRMS calcd for $C_9H_{12}O_4$ 184.0734, obsd 184.0733.

[1*S*-(1α,2α,4α)]-4-Hydroxy-1,2-cyclopentanedicarboxylic Acid Monomethyl Ester (20). From diester **5** acid–ester **20** was obtained in 76% yield as a colorless oil: $[\alpha]^{20}_D$ +2.6° (*c* 1.81); ^{1}H NMR (250 MHz) δ 2.05–2.19 (m, 2 H), 2.23–2.40 (m, 2 H), 3.12 (m, 2 H), 3.70 (s, 3 H), 4.39 (tt, J = 7.2, 3.7, 1 H), 6.92 (br s, 1 H); IR (film) 3700–2700, 1960, 1730, 1441, 1360, 1245, 1210, 1120, 1026 cm^{-1}. Anal. Calcd for $C_8H_{12}O_5$ (188.2): C, 51.06; H, 6.43. Found: C, 51.28; H, 6.31.

[1*S*-(1α,2α,4α)]-4-Acetoxy-1,2-cyclopentanedicarboxylic Acid Monomethyl Ester (21). From diester **6** (1.22 g, 5 mmol)

acid–ester **21** was obtained in 76% yield as a white semicrystalline material: $[\alpha]^{20}_D$ +3.0° (*c* 1.35); ^{1}H NMR (250 MHz) δ 2.06 (s, 3 H), 2.19–2.32 (m, 2 H), 2.39–2.54 (m, 2 H), 3.15 (m, 2 H), 3.74 (s, 3 H), 5.18 (tt, *J* = 7.2, 5.3 Hz, 1 H), 9.88 (br s, 1 H). Anal. Calcd for $C_{10}H_{14}O_6$ (230.2): C, 52.17; H, 6.13. Found: C, 51.93; H, 6.11.

[1*S*-(1α,2α,4α)]-4-Methoxy-1,2-cyclopentanedicarboxylic Acid Monomethyl Ester (22). From diester **7** acid–ester **22** was obtained in 88% yield as a colorless oil: $[\alpha]^{20}_D$ +1.2° (*c* 1.85); ^{1}H NMR (250 MHz) δ 2.08–2.34 (m, 4 H), 3.05 (m, 2 H), 3.29 (s, 3 H), 3.67 (s, 3 H), 3.87 (tt, *J* = 6.8, 5.7 Hz, 1 H), 8.65 (br s, 1 H). Anal. Calcd for $C_9H_{14}O_5$ (202.21): C, 53.45; H, 6.98. Found: C, 53.20; H, 6.80.

[1*R*-(1α,2α,4α)]-4-*tert*-Butoxy-1,2-cyclopentanedicarboxylic Acid Monomethyl Ester (23). From diester **8** acid–ester **23** was obtained in 76% yield as a white solid: mp 55–58 °C; $[\alpha]^{20}_{365}$ −5.6°; $[\alpha]^{20}_D$ −1.5° (*c* 1.31); ^{1}H NMR (250 MHz) δ 1.19 (s, 9 H), 1.96–2.28 (m, 4 H), 3.04 (m, 2 H), 3.67 (s, 3 H), 4.08 (quin, *J* = 7.2 Hz, 1 H). Anal. Calcd for $C_{12}H_{20}O_5$ (244.3): C, 59.00; H, 8.25. Found: C, 59.04; H, 8.20.

[1*R*-(1α,2α,4β)]-4-Hydroxy-1,2-cyclopentanedicarboxylic Acid Monomethyl Ester (24). From diester **9** acid–ester **24** was obtained in 80% yield as a colorless oil: $[\alpha]^{20}_{365}$ −4.2°; $[\alpha]^{20}_D$ −1.3°; (*c* 1.73); ^{1}H NMR (250 MHz) δ 1.93–2.05 (m, 2 H), 2.19–2.34 (m, 2 H), 3.35 (m, 2 H), 3.67 (s, 3 H), 4.50 (m, 1 H). Anal. Calcd for $C_8H_{12}O_5$ (188.2): C, 51.06; H, 6.43. Found: C, 50.68; H, 6.37.

[1*R*-(1α,2α,4β)]-4-Acetoxy-1,2-cyclopentanedicarboxylic Acid Monomethyl Ester (25). From diester **10** acid–ester **25** was obtained in 91% yield as a colorless oil: $[\alpha]^{20}_D$ −1.3° (*c* 1.05); ^{1}H NMR (250 MHz) δ 2.03 (s, 3 H), 2.03–2.15 (m, 2 H), 2.35–2.48 (m, 2 H), 3.32 (m, 2 H), 3.67 (s, 3 H), 5.31 (tt, *J* = 6.0, 2.6 Hz, 1 H). Anal. Calcd for $C_{10}H_{14}O_6$ (230.2): C, 52.17; H, 6.13. Found: C, 51.95; H, 6.14.

(±)-*cis*-1,4-Dioxaspiro[4.4]nonane-7,8-dicarboxylic Acid Monomethyl Ester (*rac*-26). From diester **11** a mixture of *rac*-**26** and *rac*-**18** (TLC EtOAc/*n*-hexane/AcOH, 10:5:1; R_f (**18**) 0.48, R_f (**26**) 0.53) was obtained as solid material (45% deketalization according to ^{1}H NMR): ^{1}H NMR (250 MHz) δ 2.09–2.24 (m, 2 H), 2.30–2.43 (m, 2 H), 3.23 (m, 2 H), 3.70 (s, 3 H), 3.93 (s, 4 H), 8.0 (br s, 1 H).

(2*R*-*cis*)-6,10-Dioxaspiro[5.4]decane-2,3-dicarboxylic Acid Monomethyl Ester (27). From diester **12** a mixture of *ent*-**18** and **27** (TLC EtOAc/*n*-hexane/AcOH, 10:5:1; R_f (**18**) 0.48, R_f (**27**) 0.58) was obtained as a colorless oil (35% deketalization according to ^{1}H NMR): ^{1}H NMR (250 MHz) δ 1.67–1.72 (m, 2 H), 2.25–2.50 (m, 4 H), 3.19 (m, 2 H), 3.67 (s, 3 H), 3.87 (m, 4 H), 8.38 (br s, 1 H).

(2*R*-*cis*)-8,8-Dimethyl-6,10-dioxaspiro[5.4]decane-2,3-dicarboxylic Acid Monomethyl Ester (28). From diester **13** acid–ester **28** was obtained in 46% yield as a white semicrystalline material after chromatographic separation (EtOAc/*n*-hexane/AcOH, 10:10:1; R_f (**18**) 0.30, R_f (**28**) 0.58) of *ent*-**18**: $[\alpha]^{20}_D$ −0.5° (*c* 1.64); ^{1}H NMR (250 MHz) δ 0.96 (s, 6 H), 2.26–2.44 (m, 4 H), 3.19 (m, 2 H), 3.47 (m, 4 H), 3.67 (s, 3 H). Anal. Calcd for $C_{13}H_{20}O_6$ (272.3): C, 57.34; H, 7.40. Found: C, 57.46; H, 7.35.

(2*R*-*cis*)-6,11-Dioxaspiro[6.4]undec-8-ene-2,3-dicarboxylic Acid Monomethyl Ester (29). From diester **14** acid–ester **29** was obtained in 80% yield as a colorless oil after chromatographic separation (EtOAc/*n*-hexane/AcOH, 10:10:1; R_f (**29**) 0.50) of *ent*-**18**: $[\alpha]^{20}_D$ −1.8° (*c* 1.82); ^{1}H NMR (250 MHz) δ 2.29–2.39 (m, 4 H), 3.23 (m, 2 H), 3.67 (s, 3 H), 4.22 (m, 4 H), 5.68 (m, 2 H), 9.90 (br s, 1 H); MS (EI, 70 eV) *m*/*z* (%) 256 (4), 238 (4), 225 (14), 187 (10), 169 (14), 155 (16), 125 (10), 113 (10), 99 (20), 87 (6), 81 (6), 71 (21), 70 (34), 53 (40), 54 (100). HMRS calcd for $C_{12}H_{16}O_6$ 256.0958, obsd 256.0969.

(1*S*-*cis*)-4-Oxocyclopentane-1,2-diacetic Acid Monomethyl Ester (30). From diester **15** acid–ester **30** was obtained after chromatographic separation (EtOAc/*n*-hexane/AcOH, 10:25:1; R_f (**30**) 0.21, R_f (diacid) 0.09) of the corresponding diacid in 94% yield as a colorless oil; $[\alpha]^{20}_{365}$ −7.2° (*c* 1.12); ^{1}H NMR (250 MHz) δ 2.04–2.59 (m, 8 H), 2.90 (m, 2 H), 3.71 (s, 3 H), 6.66 (br s, 1 H); HRMS calcd for $C_{10}H_{14}O_5$ 214.0842, obsd 214.0843.

(1*S*-*cis*)-4-Cyclohexene-1,2-diacetic Acid Monomethyl Ester (31). From diester **16** acid–ester **31** was obtained in 84% yield as a colorless oil after chromatographic separation (EtOAc/*n*-hexane/AcOH, 10:25:1; R_f (**31**) 0.38, R_f (diacid) 0.15) of the corresponding diacid: $[\alpha]^{20}_D$ −2.8° (*c* 1.75); ^{1}H NMR (250 MHz) δ 1.75–2.38 (m, 10 H), 3.69 (s, 3 H), 5.62 (m, 2 H). Anal. Calcd for $C_{11}H_{16}O_4$ (212.2): C, 62.25; H, 7.60. Found: C, 62.40; H, 7.77.

α-CT-Catalyzed Hydrolysis of Meso Diesters 15 and 16. (1*R*-*cis*)-4-Cyclohexene-1,2-diacetic Acid Monomethyl Ester (*ent*-31). The following procedure is typical: to a stirred suspension of diester **16** (450 mg, 2 mmol) in 0.15 M phosphate buffer solution (5 mL) of pH 8.0 was added at room temperature α-CT (400 mg). Addition of 0.5 M aqueous NaOH at pH 8.0 which was monitored by a pH-stat proceeded until ca. 1 equiv of base had been consumed (50 h). The reaction mixture was concentrated in a rotary evaporator at 2 Torr and 30 °C to a volume of 1 mL, and MeOH (30 mL) was added. The mixture was vigrously stirred for 15 min, and the solid was removed by filtration. After concentration of the filtrate in vacuo to a volume of 1 mL, 10% aqueous HCl (0.5 mL) was added, and the solution was extracted with EtOAc (3 × 10 mL). The organic phase was dried with $MgSO_4$, and the solvent was evaporated. Chromatographic separation of the corresponding diacid and drying over P_2O_5 gave *ent*-**31** (381 mg, 90%) as a colorless oil; $[\alpha]^{20}_D$ +3.5° (*c* 1.75).

(1*R*-*cis*)-4-Oxocyclopentane-1,2-diacetic Acid Monomethyl Ester (*ent*-30). From diester **15** acid–ester *ent*-**30** was obtained in 87% yield as a colorless oil after chromatographic separation of the corresponding diacid; $[\alpha]^{20}_{365}$ +6.8° (*c* 1.06).[28]

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Supplementary Material Available: Experimental procedures and characterization for all compounds (of Schemes II and III) not described in the Experimental Section (10 pages). Ordering information is given on any current masthead page.

(28) **Note Added in Proof:** After submission of this paper, enantioselective hydrolyses of diesters **15** and **16** catalyzed by PLE and PPL were published. Nagao, Y.; Kume, M.; Wakabayashi, R. C.; Nakamura, T.; Ochiai, M. *Chem. Lett.* **1989**, 239. Note, that a change in the sign of optical rotation of acid–esters **30** and *ent*-**30** takes place on going from MeOH to $CHCl_3$.