

## Preparations of Bicyclic Chiral Lactone Synthons *via* Stereospecific Pig Liver Esterase-catalysed Hydrolyses of *meso*-Diesters. Ring-size induced Reversal of Stereospecificity

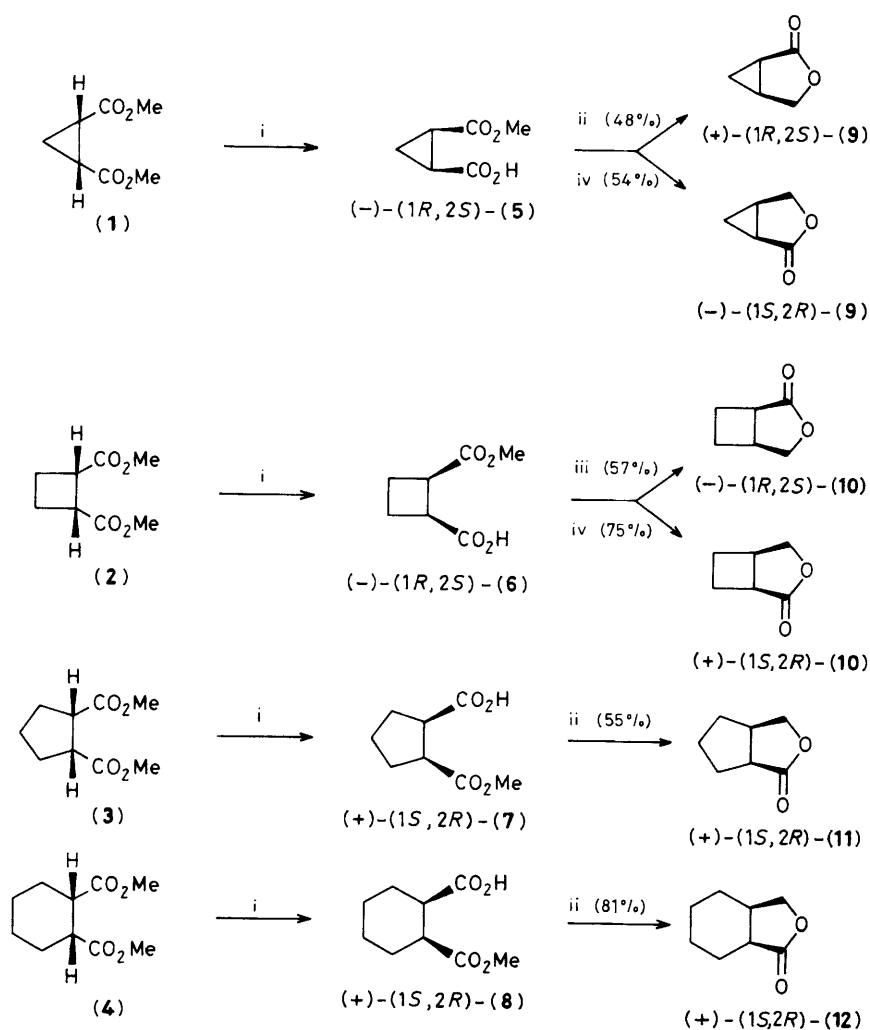
Gabriele Sabbioni, Marion L. Shea, and J. Bryan Jones\*

Department of Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 1A1

Stereospecific pig liver esterase-catalysed hydrolysis of monocyclic *meso*-1,2-diesters provides a convenient preparative route to both enantiomers of useful chiral lactones and demonstrates a sharply defined and unprecedented ring-size-mediated reversal of stereospecificity.

The ability of enzymes to catalyse stereospecific transformations of *meso*-compounds into valuable chiral synthons is now established as a method of considerable value in asymmetric synthesis.<sup>1–3</sup> For the preparation of useful<sup>4</sup> chiral bicyclic lactones such as (9)–(12), the most versatile enzyme so far documented is horse liver alcohol dehydrogenase.<sup>1</sup>

However, alcohol dehydrogenases suffer from the disadvantage that expensive and unstable nicotinamide coenzymes are required.<sup>5</sup> We now report that the coenzyme problem can be avoided in bicyclic lactone preparation by exploiting a cofactor-independent hydrolase such as pig liver esterase (PLE).<sup>3</sup> In addition a very clearly defined and novel reversal



**Scheme 1.** i, PLE, 20°C, pH 7, 2–6 h; ii,  $\text{BH}_3\cdot\text{Me}_2\text{S}$ ; iii, (a)  $\text{ClCO}_2\text{Et}$ ,  $\text{NEt}_3$ , (b)  $\text{NaBH}_4$ ; iv,  $\text{LiBH}_4$ . The products [except (+)-(1S,2R)-(11), 17% e.e.] were obtained in >97% e.e.

of stereospecificity has been observed. PLE-catalysed hydrolyses of the *meso*-diesters (1)–(4) give the corresponding half acid esters (5)–(8) (Scheme 1). These chiral intermediates may then be converted into either lactone enantiomer of the compounds (9)–(12) *via* selective reduction of the carboxy<sup>6,7</sup> or ester<sup>8</sup> group.

Preparative-scale (up to 3 g of substrate) PLE-catalysed hydrolyses of the *meso*-diesters (1)–(4)<sup>9</sup> were effected at pH 7.† For the diesters (1) and (2), the hydrolyses were enantiotopically specific for the *pro-S* methoxycarbonyl group. The ease with which either lactone enantiomer can be obtained from such acid-ester products was demonstrated by the conversion of (–)-(1*R*,2*S*)-(5) and (–)-(1*R*,2*S*)-(6) into (+)-(1*R*,2*S*)- and (–)-(1*S*,2*R*)-(9) and (–)-(1*R*,2*S*)- and (+)-(1*S*,2*R*)-(10), respectively.

With the cyclopentyl substrate (3), the enzyme's stereo-

specificity changed, with a marginal *pro-R* enantiotopic specificity of ester group hydrolysis being manifest in a 17% enantiomeric excess (e.e.) of the product lactone (+)-(1*S*,2*R*)-(11). The reversal of stereospecificity became complete for the cyclohexyl diester (4), with the optically pure lactone (+)-(1*S*,2*R*)-(12) being isolated after the reduction step. The e.e.s. of the lactones (9)–(12) were established by n.m.r. spectroscopy<sup>10</sup> and are considered accurate to within  $\pm 3\%$ . The absolute configurations were assigned by comparisons with authentic samples obtained previously.<sup>1</sup>

In addition to extending the synthetic value of pig liver esterase-catalysed hydrolyses to an important group of chiral synthons, the reversal of stereospecificity that these data reveal represents a fascinating and highly significant new aspect of the enzyme's properties. While some inversions of enzyme stereospecificity within structurally related series of substrates are known,<sup>5,11</sup> the dramatic ring-size mediated reversal reflected by the current data is, to our knowledge, unprecedented. Further investigation of the factors controlling this stereospecificity reversal are in progress.

We thank the Natural Sciences and Engineering Research Council of Canada for support and Professor M. P. Schneider

† The results of <100% enantiomeric excess obtained in other PLE-catalysed *meso*-diester hydrolyses performed at pH 8 were due, at least in part, to competing chemical hydrolyses at the higher pH (ref. 3).

for communicating his results on this topic prior to publication.

Received, 21st November 1983; Com. 1511

## References

- 1 R. Mislin, Ph.D. Thesis, ETH, Zurich, 1968; D. R. Dodds and J. B. Jones, *J. Chem. Soc., Chem. Commun.*, 1982, 1080; I. J. Jakovac, H. B. Goodbrand, K. P. Lok, and J. B. Jones, *J. Am. Chem. Soc.*, 1982, **104**, 4659; G. S. Y. Ng, L.-C. Yuan, I. J. Jakovac, and J. B. Jones, *Tetrahedron*, in the press.
- 2 D. M. Jerina, H. Ziffer, and J. W. Daly, *J. Am. Chem. Soc.*, 1970, **92**, 1056; G. Bellucci, G. Berti, G. Catelani, and E. Mastroilli, *J. Org. Chem.*, 1981, **46**, 5148; G. Bellucci, G. Berti, R. Bianchini, P. Cetera, and E. Mastroilli, *ibid.*, 1982, **47**, 3105; M. Ohno, *Fermentn. Ind. (Jpn.)*, 1979, **37**, 836.
- 3 C.-S. Chen, Y. Fujimoto, and C. J. Sih, *J. Am. Chem. Soc.*, 1981, **103**, 3580; Y. Ito, T. Shibata, M. Arita, H. Sawai, and M. Ohno, *ibid.*, p. 6739; S. Iriuchijima, K. Hasegawa, and G. Tsuchihashi, *Agric. Biol. Chem.*, 1982, **46**, 1907.
- 4 J. B. Jones, M. A. W. Finch, and I. J. Jakovac, *Can. J. Chem.*, 1982, **60**, 2007.
- 5 W. H. Baricos, R. P. Chambers, and W. Cohen, *Anal. Lett.*, 1976, **9**, 257; J. B. Jones and J. F. Beck, *Tech. Chem. (N.Y.)*, 1976, **10**, 107; C.-H. Wong and G. M. Whitesides, *Aldrichimica Acta*, 1983, **16**, 27.
- 6 C. F. Lane, H. L. Myatt, J. Daniels, and H. B. Hopps, *J. Org. Chem.*, 1974, **39**, 3052.
- 7 K. Ishizumi, K. Koga, and S. Yamada, *Chem. Pharm. Bull.*, 1968, **16**, 492.
- 8 J. W. Cornforth, R. H. Cornforth, G. Popjak, and L. Yengoyan, *J. Biol. Chem.*, 1966, **241**, 3970.
- 9 L. L. McCoy, *J. Am. Chem. Soc.*, 1958, **80**, 6558; E. R. Buchmann, A. O. Reims, T. Skei, and M. J. Schlatter, *ibid.*, 1942, **64**, 2696; L. N. Owens and A. G. Petro, *J. Chem. Soc.*, 1955, 2383; A. Cambon and R. Jullien, *Bull. Soc. Chim. Fr.*, 1973, 2003.
- 10 I. J. Jakovac and J. B. Jones, *J. Org. Chem.*, 1979, **44**, 2165.
- 11 H. L. Boter and A. J. Ooms, *Biochem. Pharmacol.*, 1967, **16**, 1563; H. M. Schwartz, W. S. Wu, P. W. Marr, and J. B. Jones, *J. Am. Chem. Soc.*, 1978, **100**, 5199.