

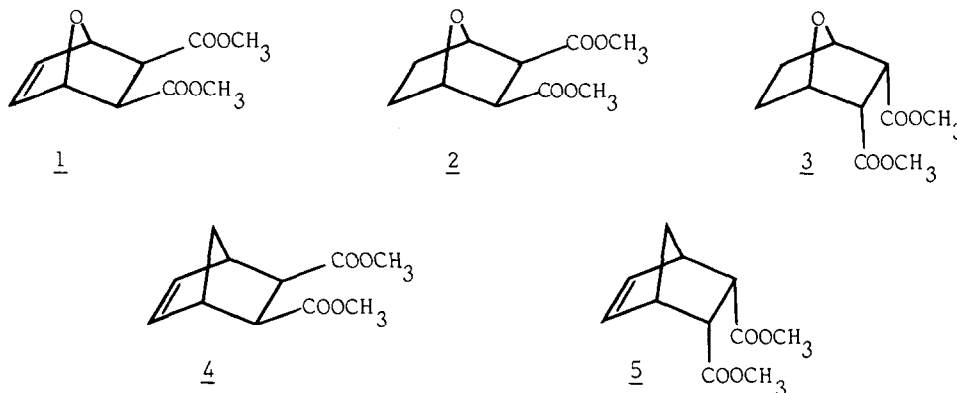
STERESELECTIVE PIG LIVER ESTERASE-CATALYZED HYDROLYSIS OF RIGID BICYCLIC MESO-DIESTERS : PREPARATION OF OPTICALLY PURE 4,7-EPOXYTETRA- AND HEXA-HYDROPHthalIDES.

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**Abstract.** The bicyclic and rather rigid meso-diester 1 - 3 have been found to be good substrates for pig liver esterase. The half-esters obtained have been converted to either one of the enantiomers of tricyclic lactones, of potential value for natural product synthesis.

The enantioselectivity showed by Pig Liver Esterase (PLE) towards hydrolysis either of diesters with a prochiral center (<sup>1</sup>) or of meso-diester (<sup>2</sup>) have been, during these last few years, the subject of extensive investigations since the optically active half-esters prepared by this approach are valuable starting materials for organic synthesis. The structural requirements of the cyclic diesters for being good substrates for PLE are not yet well known although it seems that the optical purities of the half esters decrease with increasing mobility of the cyclic system (<sup>1f</sup>). It was then worthwhile to examine the reactivity of rigid meso-diester such as the bicyclic compounds 1 - 5.



A very recent report (<sup>3</sup>) prompts us to disclose our own results in this field. We wish to report that in contrast with previous findings (<sup>3,4</sup>) the diesters 1 - 3 are good substrates for PLE, leading to the corresponding half-esters of high enantiomeric purities. These chiral half-esters have been then converted into either optically pure lactone enantiomers via selective reduction of the carboxy or ester group.

The diesters 1 - 5 (<sup>5</sup>) (5 mmol) in 0.1 M phosphate buffer solution (25 ml) were incubated with pig liver esterase (0.25 ml, 400 units, Sigma) at 30°C and pH 7. This pH value was maintained through the entire reaction by continuous addition of 1N NaOH aqueous solution. The reaction stopped after addition of about one equivalent of NaOH. The characteristics of half-esters obtained after usual work-up are shown in Table I.

Table I. - PLE-catalyzed hydrolysis of rigid bicyclic meso-diester.

Diester	Yield %	(a) Half-ester		ee %	absolute configuration	
		$[\alpha]_D^{20}$	M.p.			
<u>1</u>	86	-7.8	107°	3	75	(-)-(1R,2S,3R,4S)
	61 <sup>(b)</sup>	-10.6	110°		≥ 98	
<u>2</u>	82	-3.9	104°	3	≥ 98	(-)-(1R,2S,3R,4S)
<u>3</u>	87	-5.8	oil	50	64	(-)-(1R,2R,3S,4S)
	65 <sup>(c)</sup>	-8.8	oil		97	
<u>4</u>	85	±0 <sup>(d)</sup>	oil	45	<10 <sup>(e)</sup>	not determined
<u>5</u>		No hydrolysis observed				

a) CH<sub>3</sub>OH, c = 2

b) After one recrystallisation in cyclohexane / ethyl acetate

c) After crystallisation of the less abundant enantiomer in cyclohexane/ethyl acetate

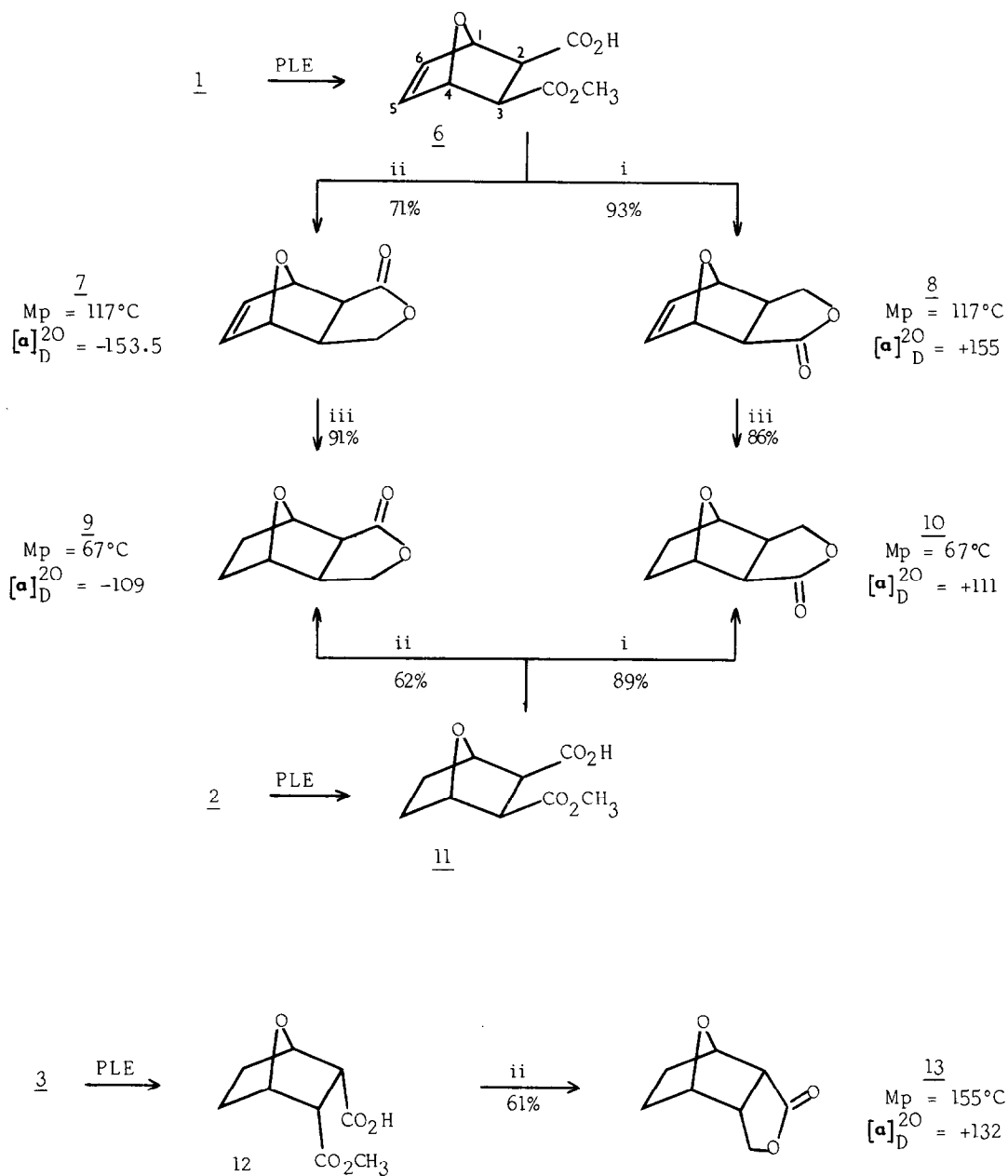
d) Optical rotation of the dicyclohexylamine salt:  $[\alpha]_D^{20} = +0.6$  (MeOH, c = 3)

e) An accurate determination could not be made, due to a very small  $\Delta\Delta\delta$  (0.005 ppm) between the signals of the ester groups of the L-ephedrine salt.

The enantiomeric excess (ee) of the half-esters was evaluated from the diastereoisomeric excess of their L-ephedrine salts determined by 250 MHz <sup>1</sup>H-NMR spectroscopy either from the signals due to the carbomethoxy methyl groups or from the signals of the proton **a** to the carboxy group (<sup>6</sup>).

The absolute configurations of 6, 11 and 12 were established by straightforward chemical transformations (scheme 1) into the known lactones 10 or 13 (<sup>7,8</sup>).

The difference observed between Ohno's work (<sup>4</sup>) and the present one can be easily understood since, in the former, the diester used bears two additional substituents in the 5 and 6 positions, or it is known that enzymatic processes are sensitive to substrate structural changes even far from the reacting site. But the apparent discrepancy between our results and Jones' report (<sup>3</sup>) is more difficult to explain, owing to the few experimental details available in this paper. However this discrepancy might



Scheme 1. i :  $\text{ClCO}_2\text{Et}$ ,  $\text{NEt}_3$  ;  $\text{NaBH}_4$ ,  $\text{MeOH}$ . ii :  $\text{nBuLi}$  ;  $\text{LiBH}_4$ ,  $\text{THF}$ . iii :  $\text{H}_2$ ,  $\text{Pd/C}$ ,  $\text{CH}_3\text{COCH}_3$ .

All  $[\alpha]_{\text{D}}$  were measured in  $\text{CHCl}_3$  solution ( $c = 1$ ).

be due to the reaction conditions which seem to have been used by Jones : in the same conditions (substrate, 1 mmole ; phosphate buffer solution, 20 ml ; PLE, 100 units ; pH 8 ; 1 hour) we observed only about 15% of hydrolysis for 2 and no detectable hydrolysis for 3.

From our experimental data, the following conclusions can be drawn : As assumed earlier (<sup>1f</sup>), ester groups are more rapidly and more selectively hydrolysed in an equatorial than in an axial position but the rigid conformation of the substrates is not always sufficient to induce a high enantioselectivity ; in contrast with the cyclohexane ring (<sup>2b</sup>), the presence of a double bond in the substrate is not favourable ; finally the presence of an oxygen in the bridge is essential for a selective hydrolysis.

Applications of the chiral lactones 7 - 10 to natural product synthesis are currently under investigation.

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- 3) J.B. Jones and C.J. Francis, *Can. J. Chem.*, 1984, **62**, 2578.
- 4) M. Ohno, Y. Ito, M. Arita, T. Shibata, K. Adachi and H. Sawai, *Tetrahedron*, 1984, **40**, 145.
- 5) Diesters 1, 4 and 5 were prepared from the corresponding anhydrides (MeONa-MeOH, SO<sub>4</sub>Me<sub>2</sub>). Diester 2 was obtained by catalytic hydrogenation of 1 and diester 3 by catalytic hydrogenation of the Diels-Alder adduct of furan and dimethyl acetylene dicarboxylate.
- 6) The two signals due to the methyl groups of the diastereoisomers of the L-ephedrine salt of the racemic half-ester 6 are well separated ( $\Delta\Delta\delta = 0.027$  ppm). However, for unknown reasons, only one signal was observed in the <sup>1</sup>H NMR spectra of mixtures of diastereoisomers when the diastereoisomeric excess was higher than 50%.
- 7) See reference 3. Compared to our results, it seems that the ee values reported in this reference for lactones 10 and 13 are quite too high.
- 8) All the lactones described gave satisfactory elemental analyses and their IR and <sup>1</sup>H NMR spectra were consistent with assigned structures.

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