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KINETIC RESOLUTION OF RACEMIC β,γ-EPOXY ESTERS WITH PIG LIVER ESTERASE (PLE, E.C. 3.1.1.1.)

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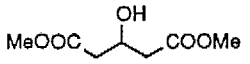
Abstract: The β,γ-epoxy esters (±)-**2** to (±)-**6** were synthetisized. The *E*-values of the kinetic resolution of **2**, **3**, **4**, and **6** with PLE and the absolute configuration of the products of the hydrolysis were determined by the conversion to known compounds.

Introduction: β-Hydroxy-esters and β-hydroxy-δ-lactones are often encountered as structural units in biologically active natural products such as amphotericin B and compactin. Therefore their synthesis has attracted much attention during the last two decades. The use of a chemo-enzymatic approach seems to be particularly attractive for preparing such synthons in optically pure form. However, it is well known that dimethyl 3-hydroxyglutarate (**1**), albeit being rapidly hydrolyzed by PLE, yields virtually racemic half-esters [1], whereas the 3-amino-analogue suffers from concomitant non-enzymatic hydrolysis [2]. On the other hand, many other 3-monosubstituted dimethyl glutarates studied so far [1][3] are attacked by PLE with fair to good enantioselectivity. To overcome this limitation different strategies for optimization have been applied, such as screening of different enzymes, introduction of protecting groups or use of other esters [4][1b]. We have reasoned that β,γ-epoxy esters, owing to their ambident reactivity towards nucleophiles, can serve as interesting chiral building blocks and as synthetic equivalents of 3-hydroxyesters. We have examined compounds (±)-**2** to (±)-**6** as substrates for this enzyme, to test if they behave similarly against PLE as 'normal' 3-monosubstituted glutarates [5].



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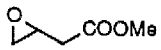

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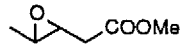

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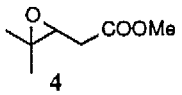

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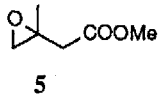

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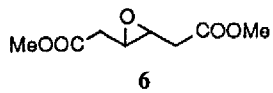


6

Synthesis of Substrates (±)-2 to (±)-6: 3-Butenoic acid, *(E)*-3-pentenoic acid, and *(E)*-3-hexenedioic acid, which are commercially available, served as starting material. 4-Methyl-3-pentenoic acid was accessible from methyl 4-methyl-2-penteneoate [6] by isomerization and concomitant hydrolysis by aqueous base. β-methallyllithium [7] was treated with CO_2 to yield 3-methylbutenoic acid.

Esterification of the five acids was easily achieved by treatment with MeOH/HCl. Purification was accomplished by careful distillation. Epoxidation of the β,γ-unsaturated esters with *m*-chloroperbenzoic acid (MCPBA) yielded, after removal of *m*-chlorobenzoic acid by several crystallizations and extractions, pure (±)-**2** to (±)-**6**. These five epoxides are sensitive to acid and base. Therefore purification by chromatography on silicagel led to a complete decomposition.

Very recently a general approach to β,γ-unsaturated esters has been described by *Murahashi* and coworkers [8] which would provide an easy access to a variety of new substrates.

Kinetic Resolution with PLE: *C.J. Sih* and his coworkers [9] introduced an elegant mathematical treatment for the determination and characterization of biochemical kinetic resolution data. Accordingly, we determined the enantiomeric ratios *E* of the hydrolysis of (±)-**2** to (±)-**6** with PLE.

The enzymatic hydrolysis was carried out as described in [1] at pH 7 on a 20 to 100 mmol scale. During the reaction 5 to 8 small samples were taken and worked up in the usual manner. The enantiomeric excess *e.e.* of the remaining esters was determined by NMR analysis using $Eu(hfc)_3$. The extent of conversion was calculated from the consumption of NaOH.

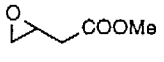
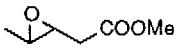
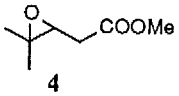
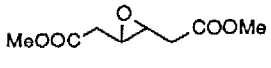
 **2** E = 11 ± 1	 **3** E = 16 ± 1
 **4** E = 17 ± 1	 **6** E = 21. 5 ± 1
Because during the hydrolysis of **5** substantial isomerization to the α,β-epoxide took place,the *E*-value could not be determined.	

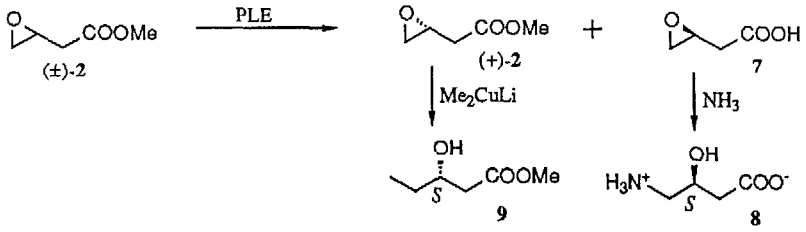
Table 1

The *E*-values determined for **2**, **3**, **4**, and **6** indicate that these β,γ-epoxy esters are fair to good substrates for kinetic resolution with PLE. Substituents in γ-position improve the selectivity probably due to steric effects.

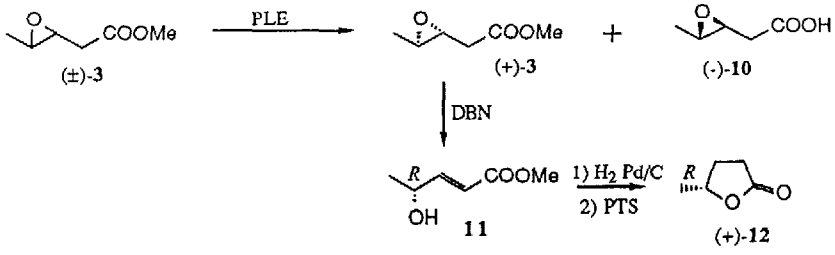
Absolute Configuration and Application: For the determination of the absolute configuration of the resultant optically active esters and acids the enzymatic hydrolysis was stopped after a consumption of ca. 0.5 equiv. of base. Therefore the $[\alpha]_D^T$ values indicated in parenthesis do not correspond to optically pure material.

Treatment of acid **7** with conc. NH_3 afforded (+)-*(S)*-γ-amino-β-hydroxybutyric acid (**8**) ($[\alpha]_D^{22}$= +19.6° (c=0.52, H_2O) after cryst. from $EtOH/H_2O$), *i.e.* the unnatural enantiomer of GABOB [10]. The reaction of the ester (+)-**2**

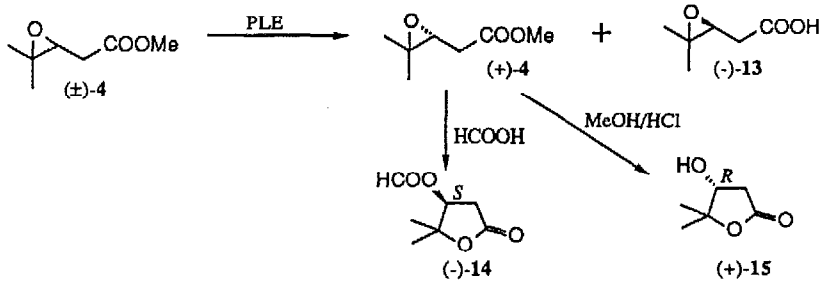
($[\alpha]_D^{22}$ = +10.67° (c=1.8, $CHCl_3$) with Me_2CuLi yielded the known hydroxyester **9** ($[\alpha]_D^{22}$ = +30.9° (c=1.3, $CHCl_3$)) [11] with *(S)*-configuration.



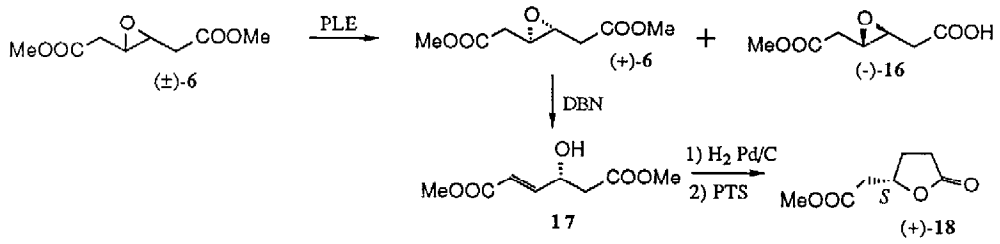
Base catalyzed isomerization of (+)-**3** ($[\alpha]_D^{23}$ = +26.07° (c=2.5, CH_2Cl_2)) with 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN) led to the unsaturated ester **11**, which was hydrogenated with Pd/C to form immediately the known lactone (+)-**12** ($[\alpha]_D^{23}$ = +16° (c=1.78, CH_2Cl_2)) [12] with *(R)*-configuration. If the homologues of **3** prove also to be suitable substrates for PLE, a new access to optically active 4-hydroxyesters or their lactones would be available.



The ester (+)-**4** ($[\alpha]_D^{21}$ = +3.23° (neat)) [13][14] was transformed with formic acid with inversion of configuration of *C*(3) to the formate **14** ($[\alpha]_D^{21}$ = -6.28° (c=3.5, CH_2Cl_2)) [13] with *(S)*-configuration. Acid catalyzed cyclization of (+)-**4** led to the lactone (+)-*(R)*-**15** ($[\alpha]_D^{21}$ = +8.2° (c=6, $CHCl_3$)) [13][15] with retention of configuration at *C*(3).



Base catalyzed isomerization of (+)-**6** ($[\alpha]_D^{22}$ = +28.4° (c=1.27, EtOH)) with DBN yielded smoothly the hydroxyester **17** (≤ 2% *(Z)*-isomer). After catalytic hydrogenation and cyclization in the presence of TsOH the known lactone (+)-**18** ($[\alpha]_D^{22}$ = +35.6° (c=0.45, EtOH)) [16] was obtained with *(S)*-configuration.



The results obtained demonstrate that the PLE hydrolysis leads preferentially always to the same enantiomer of β,γ-epoxy esters, irrespective of the substituents in γ-position. This is in agreement with our very simple model which we have recently proposed [1]. The products of the kinetic resolution with PLE are interesting chiral building blocks for natural product synthesis.

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[14] In [13] (+)-4 (*(S)*-configuration) is converted with HCOOH to (+)-**14** and we converted (+)-4 to (-)-**14** and (+)-**15**. Our lactones (-)-**14** and (+)-**15** and the cyclization mechanisms are in agreement with the literature [13][15], so the sign of **4** in [13] is probably wrong.

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