

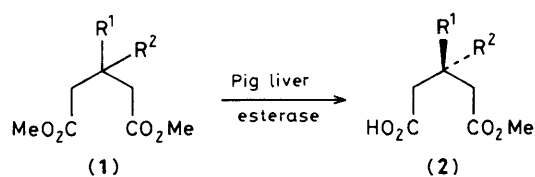
## Preparations of Chiral $\delta$ -Lactones *via* Enantiotopically Specific Pig Liver Esterase-catalysed Hydrolyses of 3-Substituted Glutaric Acid Diesters

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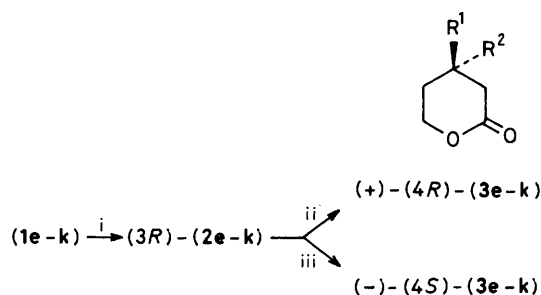
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Pig liver esterase-catalysed hydrolyses of 3-monosubstituted glutaric acid diesters are *pro-S* enantiotopically specific for a broad range of C-3 substituents and permit either enantiomer of the corresponding 3-substituted valerolactones of 100% e.e. to be readily prepared.

The ability of enzymes to discriminate between enantiotopic groups attached to a prochiral centre has been recognised for many years.<sup>1</sup> However, it is only recently that this aspect of enzyme specificity has begun to be exploited in asymmetric synthesis. Of the enzymic enantiotopically selective transformations reported so far,<sup>2-9</sup> pig liver esterase (P.L.E., E.C. 3.1.1.1)-catalysed hydrolysis of diesters is one of the easiest to carry out experimentally and synthetic interest in this aspect of the enzyme's stereospecificity is building rapidly.<sup>3-9</sup> P.L.E.-catalysed hydrolyses of 3-substituted glutaric acid diesters are particularly attractive. This is illustrated by the conversions of (**1a-d**) into enantiomerically highly enriched acid-esters (**2a-d**) respectively for use as chiral precursors of (*R*)- and (*S*)-mevalonic lactone,<sup>4,9</sup> negamycin,<sup>5</sup> verrucaric acid,<sup>7</sup> and pimaricin fragments.<sup>8</sup> The enormous asymmetric synthetic potential of the approach prompted us to investigate the enzyme's tolerance of variations in the C-3 substituents of its



- (1)  $\xrightarrow{\text{Pig liver esterase}}$  (2)
- a; R<sup>1</sup> = Me, R<sup>2</sup> = OH
  - b; R<sup>1</sup> = NH<sub>2</sub>, R<sup>2</sup> = H
  - c; R<sup>1</sup> = CH<sub>2</sub>Ph, R<sup>2</sup> = Me (malonate series)
  - d; R<sup>1</sup> = H, R<sup>2</sup> = OH
  - e; R<sup>1</sup> = Me, R<sup>2</sup> = H
  - f; R<sup>1</sup> = Et, R<sup>2</sup> = H
  - g; R<sup>1</sup> = Pr, R<sup>2</sup> = H
  - h; R<sup>1</sup> = CHMe<sub>2</sub>, R<sup>2</sup> = H
  - i; R<sup>1</sup> = cyclohexyl, R<sup>2</sup> = H
  - j; R<sup>1</sup> = Ph, R<sup>2</sup> = H
  - k; R<sup>1</sup> = CH<sub>2</sub>Ph, R<sup>2</sup> = H



**Scheme 1.** i, P.L.E., 0.1 M  $K_2HPO_4$ , pH 7.0,  $\leq 3$  days, 20 °C, ii,  $BH_3 \cdot Me_2S$  then  $H^+$ ; iii,  $LiBH_4$ .

**Table 1.** Results of reactions shown in Scheme 1.<sup>a</sup>

(1)	Yield of (2), %	Yield of (+)-(4R)-(3), %	Yield of (-)-(4S)-(3), %
e	98	86	86
f	77	45	50
g	90	45	45
h	61	54	75
i	90	80	60
j	91	50	40
k	90	48	50

<sup>a</sup> All lactones formed in > 99% e.e.

glutarate diester substrates. We now report that P.L.E.-catalysed hydrolyses of (1)  $\rightarrow$  (2) are largely unaffected by the size of C-3 monosubstituents and that, under controlled pH 7 conditions, they proceed in good yield with complete *pro-S* enantiotopic specificity.<sup>†</sup>

Preparative-scale (up to 5 g of substrate) P.L.E.-catalysed hydrolyses of (1e-k)<sup>3,10</sup> were effected at pH 7 and proceeded in each case with enantiotopic specificity for the *pro-S* methoxycarbonyl groups. The corresponding acid-esters (3R)-(2e-k) were selectively reduced with  $BH_3 \cdot Me_2S$ <sup>11</sup> to give good yields of the optically pure lactones (4R)-(3e-k).<sup>‡</sup> The ease with which either lactone enantiomer can be obtained *via* this enzymic method<sup>4</sup> is illustrated by the conversions of (3R)-(2e-k) into the (4S)-(3e-k) lactones *via*  $LiBH_4$  reduction (Scheme 1).<sup>12</sup> The results are summarised in Table 1. The e.e.s were determined by g.l.c. analyses of the ortho ester products of the optically active lactones with (2R,3R)-butanediol,<sup>13</sup> using the racemic lactones for calibration. The accuracy of this method is considered to be  $< \pm 1\%$ . The absolute configurations of (3e-k) were assigned by comparison with previously established samples.<sup>3</sup>

The results obtained demonstrate that the *pro-S* enantiotopic specificity of P.L.E.-catalysed hydrolysis of C-3 monosubstituted glutaric acid diesters is very general, and that, contrary to previous reports,<sup>4,7</sup> optically pure products are obtained provided the pH of the reaction mixture is kept  $\leq 7$ .

<sup>†</sup> Some of the <100% e.e. values reported in the literature (refs. 4,6) are due, at least in part, to competing chemical hydrolyses at the pH 8 reaction conditions used. At pH 7, only P.L.E.-catalysed hydrolysis occurs and the full stereospecificity of the enzyme is apparent.

<sup>‡</sup> The intermediate hydroxy-esters generally cyclised to the corresponding lactones to some degree during work-up (ref. 7). Accordingly, complete conversion into lactones was induced in each case in refluxing benzene containing toluene-*p*-sulphonic acid.

The synthetic value of the method is exemplified by the preparations of enantiomerically pure (+)- and (-)-(2e) as potential synthons for targets such as the vitamin E side chain.<sup>14</sup> This P.L.E.-based method is far superior to previous alcohol dehydrogenase-dependent routes<sup>2,3</sup> to the lactones (3) since the fermentation and coenzyme-recycling problems are avoided. Furthermore, these new data provide valuable additional perspective on the enzyme's specificity since, while 3-monosubstituted glutarates are hydrolysed stereospecifically, the 3,3-disubstituted analogues give rise to enantiomerically pure products only when the substituent groups are small, as in (1a).<sup>4,9</sup> With one of two C-3 substituents large, as in (1c), the enantiotopic specificity largely disappears.<sup>6</sup>

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